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Posters

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Allergology and Clinical Immunology

Serum hepcidin in inflammatory bowel diseases

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Hepcidin, a polypeptide hormone produced by hepatocytes, is the main regulator of iron homeostasis, acting as a negative mediator of iron absorption and iron release from body iron stores. Inflammation stimulates hepcidin production, thus contributing to the inhibition of iron absorption and iron release from macrophages, common features of inflammatory diseases. We determined the serum concentration of hepcidin in 52 patients with inflammatory bowel diseases (IBD). Twenty-two patients had Crohn's disease (CD), 30 had ulcerative colitis (UC). Twelve healthy controls (HC) were also studied for comparison. Complete blood counts, iron status, erythropoiesis-related parameters, as well as disease activity were evaluated in addition to hepcidin. No significant differences in hepcidin levels were observed between HC and IBD patients. In IBD hepcidin concentration was significantly related with C-reactive protein ($r = 0.3337$, $p = 0.0095$), serum ferritin ($r = 0.660$, $p < 0.0001$), transferrin ($r = -0.471$, $p = 0.0002$) and soluble transferrin receptor ($r = -0.439$, $p = 0.0005$). No relationship was observed between hepcidin and serum erythropoiet in or erythrocyte sedimentation rate. Serum hepcidin levels were higher in patients with active disease than in those with quiescent disease (6.68 ± 9.81 and 2.77 ± 3.17 nM respectively, $p = 0.0295$). Twenty-six IBD patients had anemia (mainly mild anemia). We did not find differences in hepcidin levels between anemic and non-anemic patients; however, serum hepcidin increased significantly passing from patients with pure iron deficiency anemia (IDA) to those with a combination of IDA and anemia of inflammation (AI), and those with pure AI (1.55 ± 3.00, 3.59 ± 5.64 and 14.77 ± 13.90 nM, respectively, $p = 0.0229$). A serum hepcidin concentration below 2.0 nM correctly differentiated 85 % of patients with pure IDA or IDA associated with AI from patients with AI without iron deficiency.

Our results suggest that in IBD serum hepcidin concentration is influenced by both iron stores and inflammation, and hepcidin determination can be useful in the differential diagnosis of IBD-associated anemias.

An example of successful off-label use of TNF-alpha inhibitors for the therapy of Behçet disease

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A 28 years old man was referred to our attention in November 2010 for arthralgias and lower back stiffness. The patient had a history of bilateral ipovisus previously attributed to panuveitis, treated with immunosuppressive therapy based on oral corticosteroids and cyclosporin.

Physical examination put in evidence iatrogenic Cushing's syndrome and active synovitis of the sacroiliac joints. Moreover, upon specific questions, the patient reported recurring mouth ulcers since the beginning of his medical history back in 2006. Laboratory testing showed increase of inflammatory markers and negativity of HLA-B27. MRI of the pelvis showed signs of inflammation of the sacroiliac joints bilaterally, with edema and minimal bone resorption. A new ophthalmologic evaluation confirmed the presence of active obliterative vasculitis. We formulated the diagnosis of Behçet's disease (International Study Group for Behçet Disease criteria 1990) and started (January 2011) therapy with Adalimumab 40 mg once/2 weeks with progressive tapering of steroid and cyclosporin daily dosage. At follow-up, we observed a complete clinical remission of sacro-ileitis with normalization of CPR and ESR, with associated radiographic remission. Ophthalmological evaluation demonstrated dramatic amelioration of the uveitis. Currently, the patient is maintained in complete clinical remission with Adalimumab and cyclosporin (100 mg/day). The progressive tapering of steroids until complete discontinuation determined remission of Cushing's syndrome.

This case report confirms the efficacy and safety of TNF-alpha inhibitors in the treatment of Behçet Disease with joint and ocular involvement. (Neri P et al.; Adalimumab (Humira^{TM}): a promising monoclonal anti-tumor necrosis factor alpha in ophthalmology. Int Ophthalmol. 2011; Arida A et al.; Anti-TNF agents for Behçet's disease: analysis of published data on 369 patients. Semin Arthritis Rheum. 2011; Olivieri I et al.; Efficacy of adalimumab in patients with Behçet's disease unsuccessfully treated with infliximab. Clin Exp Rheumatol. 2011; Benitah NR et al.; The use of biologic agents in the treatment of ocular manifestations of Behcet's disease. Semin Ophthalmol. 2011).

Nasopharyngeal expansive lesion: a possible first presentation of Wegener's granulomatosis

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A 57-year old woman was admitted to the Otolaryngology Department because of "Acute otitis and fever" resistant to home antibiotic therapy.
Computerized tomography (CT) scan of facial and petrous bones showed "right nasopharyngeal expansive lesion, vascular lesions of the right pharyngeal tonsil, left otomastoiditis and bilateral rhinosinusitis". She was then operated for removal of lesion.
Due to persistence of continuous-remittent fever, associated with paresthesias and weakness of all four limbs, with inability to maintain upright posture, she was moved to our Department of Internal Medicine.
Her medical history was rather poor of pathological events, while physical examination revealed pulmonary crackles, with widespread weakening of the vesicular murmur.
Blood chemistry showed increased inflammatory markers and liver enzymes, normocytic anemia, renal failure stage III KDOQI, hematuria and proteinuria (600 mg/day).
Urine and blood cultures were negative, while the autoantibody profile showed positivity (1:640) for p-ANCA (perinuclear anti-neutrophil cytoplasmic antibody). Thorax and abdomen CT scan showed "left basal pulmonary texture consolidation, thickening of right pulmonary interlobar fissures and multiple segmental *wedge-shaped* foci of *non enhancement* within the spleen". The brain Nuclear Magnetic Resonance (NMR), performed for the persistence of the neurological symptoms, showed bilateral widespread lesions, due to cerebral vasculitis.
The renal, pulmonary, neurological and upper airway involvement, the increase of inflammatory markers with p-ANCA positivity in the absence of eosinophilia and history of asthma, suggested the presence of Wegener's Granulomatosis. This suspicion was confirmed by nasopharyngeal histology of the lesion, which showed "necrotizing granulomatous vasculitis".
Therapy with prednisone 1 mg/kg/day and cyclophosphamide 2 mg/kg/day was started with initial symptomatic improvement, but the onset of lymphopenia, widespread mycotic infections, bacterial pneumonia due to *Klebsiella pneumoniae* and subsequent coma, that a brain CT scan correlated with possible encephalitis, make necessary discontinuation of immunosuppressive therapy. This clinical setting, resistant to both immunosuppression and antibiotic and antimycotic therapy, led to exitus.
Nasopharyngeal granulomatous lesion is an uncommon clinical presentation of Wegener's Granulomatosis. Due to the rapidly progressive and potentially fatal course of this disease, early recognition and treatment is paramount in preventing severe organ damage.

Esophageal perforation: a rare, severe complication of eosinophilic esophagitis

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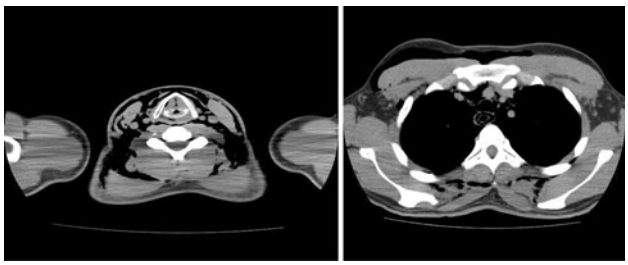
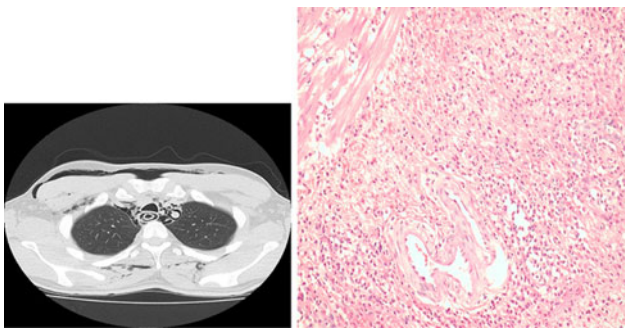
Case Report: A 32 yr old man presented to ER with severe dysphagia and dyspnea, suddenly arisen after a chicken meat based meal. A chest and neck CT revealed mediastinal and subcutaneous emphysema, with gas diffusion among the muscular layers of the neck. Intraoperatory upper GI endoscopy showed severe, diffuse desquamative esophagitis. The patient underwent esophageal resection with anastomosis of the stomach to the pharynx. Pathologic examination of the resected esophagus showed a large area of mucosal and submucosal necrosis and an extensive inflammatory infiltrate with abundance of eosinophils, affecting all layers of esophageal wall. Recovery was uneventful. The patient since childhood had had allergic rhinitis and allergic symptoms after ingestion of chicken meat, eggs and shellfish; a diagnostic workup done 2 months after the esophageal perforation showed elevated eosinophils (536/mmc) and high levels of serum IgE (333 KU/mL); skin prick test, prick by prick and RAST showed Ist type hypersensibility to chicken meat and eggs; multiple colonic biopsies during colonoscopy showed diffuse eosinophilic infiltrates. A diagnosis of Eosinophilic esophagitis and gastroenteritis was made; a diet devoid of chicken meat and eggs was begun, as well as therapy with steroids, antihistamines and antileucotrienes. After 6 months the patient is well.
Conclusions: Eosinophilic esophagitis is a rare clinical manifestation of food allergy. Prompt diagnosis and treatment of the disease can prevent catastrophic complications such as the one we described.





The strange fever of a diabetic patient: a case of non-infective origin of FUO

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A 68 year old patient came to our attention due to a chronic fever (up to 38 °C), not preceded by chills, appeared since a month. Accompanying symptoms included arthralgia, marked asthenia, malaise and a transient cutaneous erythematous rush localized in the trunk and limbs. Apart from a mild diabetes mellitus (treated with oral hypoglycemics) and reported allergies to unspecified drugs, the clinical

history was unremarkable. Physical examination was negative, except for a light systolic murmur, which the patient was aware of. Culture and microbiological tests performed on blood and urine samples were repeatedly negative. Other tests showed a neutrophilic leukocytosis ($27.83 \times 10^3/mm^3$ WBC, 86.8 % neutrophils), an increased C-reactive protein (CRP 32 mg/dL) and mild normochromic, normocytic anemia (Hb $\sim$10 g/dL). The patient was treated empirically with different wide spectrum antibiotic regimens (i.e., standard doses of ciprofloxacin at the beginning followed by vancomycin and gentamycin) with no clinical or biochemical improvement. Several exams including CT total body, abdominal ultrasound and PET were all negative. A trans-esophageal echocardiogram revealed tiny ($\sim$2 mm), bulky lesions located on the leaflets of the aortic valve suggestive of those peculiar types of non-bacterial thrombotic vegetations detectable in rare conditions, e.g. cases of marantic or Libman–Sacks endocarditis. The presence of minimal pericardial effusion was also identified. An autoantibody profile revealed a positivity for antinuclear antibodies (1:80), anti-DNA (64 IU/mL) and anti-cardiolipin (IgG 13 U/mL, IgM 124 U/mL) and lupus anticoagulant. Based on these findings, a diagnosis of undifferentiated connective tissue disease was established and the patient was treated accordingly (tapering doses of methylprednisolone starting with 1 mg/kg, i.e. $\sim$60 mg/day). As a result, there was a progressive clinical response and normalization of inflammatory indexes. This challenging case brings to our attention the importance an accurate differential diagnosis in cases of fevers of unknown origin related to systemic autoimmune diseases not fulfilling classification criteria for defined connective tissue diseases. In these conditions, characterized by nonspecific clinical manifestations, the follow-up is essential to establish a diagnosis over time.

Increased intimal media thickness in patients with NAFLD is correlated with insulin resistance and levels of TNF-alpha

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Aim: To identify clinical parameters which are associated to subclinical atherosclerosis in obesity and Nonalcoholic Fatty Liver Disease (NAFLD).
Methods: 82 non diabetic obese patients undergoing bariatric surgery (sleeve gastrectomy or gastric bypass) were characterized before the intervention with oral glucose tolerance, euglycemic hyperinsulinemic clamp, lipid and inflammatory biomarkers and measurements of intima-media thickness (IMT), as a marker of subclinical atherosclerosis. In all patients liver steatosis was assessed by echography and histological analysis from a liver biopsy performed during the intervention.
Results: Obese subjects were divided on the basis of the degree of steatosis (NS = no steatosis n = 7, MildS = mild steatosis n = 17, ModS = moderate steatosis n = 37, SS = severe steatosis n = 21). The degree of steatosis was correlated with insulin resistance, assessed by HOMA index (p 0.004) and Glucose Disposal Rate (p 0.003). SS patients also showed increased levels of fasting plasma glucose and insulin, HbA1c. We found that IMT is significantly and progressively increased from NS to SS patients (p 0.009, ANOVA) and is significantly correlated with insulin resistance (p 0.038) We didn't observe differences in lipid profile, BMI, waist and age even if MildS and SS showed increased levels of circulating TNF-alpha. TNF-alpha levels were correlated with insulin resistance assessed by glucose disposal rate (p 0.05).
Conclusions: Patients with NAFLD showed an increased subclinical atherosclerosis and Insulin Resistance, associated to increased levels of soluble TNF-alpha.

Basophils autoinduced degranulation (BAD) stimulated with autologous serum, by a two colour method flow cytometry. A valid support for the diagnosis of chronic autoimmune urticaria

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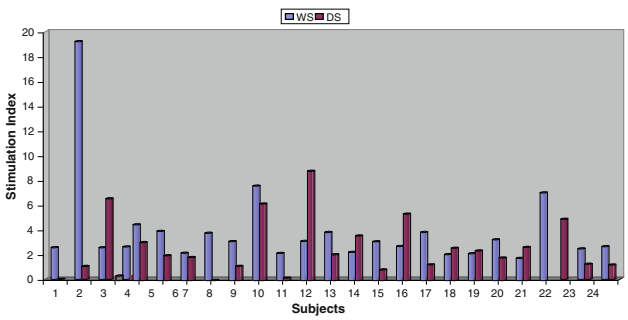
Urticaria is a syndrome that includes a wide range of diseases. Since 1962 Rorsman hypothesized that a proportion of chronic idiopathic urticaria is the expression of an autoimmune process dependent by IgG and, sometimes, IgE, subsequently confirmed by Hide and Niimi. Later the involvement of the complement in this process was demonstrated too. There aren't clinical or histological features that can be used as a paradigm in the diagnosis of CAU. The foundation of the diagnosis is the demonstration of the presence of anti-FcεRIα and anti-IgE autoantibodies in the serum of patients. The Autologous Serum Test (ASST) is an useful screening procedure, but the sensitivity and specificity is of 70–80 % and this test requires further confirmatory methods. BAD test, marking CD63, performed on whole blood stimulated with autologous test, is useful for the quantitative determination of the basophils degranulation by flow cytometry. Recent studies have shown that the sensitivity and specificity of this method is of 95.5 and 90.5 % respectively. With heparinized blood of patients with CU we prepared negative controls, positive controls and the samples stimulated with autologous whole and decomplemented serum., and everything was labeled with mo-Ab anti-CD63-FITC and anti-CCR3-PE, incubated, lysed and read by flow cytometry. BAD test, performed on 100 patients with CU, have evidenced that 24 of these showed an increase of CD63 on basophils stimulated with whole and/or decomplemented serum and hence they suffered from CAU. Our results lead us to hope that BAD could become a routine test in the diagnosis of CAU, to perform before ASST. The sensitivity of BAD could be enhanced by associating the basophil activation marker CD203c.



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A woman with rash, eosinophilia and systemic symptoms

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We describe a case of a 74-year-old woman with fever, diarrhea and a pruritic rash involving trunk, face and limbs. The patient was a previous smoker, affected by hypertensive heart disease and reduced left ventricular function with demonstration of not significative coronary arteries lesions at elective angiography performed 1 month before admission. Medical history includes a recent hospitalization for pneumonia and recurrent urinary tract infections caused by *E. coli* and *E. faecalis*, treated with levofloxacin and teicoplanin; allopurinol therapy was also started for first detection of hyperuricemia. Cutaneous rash appeared few days later so that antibiotics and allopurinol were discontinued and the patient was discharged with methylprednisolone and hydroxyzine. For the persistence of the rash and the onset of fever and diarrhea, after 7 days the patient presented to our Emergency Department. At arrival in our department the patient was dyspnoeic and hypoxia was present at emogasanalysis (pCO_2 25 mmHg, pO_2 65 mmHg, PaO_2/FiO_2 330), so oxygen therapy was started (SpO_2 97 % with FiO_2 32 %); blood pressure was 110/55 mmHg, heart rate 73 beats/min and temperature 37.4 °C. On physical examination a very itchy macular rash was present all over the body, associated with periorbital edema; breaths sounds were present bilaterally; cardiac systolic murmur 2/6 was present on aortic outbreak; no jugular vein distension, no pedal edema and no hepatomegaly were evident. The remainder of the examination was normal. The ECG showed sinus rhythm with occasional ventricular extrasystoles without alteration of ST-T and a chest X-ray showed only signs of congestion. A two dimensional transthoracic echocardiography showed hypokinetic-dilated cardiomiopathy (predominantly apical hypokinesia) with reduced systolic function (EF 35 %) and blood tests showed leukocytosis (15800/mm3) with eosinophilia (maximum 26 %, 3900/mm3), rise in liver enzymes and increase in serum creatinine (maximum 2.87 mg/dL). We started therapy with methylprednisolone (20 mg intravenous) and hydroxyzine. After few days the patient became afebrile, the morbilliform rash has evolved into erythroderma and finally into desquamation; kidney and liver function normalized and the eosinophil count decreased. Blood and urine culture tests were negative. Eosinophilia in this case was associated with a cutaneous rash, hepatic and kidney dysfunction. In this clinical context (eosinophilia with multiorgan involvement), the differential diagnoses includes Churg–Strauss syndrome (CSS), idiopathic hypereosinophilic syndrome and drug-induced eosinophilia. The negative history of asthma and rhinosinusitis and the absence of transient pulmonary infiltrates and mononeuropathy does not fulfill the criteria for CCS diagnosis. Hypereosinophilic syndrome is a diagnosis of exclusion when no apparent cause of eosinophilia is diagnosed, which was not the case in this patient. In fact the recent introduction of allopurinol raised the suspicion of Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome that is characterized by fever, cutaneous eruption, and involvement of several internal organs—most commonly the liver and, to a lesser extent, the kidneys, lungs, brain and heart with myocarditis. The cutaneous reaction is due to a delayed-type hypersensitivity reaction. The rash presents as a widespread erythematous eruption on the face, trunk and extremities and is accompanied by fever, facial and periorbital edema, and/or exfoliative dermatitis. Desquamation may occur with healing. The most common drug class implicated are anticonvulsants (phenytoin, lamotrigine, and carbamazepine), allopurinol, minocycline, dapsone and sulfonamides. Moreover, as the rush resolved with methylprednisolone and hydroxyzine, a two dimensional transthoracic echocardiography showed an improvement in global left ventricular systolic function, in particular of apical hypokinesia (EF 45 vs. 35 % while she was febrile). We performed a myocardial scintigraphy with dipyridamole, which did not detect inducible ischemia. The values of myocardial enzymes have remained consistently normal. A significant reduction in left ventricular EF could be considered a myocardial involvement as part of DRESS syndrome even if without a rise in myocardial enzymes. Given the context of transient hypokinesia of the apex with a significant reduction in left ventricular EF and the absence of critical coronary disease we hypothesized the presence of stress cardiomyopathy Tako Tzubo-like although without electrocardiographic changes and rise in myocardial enzymes.

Allergy: an increasing cause of coronaropathy in young?

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Case Report: A 24 year old young female was admitted to the internal medicine department with recurrent episodes of abdominal pain and diarrhoea. Risk factors for organic digestive diseases were absent. She reported lactose intolerance, gastroesophageal reflux disease, asymptomatic cholelithiasis.

Her past medical history was remarkable with acute inferior myocardial infarction with ST segment elevation in D3 and aVF and depression in D1, aVL, V1-V6, at 23 years of age. Coronarography showed diffuse coronary spasm and stenosis of right coronary with collateral circulation; angioplasty on coronary lesion and intracoronary administration of nitrates were performed with almost complete

resolution of obstruction and vasospastic phenomena. She was discharged from the cardiology department, medical treatment with antiplatelets and calcium-antagonists was started. Cardiovascular risk factors were excluded: particularly cocaine use, cigarette smoking, thrombophilia, familial hypercholesterolemia, obesity, hypertension, hypercholesterolemia, diabetes were absent. Churg–Strauss vasculitis was also excluded. She had a previous history of anaphylactic shock and status asthmaticus induced by camphor inhalation. She was suffering, since the age of 20 years, from allergic rhinitis and asthma recurrent despite therapy. Allergic tests showed mild eosinophilia, mild increases of PRIST, RAST and skin prick test positive to pollutants, patch test positive to nickel.

Discussion: The patient's medical history was dominated by two conditions: (1) severe and early coronary disease, (2) allergic disease poorly controlled by therapy. All possible risk factors or known causes of acute coronary syndrome were absent. Also, there were no criteria for the diagnosis of vasculitis, hyper-IgE syndrome, true eosinophilia, which may give rise to cardiologic complications. There was a temporal association between onset of acute coronary symptoms and exacerbation of allergic asthma after taking ibuprofen.

During allergic reactions patients may have cardiac events resulting from myocarditis or symptoms of myocardial ischemia, as a result of the shock. More rarely, ischemic events may be an expression of coronary spasm resulting from the release of mast cell mediators (histamine, leukotrienes, tryptase). This condition, known as allergic angina or Kounis syndrome, is classified into: TYPE I: from coronary spasm; TYPE II: spasm of coronary on atheromatous coronary thrombosis; TYPE III: thrombosis of the stent. The diagnosis is based on exclusion of other possible causes of acute coronary syndrome associated with an allergic reaction.

We believe that the clinical case we report fulfil diagnostic criteria for Kounis syndrome type II because myocardial infarction followed an allergic reaction and occurred in the right coronary artery district that had a stenosing atheromatous plaque. The continuous increase in the incidence of allergies in young generations should alert physicians about the potentially increasing risk of this type of coronary disease in the near future.

Coexisting systemic lupus erythematosus and Niemann–Pick disease: a case report

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A 30-year-old woman was admitted to our clinic, with a 2 week history of fatigue, fever and severe anemia. She was first diagnosed as having Systemic Lupus Erythematosus (SLE) in 1991, given the presence of >4 classification criteria (total protein excretion >0.5 g/24 h, positive ANA and anti-DNA double strand antibodies, nonerosive arthritis, pleural effusions). In 1992 the diagnoses of cerebral vasculitis and biopsy proven proliferative glomerulonephritis (IVth class) were posed, together with severe mitral valve regurgitation. Previous therapies included Cyclosporin A, Methotrexate and prednisone, without experiencing clinical remission. Multiple courses of i.v. cyclophosphamide (400 mg/monthly) and high dose intravenous dexamethasone pulses had been administered, but proteinuria, leukopenia with lymphopenia and episodes of severe anemia requiring blood transfusions were unresolved. Since 2003 she showed reduced exercise tolerance and dyspnea, with lung function parameters consistent with severe restrictive lung disease; in 2004 she presented a deep vein thrombosis. We observed this patient for first time in 2005, when she was referred for evaluation: severe anemia and leukopenia were persistent in the last 2 years, arthritis and asthenia were her main complaint. Physical examination did not reveal lymph node or spleen enlargements, but liver edge was palpable 3 cm below the right costal margin. Periocular xanthelasma and joint deformities compatible with Jaccoud arthropathy were observed. Abdominal ultrasonography showed slightly enlarged "bright" liver. Evaluation for a hypercoagulable state for previous DVT and prolonged aPTT was positive for IgG anticardiolipin assay, hence in agreement with antiphospholipid syndrome. At current admission 2 years later, she had irregular fever since 14 days. Physical examination revealed severe paleness, pulse 111/min and regular, mild pitting edema of feet and vesicular murmur reduction at left lung base. An holosystolic 3/6 mitral regurgitation murmur was audible at heart auscultation. Laboratory values were as follows: Hgb 5.5 g/dl, RBC 2.31×10^6/μL. MCV 72.7 fL reticulocyte count 1.54 %. WBC 4,800/μL with extreme lymphopenia and normal neutrophils and platelets. There were no signs of active hemolysis, direct and indirect Coombs' tests gave negative results, serum iron and ferritin levels were normal, complement levels reduced, 24/h protein excretion was 1.13 g. Patient medication included MMF 2 g/day, prednisolone 30 mg/day, furosemide 25 mg/day, irbesartan 300 mg/day. Abdomen ultrasonography confirmed hepatomegaly, reporting also splenomegaly (15.8 cm). MMF was suspended on 3rd day, bone marrow aspirate was performed to investigate if haematological picture was related to SLE activity, rule out drug induced myelotoxicity or other causes of cytopenia. May–Giemsa stained smear was hypocellular, with <30 % of space occupied by haemopoietic tissue, which had normal morphology and development. Nearly 70 % of space was occupied by sea-blue histiocytes raising suspect of Niemann–Pick disease (NPD), an inborn lysosomal storage disorder. Despite transfusion support, treatment with broad-spectrum antibiotics, high dose intravenous methylprednisolone and immunoglobulins, the patient died after severe bone marrow aplasia, septicaemia and multiple organ failure. NPD is an autosomal recessive lysosomal storage disorder, caused by deficient activity of acid sphingomyelinase encoded by SMPD1 gene. Type B NPD is characterized by quite heterogeneous clinical features but in most cases hepatosplenomegaly, pulmonary involvement and hyperlipidemia are observed, often presenting in adulthood. Several mutations in SMPD1 causing NPD have already been described and characterized in the Italian population. Our proband presented cytopenia, lung restrictive disease, slight hepatomegaly without overt neurological involvement. She was found to carry two novel SMPD1 mutations in compound heterozygosity: p.A36V and IVS2 +8 T>G. Notably, overlapping features exist between a protean multisystemic disease such SLE and lysosomal storage disorders. To our knowledge, this is the first report of coexistence of SLE with antiphospholipid syndrome and NPD.

Alveolar haemorrhage in a patient with Henoch–Schoenlein purpura and common variable immunodeficiency: successful treatment with rituximab

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In 2000, a 46 year-old male with history of recurrent airway infections developed episodes of abdominal pain, arthritis and palpable skin purpura without overt renal involvement. He had serum IgG 377 mg/dl, IgM 20 mg/dl, normal IgA (increased during relapses of cutaneous vasculitis) and low CD19+ B cells. Causes of secondary

humoral immunodeficiency (e.g.renal loss, drugs) have been ruled out. Poor response to vaccination was observed. Skin biopsy showed the presence of leukocytoclastic vasculitis with endothelial deposits of IgA. A diagnosis of Henoch-Schoenlein purpura (HSP) concurrent with Common Variable immunodeficiency (CVID) was reached, and he has been treated over the years for multiple relapses with steroids, intravenous and oral cyclophosphamide (CYC), methotrexate and replacement with intravenous immunoglobulins. During the last HSP relapse, he also developed dyspnea and hemoptisis. Chest CT showed bilateral patchy alveolar infiltrates suggesting pulmonary haemorrhage and capillaritis, confirmed by bronchoalveolar lavage. Based on most recent experiences on the use of B cell depleting agents, such as rituximab, in vasculitis and in different autoimmune manifestations, even in the context of CVID, we chose to use Rituximab (RTX) after failure of steroids. He received two 800 mg doses of RTX at 2-week intervals and a single i.v. 500 mg dose of CYC. He was discharged after a rapid regression of cutaneous, abdominal and respiratory symptoms, confirmed by clearing of infiltrates at chest-CT and normalization of laboratory findings. He is now doing well and the re-treatment with RTX is planned at B cell reconstitution. Diffuse alveolar hemorrhage is a life-threatening manifestation of pulmonary vasculitis. Pulmonary involvement in HSP is rarely observed. We describe an adult patient affected by CVID and recurrent HSP, successfully treated with RTX for occurrence of alveolar haemorrhage. Further experience is warranted to assess the efficacy of RTX for pulmonary involvement in vasculitis. Additionally, the use of RTX or other B-cell targeted treatments in difficult-to-treat forms of Henoch-Schoenlein purpura deserves more clinical experience.

Myelitis in the course of common variable immunodeficiency (CVID): 2 cases

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Common variable immunodeficiency (CVID) represents a heterogeneous group of primary antibody deficiencies with complex clinical and immunologic phenotypes, that can occur at any age. Acute myelitis should be added to the broadening spectrum of neurologic complications in common variable immunodeficiency. We here report on two patients with recurrent myelitis as the first manifestation of CVID.

Both patients were female, respectively of 71 and 57 years old, with a previous history of recurrent myelitis of unknown origin, in the first case three episodes in 1 year, and in the other one two episodes in the teenage period. They were admitted to our department with little autonomy, ataxic and spastic gait on enlarged base, mild upper limbs hyperreflexia, reduced lower limbs reflexes, ipo-dysesthesia with umbilical upper level. Neurogenic bladder was present in both patients. The second patients presented left eyelid ptosis, miosis and hyporeflexia to the photomotor reflex.

In both cases spinal cord magnetic resonance showed inflammatory changes in cervical and in lumbar region in T2-weighted images in the first case and in cervical and dorsal region in the second case. Laboratory evaluation showed decreased serum levels of all immunoglobulin isotypes in both patients.

As induction therapy, they were successfully treated with high-dose methylprednisolone boluses associated with high dose of intravenous immunoglobulin (IVIg, 2 g/kg on two consecutive days monthly for 3 months). An initial clinical response was evident after the first IVIg infusion cycle, with improvement of the neurological symptoms.

In the first case, as remission-maintaining drug, we decided to use subcutaneous immunoglobulin (SCIg, Vivaglobin ® and then Hizentra ® CSL Behring), at 0.2 g/kg/week, at higher dose than usually employed in replacement therapy in CVID. At two-year follow-up control, the response to treatment was good, with complete motor recovery. No relapses occurred. The second patient has just begun the induction phase of treatment.

Conclusions: Our cases suggest the importance of a specific treatment for the CVID associated autoimmune conditions. Moreover, SCIg seems to be effective and safe in maintaining remission in recurrent severe inflammatory myelitis associated with CVID. Further study is needed to delineate the role of SCIg in the prevention of relapses.

A strange case of diplopia

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A patient of 70 years came to our attention for diplopia and divergent squint of the left eye for a week; in history hypertension for 20 years, transient ischemic attack 9 years ago. The general physical examination was normal excepting for a left supraclavicular lymphadenopathy. The neurological examination was normal excepting for a deficit of the left medial rectus muscle. The CT scan without contrast medium performed at the emergency department showed no intra or extra axial hemorrhage. A brain MRI showed marked contrast enhancement of all the cerebellar folia, the coating surface of the brainstem, the seventh and fifth cranial nerve (especially the left) with focal paravermian parenchymal enhancement of the maximum diameter of 1 cm bilaterally. Pathological contrast enhancement also along the corpus callosum. The MR imaging, albeit nonspecific, deposed for a meningo-encephalic malignant invasion or, alternatively, for inflammatory involvement (Tuberculosis?). In order to exclude a meningo-encephalitis the patient underwent a lumbar puncture: the physical–chemical and the microbiological examination of the liquor resulted normal, but cell count showed large size anomalous cell forming the 80 % of the overall cellularity. Once excluded the inflammatory involvement, we required a total body CT scan that detected a large diameter supraclavicular left lymph node, and a diffuse lymphadenopathy in the groin bilaterally and at the celiac trunk. The absence of hepatic repetitions and the typical lymphadenopathy above and below the diaphragm suggested the diagnosis of lymphoma with central nervous system involvement; therefore we proceeded to a supraclavicular lymph node biopsy in order to confirm the diagnosis. Surprisingly, the immunohistochemical examination showed diffuse positivity for neoplastic, non-haematological cells of epithelial origin. The immunophenotyping carried out on a second sample of CSF confirmed the presence of a population of large size CD45 negative and therefore not attributable to haematological origin. What was the gastroenteric localization? Given the absence of liver involvement, at first we opted for the execution of an esophagogastroduodenoscopy; subsequently a proctosigmoidoscopy found a heteroplastic development substenosing the lumen of the ascending colon. Histological examination recognized undifferentiated adenocarcinoma.

A misleading macroglossia

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FM, a female patient 75 years old, came to our attention for worsening dyspnea, edema of the lips, macroglossia, and difficulty in swallowing; these symptoms appeared about 4 months before. In her medical history: Monoclonal gammopathy of undetermined significance (MGUS) type IgG lambda diagnosed 20 years before and multi nodular goiter treated by thyroidectomy 5 months before. At a previous admission to another hospital hereditary angioedema had been excluded by C1 inhibitor functional level evaluation; a moderate of right pleural effusion and a posterior layer of pericardial effusion (10 mm) had been found. Suspecting post-surgery hypothyroidism, serum concentration of thyroid hormones had been evaluated showing elevated TSH concentration (63 μUI/ml). A triiodothyronine replacement therapy had been therefore initiated discharging the patient with a diagnosis of iatrogenic hypothyroidism, with further evaluation of thyroid hormones in the normal range. At the admission to our department the patient appeared debilitated, tachipnoica at rest. Physical examination of the chest showed a diffuse reduction of the vesicular murmur and a complete abolition of the murmur at the right base. A high resolution chest CT showed parenchymal consolidation in the right lower lobe with ipsilateral pleural effusion and a contralateral slight layer of effusion, mediastinal and axillary lymphnodes bilaterally. Empirical antibiotic therapy was started in the suspect of lobar pneumonia, at the same time specific tests for the detection of Mycobacterium tuberculosis were performed and resulted negative. After 2 weeks of unsatisfactory response to antibiotic therapy, a exploratory thoracentesis was performed which resulted negative for the detection of neoplastic cells. Moreover, suspecting pleural mesothelioma, the patient underwent video thoracoscopy with histological examination of the parietal pleura: chronic inflammatory infiltrates, lymphohistiocytosis. In the meantime an echocardiogram detected increased pericardial effusion and increased thickness of the free wall of the right ventricle. Considering the results from urine and serum immunofixation showing Bence-Jones proteinuria lambda type and the high serum monoclonal IgG lambda amount, we proceeded to periumbilical fat biopsy in the suspected of light chain amyloidosis. The histological examination confirmed the clinical suspicion, with positive Congo-red histochemical staining, birefringence under polarized light and positive immunohistochemistry for lambda immunoglobulin chains.

Hypereosinophilia in clinical practice: a common starting point leading to different conclusions. Report of 10 cases seen in an Internal Medicine Unit

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Introduction and Objective of the Study: Hypereosinophilia is a condition most frequently secondary to allergic disease, infestation, haematological or autoimmune diseases and more rarely, primary and idiopathic. To date, many controversies and open questions in the definitions and classification of the hypereosinophilic syndromes are still unresolved. Patients presenting with hypereosinophilia are frequently involved in a long diagnostic work up before to be correctly managed. We report a series of cases referred to our clinic for different clinical issues all sharing hypereosinophilia for which different diagnosis were provided.

Patients and Methods: 10 patients, 3 females and 7 males, aged from 18 to 72 years (media 47.9 ± 16), with maximum value of eosinophilic count from 790 to 50.570/mmc. Case 1: female, 18 years, she arrived to our attention for epigastralgia and an important weight loss; Case 2 and 3: a women of 72 years, and her daughter, 35 years, both affected by recurrent abdominal pain and persistent eosinophilia at blood tests. Case 4: male, 54 years, a history of asthma and allergic sinusitis, suddenly complicated by peripheral neurological symptoms. Case 5: male, 50 years, the patient presented a life-threatening multiple organ involvement, characterized by myocarditis and systemic vasculitis causing cerebral ischemia and retroperitoneal bleedings. Case 6: male, 62 years, affected by dyspnea, abdominal pain, pleural effusion and ascites. Case 7 and 8: both males, 56 and 59 years respectively, with recent history of asthma presenting with sudden dyspnea and diffuse pulmonary infiltrates. Case 9: male, 38 years, referred by cardiologist for acute heart failure with dilated cardiomyopathy and severe pleural and pericardial effusion and more than 25.000/mmc eosinophils in blood. Case 10: the last one is a young male of 35 years with persistent eosinophils count more than 2,500/mmc, totally asymptomatic with at least 3 years follow up. In all cases allergic origin, parasitological causes, haematological or immunological diseases were searched. When possible, histological examination of involved tissues was performed, demonstrating eosinophilic infiltrated.

Results: Case 1: endoscopy with gastric biopsy revealed diffuse mucosal erythema and eosinophilic infiltrated, respectively, therefore eosinophilic gastroenteritis was diagnosed and put in therapy with low dose prednisone. Case 2 and 3: eosinophils in ascitic fluid and several ileal and colonic samples led to diagnosis of eosinophilic gastroenteritis in a familiar form, local or systemic steroid therapy was necessary to control the recurrent relapses. Case 4: EMG demonstrated a severe multineuropathy and p-ANCA positivity has led to diagnose a Churg–Strauss syndrome; Case 5: was diagnosed as clonal hypereosinophilic syndrome, beside the negativity of cytogenetic analysis for the principal PDGFRA mutations, because we experienced no response to high dose steroids and hydroxyurea but a extremely rapid improvement using very low doses of Imatinib mesylate. Case 6: demonstration of high levels of eosinophils in pleural and ascitic fluid and at pleural and gastric biopsies conduced to the diagnosis of hypereosinophilic syndrome interesting serous and gastrointestinal tract; patient responded partially to corticosteroid therapy, requiring association with azathioprine and cyclosporine. Case 7: was diagnosed a chronic idiopathic eosinophilic pneumonia but several immunosuppressive regimens failed to control the symptoms and the patient needs persistent high dose steroid therapy. Case 8: the positivity of p-ANCA led to diagnosis of Churg–Strauss with only pulmonary involvement. Case 9: was diagnosed as HES with cardiac and pulmonary involvement and now he is well but with persistent need for steroids and azathioprine. Case 10: the last one, after exclusion of all the causes, clonal and myeloproliferative disorders included, is now considered as having an idiopathic hypereosinophilia (probably HES) requiring only a close follow up.

Conclusions: In all cases, except the last, the starting point was a symptomatic hypereosinophilia with different expression of clinical severity due to different organ involved and the hypereosinophilic extent. In our experience the particular involvement of a single organ, the ANCA positivity and the PDGFR mutations, when present, are the main diagnostic tools to help to differentiate among these apparently similar, but clinically different pathological entities.

Fungi and allergic disease, a case report

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B.A., a non-smoking 25 year old male was sent to our department because of recurrent cough (2–4 exacerbations a year) beginning in childhood, sometimes associated with purulent rhinitis. Sensitization to house dust mite had been found out at the age of 14 and the boy had underwent SCIT for 3 years with modest benefit. About 10 years later, the patient had been revaluated by a specialist because of symptoms persistence (cough and dyspnea) and a fixed moderate airway obstruction had been found. The medical examination detected; (a) allergic sensitization to *A. fumigatus* (SPT+; tIgE 819 kU/l; sIgE); (b) pansinusitis at the maxillofacial-CT; (c) a normal chest-radiography. The clinical picture was suggestive for allergic Aspergillus hypersensitivity (AH) and the patient started inhaled corticosteroids without significant benefit. A chest-HRCT, 2 months later performed, showed a lengthened parenchymal consolidation of the posterior basal segment of the lower left lobe with some associated bronchiectasis.

At admission, patient's general conditions were quiet good; BMI 17 (steady weight); fixed moderate airway obstruction under inhaled corticosteroids persisted; FeNO test 30 ppb (n.v. <25) was consistent with results in asthmatic patients treated with topical corticosteroids; purulent rhinitis with postnasal drip at rhinofibroscopy. The allergic sensitization to *A. fumigatus* was confirmed, RAST and ISAC tests to detect sIgE to recombinant allergens were performed [+rAspf4 (glycosidases), −rAspf6 (MnSOD), +rAspf1 (proteases), +rAspf3 (perixosimal membrane protein)], while other asthma causes were excluded. Routine laboratory test showed mild neutrophilia and acute inflammation markers (PCR 11 mg/dl, fibrinogen 741 mg/dl). The second day after admission the patient complained of chest pain of the right hemithorax. Chest-radiography evidenced parenchymal consolidation of the anterior middle and lower right lobes with minimal pleural effusion. A chest-CT [with HR and contrastographic study, performed to exclude a pulmonary embolism (PTE) and to better define the consolidation pattern] excluded PTE and showed: a banded parenchymal consolidation of the medial segment of the right middle lobe connected to the hilum, with "ground-glass" and "tree-in-bud" pattern opacities of the adjacent parenchyma; multiple nodular, partially flow-together, opacities of the posterior basal segment of the left lower lobe suggesting alveolar inflammation. Hence, the patient underwent a fibrobronchoscopy which evidenced white dense mucus impaction of both bronchial hemisystems corresponding to the CT findings areas, that were removed. After the procedure, a low-grade fever appeared and the PCR lightly increased. Blood culture and serological tests for Mycobacteria, Legionella (and urinary antigen test), Mycoplasma and Chlamydia were negative. The bronchial washing and BAL fluid specimens tested negative for galactomannan, mycobacteria and acido-alcohol resistant bacilli, whereas 1 CFU *A. fumigatus* (of unknown meaning) was isolated from bronchial fluid and >100,000 CFU of MSSA grew in both specimens. Bioptic specimen of the right lung parenchyma tested negative for Aspergillus colonies and eosinophilic infiltration. The presence of any immunodeficiency disorder was researched in the light of the staphylococcal pneumonia, but no abnormalities were found [HIV test, sera Ig level, C3, C4 and flow-cytometry study of the lymphocytic population). Autoreactive antibodies c-ANCA, p-ANCA tested negative. The ventilatory function was gradually and spontaneously improving so that systemic corticosteroids were not initiated. Chest-X-rays control, performed 7 days after, showed reduction of the right lung consolidation area, and the topical therapy, optimized at admission, was kept on after the discharge. At a 3 months later revaluation, the patient referred good control of the symptoms, despite a partially reversible moderate airway obstruction, and in the light of sera *A. fumigatus* IgG+, which result was provided by the laboratory a month after the patient discharge, the clinical picture was highly suggestive of ABPA (allergic bronchopulmonary aspergillosis. Hence, we decided to undertake systemic antifungal drugs (itraconazole 200 mg/die) and improve the basic therapy (budesonide) with prednisone 0.5 mg/kg/die for 10 days. Amelioration of the ventilatory function was documented after a month of itraconazole + topical steroids. If after further 3 months of such treatment, steroid sparing Aspergillus eradication or asthma control improvement won't occur, omalizumab would be the next step therapy.

Here we presented a case of ABPA with bronchiectasis in a young asthmatic boy, with a rather delayed diagnosis because of the lack of peripheral or pulmonary eosinophilia (probably due to inhaled steroids and intercurrent staphylococcal pneumonia), and the delayed availability of the sera IgG test.

ABPA is a T_H2 hypersensitivity lung disease caused by bronchial colonisation with *A. fumigatus* that occurs in immuno-genetically susceptible subjects. Only a minority of AH subjects develop the complete picture of ABPA (0.7–3.5 % of asthmatic patients), and even though clinical, immunological and radiologic criteria have been established, differential diagnosis between the two entities can be difficult sometimes. The sIgE pattern to different *A. fumigatus* proteins (corresponding to different biological functions), performed with recombinant allergens, would be resolving of hypersensitization due to only environment exposure or to the colonisation of the bronchial system by the fungi. In the present case, the positivity of sIgE to rAspf4 (suggesting spores metabolism germinating in a hostile environment) was concordant with most authors findings in ABPA, and an expensive test as ISAC providing only two allergens for *A. fumigatus* (rAspf1, rAspf3 corresponding to proteases and stress response proteins) even though improved the global sensitivity of *A. fumigatus* colonisation, didn't resolve the diagnostic question. More studies with recombinant allergens aimed to distinguish between AH and ABPA, and the availability of assays that detect sIgE to more allergens with a better cost-effective ratio would be necessary for a better diagnostic and therapeutic approach.

Necrosis of the toes and hemolytic anemia. What is the best management?

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A 70 years old woman affected by Diabetes mellitus type 2 and severe peripheral arteriopathy with necrosis of four toes came to our attention for anemia (Hb: 8 g/dl) and positivity to direct antiglobulin test (DAT): IgM warm autoantibody. The patient was candidated to the amputation of the left leg, but the antiglobulin positivity stopped the authorization to the red blood cell transfusion precluding the surgery. First of all, the patient underwent a total body CT scan and immunophenotyping from both peripheral and bone marrow samples in order to exclude the presence of monoclonal lymphocyte proliferation. Assuming that the presence of autoantibodies was attributable to the chronic inflammatory stimulus from the lesions of the left leg and considering also the high risk of sepsis (repeated swabs from the

lesion showed the presence of multi drug resistant *Pseudomonas aeruginosa*), we started a specific antibiotic treatment and we recognized the need to send the patient to the surgical procedure as soon as possible.

In order to raise hemoglobin level, according to the guidelines [1], after a short period of corticosteroid treatment (prednisone 1 mg/kg of body weight), with only a slight improvement in hemoglobin levels, we planned rituximab infusions of 375 mg/m^2 weekly for 4 week. Three weeks after the first rituximab infusion, patient's hemoglobin was 8.5 g/dl and IgM warm anti-erythrocyte still persisted. We did not expect to obtain a negative DAT test by the rituximab infusion, considering the short time we had to remove the chronic inflammatory stimulus, however the anti-CD20 treatment wasn't as effective and fast as we expected in raising hemoglobin levels. Given the risk of septic shock threatening the life of the patient, we decided to start subcutaneous erythropoietin administration 40,000 UI twice a week in order to raise hemoglobin values and to reduce the probability of transfusion during the surgery [2]. Three weeks later the patient successfully underwent the surgical procedure with a hemoglobin concentration of 9.5 g/dl.

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A singular case of hemolytic anaemia

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A 56 years-old Caucasian man with Beta-Thalassemia minor and Gilbert syndrome, presented with hemoglobinuria during sky trip. He referred also asthenia, dyspnea and headache. His blood work revealed severe anaemia (Hb 7 g/dl), mild increase of total and indirect bilirubin (1.50 mg/dl; 0.52 mg/dl). C3 and C4 were decreased, instead haptoglobin, LDH and kalium values were normal. A direct antiglobulin test was positive for cold type IgM and complement. A total body CT scan, peripheral blood smear and bone marrow biopsy were performed in order to exclude hemolytic anaemia secondary to lymphoproliferative disorders and solid tumors. Virological tests and autoimmunity studies were performed and were negative. Toxic and iatrogenic causes were excluded.

A primary chronic cold agglutinin disease (CAD) was performed and therapy with corticosteroid (intravenous methylprednisolone 2 mg/kg) without a significant clinical and laboratoristic response. According to guidelines, we treated the patient with Anti-CD20 monoclonal antibody (Rituximab) at the dosage of 375 mg/m weekly for weeks, associated with low-dose corticosteroid. Hemoglobin was stabilized already after the first administration and after 4 weeks we obtained a partial response, with an increase in hemoglobin levels by 20 g/l, improvement of clinical symptoms and transfusion independence [1].

Our case demonstrates that haemolytic anaemia associated to CAD can be unresponsive to steroid therapy and Rituximab is an effective treatment for this disease [2].

Despite all the paraneoplastic study was negative, a periodic surveillance is required, because of the development of occult lymphoproliferative disorders.

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What is most likely can be misleading: a case of Guillain–Barre's syndrome

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M. M. male, 67 years old, affected by acute myeloid leukemia from 3 years, underwent a recent chemotherapic treatment. The patient came to the emergency room for paraesthesia, tetra hypostenia of upper and lower limbs since last week. A Cranial CT scan performed few days before the hospitalization was negative and neurological and blood tests showed carential or post-chemotherapic motoneuropathy. The patient has been treated at home with wide spectrum antibiotic, antifungal and antiviral therapy because of a fever and a chest CT scan that showed multiple pulmonary opacities. At the admission, the patient was alert and well oriented. He was asthenic with osteotendineal areflexia, apyretic, eupnoic and normotensive. The blood tests showed Hb 8.8 g/dl, PLT 12.000, GB 830, N 148, CRP 76, ESR 60. All of the bacteriological, virological and mycological test for the identification of the causative agent for pneumonia were negative. Transfusional (RBCs and PLT) and enhanced antibiotic therapy were administered. No vitamin therapy for deficiency neuropathy was performed. Neurological and blood tests, performed in the emergency room just before the admission, concluded for carential, paraneoplastic or post-chemotherapic peripheral motoneuropathy in immunosuppress ed patient with diffuse bronchopneumonia. Electromyography has been required. In the next 24–48 h we assisted to a gradual and progressive deterioration of the patient's clinical condition with progressing worsening of both the motor peripheral deficiency and the dyspnea, with a typical diaphragmatic breathing and lack of recruitment of accessory respiratory muscles. Fever and dysphagia appeared. Blood gas showed an hypoxemic-hypercapnic respiratory failure; for this, noninvasive mechanical ventilation was positioned (BPAP). Due to the severity of his clinical conditions, the patient could not undergo electromyography. An echocardiography excluded pulmonary hypertension and right heart failure and chest X-ray showed an extension of the infectious foci. Given the fast evolution of the bad respiratory and neurological conditions, we suspected a diagnosis of post-infective Guillain–Barre syndrome. We supposed to do a lumbar puncture, but it was contraindicated due to the severe thrombocytopenia; the neurological advice suggested an immunoglobulin therapy as suspect of an autoimmune neuropathy. The clinical situation remained stable for other 4 days. On the fifth day of therapy with IGG, the patient showed a neurological improvement for both tetraparesis and breathing; there was the recurrence of the accessory respiratory muscles normal motility, which allowed to stop the BPAP. At discharge, the patient was apyretic, eupnoic with gradual functional recovery of the upper limbs motility; nearly his dysphagia and distal paresthesias had a complete

resolution with initial ability to hold the standing position. Because of the severe thrombocytopenia and the persistence of severe immunosuppression, no further diagnostic investigations were performed. Ex adiuvantibus diagnosis of autoimmune neuropathy was postulated.
Conclusion: Sometimes the most likely diagnosis does not exclude others less frequent but potentially more serious diagnosis, that require specific diagnostic tests and therapies. This furtherly hindered by continuos pressing the rapid hospital turnover.

Effect of physiological exercise on osteocalcin levels in subjects with adrenal incidentaloma

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Background: In the present study we have evaluated whether physical exercise affect low osteocalcin concentrations observed in patients with subclinical hypercortisolism.
Methods: Sixteen patients (10 men and 6 women, age 38–55 years) with adrenal incidentaloma were studied. Fifteen healthy volunteers matched for age (range 35–47 years) were used as controls. Subjects were submitted to a 8 week exercise-training program with cycle-ergometer for 1 h/day 3–4 days/week at 60 % of their individual VO_2 max. Before and after this period, resting venous serum osteocalcin and GH concentrations were measured in the same batch. The blood sampling after 8 weeks of the training program were performed after resting for one day. All patients and controls underwent also the following endocrine evaluation: serum cortisol, plasma ACTH.
Results: Our results demonstrate a significant increase of osteocalcin after physical exercise and a positive correlation between osteocalcin and GH. This later might suggest a role of GH in the increased osteocalcin secretion.
Conclusions: The data of the present study suggest a positive effect of physical exercise on bone metabolism in patients with adrenal incidentaloma.

Tocilizumab efficacy in a HIV and HHV8 negative case of multicentric Castleman's disease

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A 57-year-old male patient was referred to our Center presenting a 1-year history of cutaneous erythemato-purpuric papules on his trunk (Fig. 1), increased erythrocyte sedimentation rate (ESR) >120, C reactive protein (CRP) >5 mg/dl levels and polyclonal hypergammaglobulinemia (4.72 g/dl). Few months prior to admission he started to present fever, asthenia and diffuse marked lymphadenopathy (Fig. 2). A lymphoproliferative disorder was suspected and a biopsy of a lymph node in the left armpit was performed. The histological analysis showed the histomorphological and immunophenotypical features of Castleman's Disease (CD) plasma cell variant. HIV infection was excluded by PCR and serological tests. HHV8 infection was excluded by PCR assay on plasma and by immunohistochemistry. No standard therapy for Multicentric CD (MCD) is described. The use of glucocorticoids, immunosuppressants, chemotherapeutic agents and monoclonal antibodies has been reported. Particularly, Rituximab (an anti-CD20 monoclonal antibody) demonstrated to be effective treatment occurring in HIV-positive patients as well as in the rare HIV-negative MCD patients. Our patient was treated with Rituximab 375 mg/m^2 IV per week for 4 doses obtaining minimum amelioration. A new course of Rituximab was performed with the same schedule 3 months later. A partial response was achieved, however 9 months later asthenia, lymphadenopathy and skin lesions progressively increased. The unsuccessful treatment with Rituximab lead us to try an alternative treatment. Based on the central role of interleukin 6 (IL-6) in MCD pathogenesis, as showed by most recent literature, the patient underwent a new treatment course of Tocilizumab (anti IL-6 receptor) 8 mg/kg IV monthly plus methotrexate 15 mg/week. Actually nearly complete remission is obtained at the sixth course of Tocilizumab.

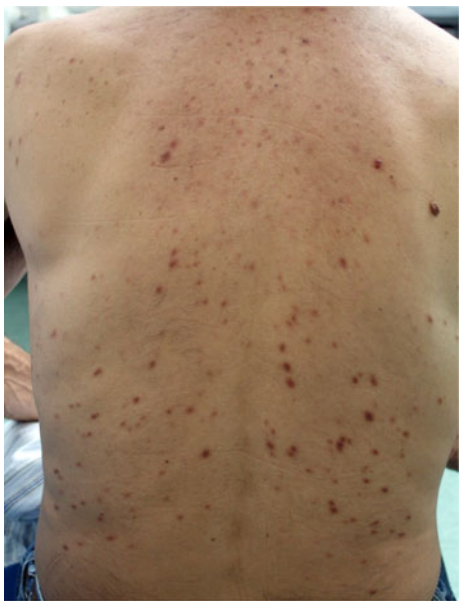

Fig. 1 Skin lesions in MCD

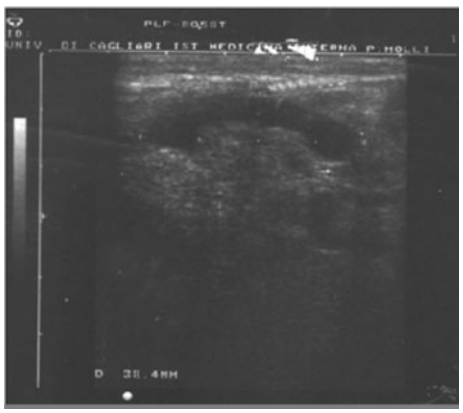

Fig. 2 Left armpit lymph node

Listen to the brain, but don't always blame it!

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A 65 year-old man presented to our Emergency Department (ED) complaining of loss of consciousness. His history was relevant for previous alcohol abuse (until one year before), ibuprofen abuse, chronic renal failure, and prostatic hypertrophy for which he was being treated with alfuzosine and dutasteride. Two weeks before he had been admitted to the nephrology unit for postrenal acute renal failure and discharged with a semi-permanent foley catheter after 1 week. He reported a first episode of syncope without prodromes during this hospital stay, with frontal head trauma for which no imaging investigation was conducted. He reported nausea, anorexia and progressive lethargy once back at home; a second episode of syncope without prodromes had occurred that morning, so the patient had been brought back to hospital. His vitals were substantially normal, and the only relevant findings at physical examination were a widespread hematoma in the left fronto-orbital region and lethargy. White blood count (WBC) and CRP were elevated. Head CT showed two subacute contusive hemorrhagic lesions in the temporal lobes, with surrounding oedema, a small subdural hematoma in the right frontal region and traces of subarachnoid hemorrhage in the tentorium. A chronic sinusitic process in the maxillary sinuses was incidentally found. The CT ruled out a neurosurgical indication and showed no signs of intracranic hypertension or ongoing bleeding. Considering the elevated WBC and CRP in a patient with chronic renal failure, a recent hospital admission and a urinary catheter in place, a UTI was suspected and an empiric broad spectrum antibiotic therapy was started. He was admitted to the general medicine ward. On the following day the patient suddenly became restless and uncooperative. He complained of severe headache and nausea. Temperature was 39.2 °C, HR 120/min, BP 220/120 mmHg. Pupils were miotic and there was moderate nucal rigidity, but this was consistent with the presence of blood in the subarachnoidal space as well and thus couldn't be used as an evidence of CNS infection. A new head CT didn't show any changes and no indication for surgery was confirmed. Blood samples were drawn for cultures, but a lumbar puncture was not performed due to the risk of herniation in the presence of cerebral oedema. The neurological changes were attributed to the febrile peak and treated with antipyretics and anti-hypertensives. In the following 2 days the fever subsided, with neurological improvement, but on the third day temperature spiked again to 39 °C, accompanied by signs of cognitive impairment, and massive herpetic lesions appeared circumorally and in the nasal mucosa. Suspecting an acquired immunodeficiency state, an HIV test was performed but resulted negative. Blood cultures, meanwhile, grew *S. pneumoniae* sensitive to ceftriaxone, which was the antibiotic the patient was already taking; thus no change in the antibiotic therapy was reckoned necessary. Given the striking personality changes occurring with fever, the presence of fever with a downward trend of WBC and CRP and the presence of herpetic lesions, an herpetic encephalitis was suspected: empiric treatment with acyclovir was started and a lumbar puncture was eventually performed around 48 h after starting the antiviral therapy, since this would not have affected the result of the HSV-DNA PCR [Wildermann B, Neurology 1997;48:1341], but resulted negative, as all other liquor analyses. During the following days the patient didn't improve and WBC, which so far had been decreasing, spiked again. A severe sepsis sustained by *S. pneumoniae* was suspected, with the primary focus being the maxillary sinuses. However, since the bacterial strain was sensitive to the antibiotic in use, another cryptic focus of infection was sought: a transoesophageal echocardiogram was performed and resulted normal. The following day the patient reported loose stool accompanied by abdominal distension and tenderness: given the longstanding therapy with ceftriaxone, a *C. difficile* colitis was suspected and confirmed by stool analysis. Metronidazole determined prompt improvement. This case shows how delirium is often sustained by non-neurological causes; in patients predisposed to acute neurological impairment (elderly patients, people with cerebral lesions of any kind) the differential diagnosis of new onset cognitive impairment should always take into account systemic diseases (notably infections, but also uremia and other metabolic conditions) which may mimic a neurological event. It should also be noted that *C. difficile* colitis can initially present with isolated leukocytosis and fever, with diarrhoea appearing later, especially in the elderly.

Sarcoidosis as presentation of CVID

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Common variable immunodeficiency (CVID) is a heterogenous immunodeficiency disorder characterized by different clinical presentations, some not fulfilling the usual case of recurrent sinopulmonary infections and/or diarrhea enteritis. In about 10 % of cases the initial presentation is a granulomatous lesion occurring in spleen, lymph nodes, liver, lungs, skin or conjunctiva. The histopathology is similar to sarcoid lesions, despite a clear association between CVID and sarcoidosis is estimated to occur in a more limited percentage of cases (Matucci et al., 2008). Most cases belong to group I CVID classification, either with B cells <1 % of with absent CD21low B cells.

We describe a CVID case, female aged 56 years observed first at our Center in November, 2009, but with a history dating from before 1988, with recurrent pulmonary infections, chronic diarrhea and sinusitis, treated since 2004 with IVIgs (20 g every 2 months); she was diagnosed with cutaneous sarcoidosis in 2006 after a biopsy of a suspect ulcer lesion on the left leg. Cutaneous granulomatous lesions appeared soon after in the periocular and perioral regions of the face and others in both legs.

Calcium levels, ACE, G6PDH were normal, tuberculin test acc. to Mantoux neg, no other granulomas were detected in different body sites, checked by HRTC and US.

She was treated with sc Igs which allowed reconstitution of protective levels (from 364 to 686 mg/dL of serum IgG), and several treatments for cutaneous and pulmonary newly developed lesions, suggesting sarcoidosis. HCQ and then dapsone were attempted, with steroids. An ocular infection developed, leading to severe loss of sight, and a basal carcinoma of the lip, plus other granulomatous lesions of the tongue. Different histopathological responses were elicited, some suggesting a Wegener's granulomatosis, others diffuse granulomatous disease.

The case, complicated by the presence of a daughter with IgA defect and ANA positivity, suspected of harbouring a mutation of Fas, is representative of the non canonical presentations of common immunodeficient patients in adult age with CVID, which may defy internists and clinicians summoned for their ailments if they are not alerted to such unusual presenting symptoms and signs.

Vertigo and hearing loss: a patient for internal medicine

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A 45 year old white man came to our attention from the emergency room presenting vertigo and bilateral hearing loss.
The patient was a smoker and he had G6PD deficiency. Left hearing loss occurred 1 week after an episode of fever, productive cough with occasional haemoptysis treated initially with quinolone antibiotic therapy and later with macrolide. The first otorhinolaryngologic (ORL) evaluation suspected ear wax plugs, but despite multiple irrigations the hearing loss worsened to bilateral. Vertigo, postural instability and ataxia also occurred. At the entrance to the our department the patient was alert, oriented, cooperative; he had important hearing loss. Physical examination was negative. Neurological examination showed left walking deviation, dysmetria, no focal neurological deficits or signs of meningeal irritation. Laboratory data showed mild elevation of flogistic parameters and mild normocytic, normochromic anemia. Cultural samples, Syphilis test and neurotropic virological test were negative. A CT scan of the paranasal sinuses was performed showing sclerotic appearance of the right mastoid. According to the symptoms and the neurological evaluation a further neuroimaging study was performed. Brain MRI showed signal alteration of the membranous labyrinth on the right and most evident in the cochlear impregnation, subtle bipallidal signal hyperintensity and focal hyperintense signal on the left; inflammation of sinus and mastoid.
In consideration of the central nervous system involvement a study of the cerebro-spinal fluid was performed with evidence of 20 cells/mm^3 characterizable as lymphocites; immunochemical test of the protein showed a proportional increase in the ratio of IgG and albumin compatible with barrier damage; molecular study was negative for neurotropic viruses.
In consideration of the hearing loss despite antibiotic therapy, audiometry was performed; it revealed severe bilateral sensorineural hearing loss to all frequencies and cochleovestibular tests showed bilateral vestibular paresis, more pronounced on the right.
The results of all examinations performed allowed to exclude a neoplastic or infectious genesis of the symptoms presented, while the presence of bilateral labyrinthine lesion and nuclear alterations were suggestive of an autoimmune disease type Cogan's syndrome, also in accordance with the neuroradiologist and the otorhinolaryngologist. Antinuclear antibodies were positive at a titer 1:80, ENA: sRNP 1.5; ANCA negative. Systemic corticosteroid treatment (1 mg/kg/day) was started and the patient underwent cochlear implantation. An ocular or systemic involvement was not present in our patient.
The Cogan's syndrome is a rare syndrome, the therapy is based on immunosuppresant agents, but the final solution is often cochlear implantation.

FDG-PET/CT in the diagnosis of lower limbs arteritis

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Introduction: Hybrid Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) is a useful tool in the diagnosis of about 1/3 of patients with Fever of Unknown Origin (FUO). FDG-PET is able to localize and delineate areas of high metabolic activity, such as neoplastic proliferation and inflammation. However, knowing when to use FDG-PET is more important to the examination itself especially for the "masking effect" of immunosuppressive treatment.
Materials and Methods: We describe a case of femoral artery vasculitis diagnosed by duplex ultrasound and FDG-PET/CT after careful analysis of symptoms.
A 69-year-old man, with minimal atherosclerotic risk factors, presented to our department with a 5-month history of FUO (apparently started 3 weeks after vaccination), upper respiratory tract symptoms, dizziness, progressive bilateral leg claudication after walking 100 meters on level ground.
The patient reported an antibiotic and then steroid therapy. The instrumental and blood tests were all normal except for small abdominal and mediastinal lymph nodes shown on CT. FDG-PET/CT performed on steroid treatment, to exclude malignant etiology, was negative.
Evening fever with persistently raised inflammatory markers restarted at the end of treatment with corticosteroids. The viral serology, immunological tests and neoplastic markers were negative. Chest radiographs, abdominal ultrasound, thyroid and abdominal ultrasonography, colonoscopy and CT angiography of the skull as well as ultrasonography of the temporal artery were also negative.
The patient complained of intermittent claudication of the lower limbs; he denied new onset headache, jaw claudication. Examination of the temporal arteries was unremarkable. FDG-PET/CT was performed for a suspected lower limbs arteritis. This examination confirmed the arteritic hypothesis while the lower limb ultrasonography showed periarteritic thickening corresponding to the area of increased FDG uptake.
Conclusion: Sometimes the clinical manifestations of large-vessel vasculitis can be very subtle and confounding.
In this case, the get back fever and leg claudication after steroid suspension led to diagnosis.
Large-vessel vasculitis represents up to 17 % of all cases of FUO in elderly patients. In the absence of symptoms referable to temporal arteritis, temporal artery biopsy is positive in less than 50 % of the cases. Therefore, it was not performed in the diagnostic workup of this case, preferring to it functional tests and diagnostic imaging. FDG-PET/CT has, in fact, an excellent sensitivity in detecting inflammation of the aorta and its collateral branches and is therefore preferred in extracranial involvement. Since the amount of metabolic tracer uptake is associated with the disease activity, performing this examination on steroid treatment can give false negative results.

A case of hereditary angioedema presenting as recurrent fever with abdominal pain

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Hereditary angioedema (HEA) is an autosomal dominant disease, in approximately 75 % of cases, that causes recurrent attacks of severe edema of various body parts. The most commonly involved viscera are the respiratory and gastrointestinal system. Involvement of the gastrointestinal tract, with resultant abdominal pain, occurs in 43–93 % of patients with HAE.

A 60-year-old man with fever of short duration and abdominal pain, vomiting and diarrhea was referred for a possible autoinflammatory fever.
The patient had well-compensated arterial hypertension and type II diabetes treated only with diet, presented to our department with history since infancy of recurrent fever with abdominal "cramping" lasting 24–48 h with associated nausea, vomiting and diarrhea every 20–25 days. Upper and lower gastrointestinal tract endoscopy was unremarkable. A CT performed during an attacks showed fluid in the peritoneal cavity. Three years before admission, the symptoms worsened after ACEi therapy.
Past medical history revealed occasional localized non pitting swelling of upper limbs and genitalia and a two vessel CABG 7-years before, complicated by laryngeal edema. The patient was also in therapy with beta blockers, aspirin, PPI, and alpha-blocker for BPH. Quantitative and functional analyses of C1 esterase inhibitor (C1 INH) and complement components C4 and C3c was performed for suspect of Hereditary Angioedema; indeed blood tests showed low C1 INH 2.8 mg/dl (22.0–44.0), low C4 <6.45 mg/dl (10–40) and C3c in normal range. This assay, performed in daughter, with mild symptoms, showed decreased C1 INH level too.
After discontinuation of ACEi the symptoms improved; then Icatibant, a bradykinin antagonist, was prescribed in case of HAE acute attacks.
Conclusion: Intestinal angioedema may be unrecognized and can lead to years of delay in diagnosis; moreover, sometimes, a pyrexia may be present during the attacks.
Angioedema resulting from ACE inhibitor use can be distinguished from HAE and AAE only by history, C1-INH levels and complement assays. However, ACE inhibitors trigger attacks when taken by individuals with HAE.

A woman with fever and mental confusion

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A 41-year-old woman, referred from another hospital, was admitted to hospital due to prolonged fever and mental confusion.
Her medical history included autoimmune hypothyroidism, distal arthritis with ANA positive (ENA negative) started in 2007 and manifested itself as morning stiffness, joint pain, and swelling mostly in her hands and treated with leflunamid for 2 years.
The magnetic resonance imaging (MRN) of the brain after the administration of gadolinium showed cortical, subcortical and in white substance hyperdense lesions. A lumbar puncture was performed without evidence of abnormalities, transesophageal echocardiography and transcranial Doppler were negative for vegetations and emboligen disease, pneumonary multifocal infiltrates, pleural and pericardial effusions were seen on total body CT whereas the investigation for legionellosis, salmonellosis, shigellosis, bartonella, borreliosis, aspergillosis, brucellosis and syphilis were negative. Eosinophilia and significant proteinuria were constant.
Upon physical examination, she appeared acutely ill, in poor general health, pale, feverish, with altered mental status. Bibasal crackles and erythematous facial rash were present. Laboratory tests showed anemia, eosinophilia, systemic inflammatory indicators elevated, C3 reduced. The measurement of thyroid hormones detected impaired replacement therapy. Given the available data, the initial diagnostic hypotheses were multiple: localized pyogenic infection (atypical pneumonia, hidden abscess), bacterial-fungal or viral systemic infection, endocarditis, granulomatous disease, collagen vascular-hypersensitivity disease or neoplasm. Abnormal findings in CT images led us to perform a bronchoscopy with bronchoalveolar lavage which detected severely inflammed mucosa but no atypical cells or mycobacterial infection. Blood cultures were sterile. Serological testing for viral hepatitis, HIV, Treponema pallidum, ANCA, rheumatoid factor, anti-citrullinated peptide antigen antibodies and Quantiferon were negative. The assaying of lupus serologic tests was performed and we detected titer of antinuclear antibodies (ANA) (>160 homogeneous pattern) and anti- double-stranded DNA antibodies were strongly positive; direct Coombs test was positive (tot 9/12, IgG 6/12). An electroencephalogram revealed widespread severe abnormalities.
The most likely diagnostic hypothesis pointed to systemic lupus erythematous with cutaneous, pleural, interstitial lung, cerebral manifestations and secondary anemia. The patient was treated with cyclophosphamide pulse followed by 1 g of intravenous methylprednisolone daily for 3 days; the controls of proteinuria showed it had rapidly disappeared. After a few days her clinical conditions began to improve and she was discharged in a week. When asked, the patient reported having suffered from photosensitivity for years.

A clinical case of severe reaction to drug

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A 72-year-old woman was admitted to hospital because of extensive erythematous skin eruption, severe oral mucositis, and catarrhal conjunctivitis accompanied by vomiting.
Her medical history included major depression in bipolar syndrome treated with valproic acid, arterial hypertension on treatment with a calcium channel blocker, and a histeroannessiectomy several years prior due to fibroma. Two weeks before admission, the patient consulted her psychiatrist and started therapy with lamotrigine in the dosage of 25 mg once a day for the first week, and 50 mg once a day to follow.
Upon physical examination, she appeared critically ill. Esfoliative-bollous rash was present—above all on the face and chest—with eye and oral mucosal involvement, purulent discharge in the conjunctival with erosions and crusting of eyelids, and intense dehydration. 12 h after admission, her temperature was 38.5 °C and blood pressure was 120/70. Nothing pathological was reported upon the evaluation of the chest and abdomen. Laboratory tests showed increased lactate and d-dimer, elevated C-reactive protein (105 mg/L) and hyperferritinemia. White cell count, differential count and urinalysis were normal. Serum albumin was 2.46 g/dl. Her chest X-ray was negative.
Given the available data, the initial diagnostic hypotheses were multiple: staphylococcal scalded skin syndrome, toxic epidermal necrolysis (TEN), exfoliative dermatitis, phototoxic skin reactions, drug reaction with eosinophilia, phototoxic skin reaction, hypersensitivity vasculitis, pseudoporphyria, acute generalized exanthematous pustulosis and paraneoplastic pemphigus.
Blood cultures were performed with negative results. Serological testing for viral hepatitis and HIV were negative. The most likely diagnostic hypothesis pointed to an adverse reaction to drugs, mainly on the bases of anamnestic data about the introduction in therapy of lamotrigine.
Hydration and high dose corticosteroid therapy was initiated and lamotrigine was discontinued. A dermatologist was consulted and he confirmed the hypothesis of TEN, probably due to lamotrigine. Over 24 h there was a worsening of clinical conditions with extension of skin lesions to the legs and perineal region. A cutaneous examination showed involvement of about 70 % total body surface area with skin necrosis, tenderness, and positive Nikolsky's signs.

Because of the high risk of infection, the patient was transferred to the intensive care burn unit. There she received supportive systemic therapies with aggressive fluid and electrolyte management, opiate analgesics for pain control, and anticoagulant therapy with heparin for prophylaxis of thromboembolic events.
Meticulous wound care—showers with mild soap and gauze dressing—was performed daily to prevent secondary infection. Ocular complications were treated with topical lubricant-antibiotics and steroid drops. She also received treatment with endovenous immune globulin 0.75 g/kg daily for 5 days and high doses corticosteroids (125 mg methylprednisolone) for 2 days and later reduced.
After 3 weeks her clinical conditions began to improve and she was admitted on intermediate care. She was discharged 2 weeks later with complete resolution of skin lesions and without ocular outcomes.

Case report: systemic nickel allergy syndrome and dental alloy capsule

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Caucasian woman 50 year old, known as a atopic with serious allergy to birch pollen; 4 days later a cosmetic contacts she show a sudden orticariod cutaneous reaction with erythema and pruritus, spread all over her body more intense on her cheek; Immediately she started using soap and facial cream nickel tested. The reaction lasted for a long time and required a treatment with high dosages of steroid and antihistaminic oral drugs to slow it down. Two months later the allergy having stopped she was subsided to dermal patch tests with a high response to nickel and the diagnosis done was ACD (allergic cutaneous dermatitis); this was known, but limited to jeans buttons and to nickel "jewels". The dermal patch recruited the previous reaction with erythema and micro haemorrhages especially on her cheeks and on her neck, angioedema, perioral syndrome and hurting pain in her armpits. Although having suspended every possible cutaneous contact with known nickel contents objects and soap the systemic reaction reappeared very often and she felt asthenic, with frequent unusual headaches and abdominal pain. A low nickel content diet was begun and her synthetic clothes were substituted with cotton and natural fibres one washed with nickel test soap. She couldn't also tolerate any more any other heavy metal objects (like titanium, stainless steel, gold…). The diagnosis of systemic nickel allergic syndrome was done. Systemic Nichel Allergy Syndrome has been recently identified either than topical manifestations (contact dermatitis, pompholyx, hand dermatitis dyshydrosis, urticaria) it has also general symptoms symptoms (headache, asthenia, itching, and gastrointestinal disorders related to histopathological alterations of gastrointestinal mucosa, borderline with celiac disease) and shows a chronic course. Several studies have been conducted on genetic factor and all have proved a familiar influence on it, nowadays has not identified a specific HLA), but among nickel-sensitive subjects in the Tcell receptor the Vβ1 gene dominated in most (75 %) of the CD8+ samples. This preliminary study suggested that the pattern of Vβ genes induced by nickel stimulation is individual. Investigations of specific genetic factors have been inconclusive. Nickel appears to act as an atypical hapten and activates T cells through a variety of mechanisms, which may make defining a specific genetic factor challenging. The issue of variations in environmental exposure is critical. In fact, described recently are null mutations in the filaggrin gene complex and an alteration of toll-like receptor 4 (TLR4) in allergic patients have recently described. Her improvement was very slow with very frequent relapses, since a hurting pain on the only dental capsule, which was 20 years old, revealed the original cause of the sensitization, the capsule was removed and substituted with a metal free one, and nevertheless she required a new steroid treatment to tolerate this one. Many metal like nickel, cobalt and chromium are present in many alloys used in implants, that became a potential sensitizer after corrosion or oxidation and consequent ionization process and releasing of metals in different quantities depending on the polymerized forms. When metals come into contact with biologic fluids, they undergo corrosion to release ionic compounds, which may then bind to endogenous proteins to form metal-protein complexes. Other activation mechanisms have been described in regard to nickel (e.g., nickel may directly activate the T cell receptor in a way that is reminiscent of superantigen). Most information regarding putative sensitivity reactions to endovascular, cardiovascular, orthopedic, and dental metal implants are based either on anecdotal case reports or on data gathered from relatively small cohorts. Very few prospective data are available. For decades, it was believed that only selected highly susceptible patients (<1 %) developed skin complications due to metal implants; however, a recent case study showed that a significantly higher number of patients (5 %) developed eczematous reactions directly associated with metallic implants [21]. Those individuals with a preexisting metal sensitivity who receive an implant containing the offending metal had a higher rate of cutaneous dermatitis compared to those without metal allergy. Another study examining this exact situation suggests that there may be no adverse reactions to implanting the allergenic metal. Further prospective and well-powered studies are needed to definitively answer this question. In the majority of cases, the removal of the allergenic metal device results in clearing of the skin condition. Based on these data, a recent study recommend that patients who develop a cutaneous eruption months to years after receiving a metal implant should be patch-tested with an appropriate series of metals. If relevant allergens are identified and corticosteroid therapy is insufficient to clear the eruption, removal of the implant may be considered. A perfectly functioning dynamic implant causing no pain and without evidence of loosening should not be removed.

Clinical mimicry: urticaria and systemic lupus erythematosus

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Urticaria angioedema syndrome (UAS) is known since ancient times. Despite the revolutionary immunological knowledges, UAS represents a fascinating and intriguing disease, for its pathophysiological aspects not yet fully clarified. A more careful analysis, a critical review of the different possible causes, through a survey of factors not properly considered or deemed to be without meaning, can often lead to define UAS as "idiopathic" or "cryptogenic". Moreover, many reports support that UAS is not always mediated by "allergic" reaction. In this regard, a particular attention must be focused on the occurrence of a *clinical mimicry,* in which urticaria, alone or in combination with angioedema, may be the epiphenomenon of other different diseases.
Here we report the particularly interesting case that occurred to our attention. A woman, aged 40, non-smoker, with a long history of allergy, at the beginning of December 2011 started to show clinical manifestations characterized meanly by erythematous itchy wheals at first to the hands and then involving the whole body. The dermatologist diagnosed a "common" urticaria and recommended a short course of low dose prednisone. At the end of December, for clinical

worsening of the urticaria, the patient went to the Emergency Unit, where she was treated with 4 mg betamethasone and 10 mg chlorphenamine both for im. Without a definition of the possible causes of urticaria, the patient was discharged with the advice to consult a rheumatologist. In January the manifestations increased and became generalized and severe, so the patient consulted a rheumatologist. After the examination of the case, the rheumatologist concluded that urticaria was not attributable to rheumatological causes and he recommended an allergy visit. The allergist prescribed laboratory tests, including those concerning autoimmunity. At the same time, as well as urticaria, the patient also had fleeting pain of small and large joints, cough, mild exertional dyspnea, intense ocular hyperemia. The laboratory results showed an high titer ANA positivity (1/640), hypocomplementemia (C3: 24 mg/dl and C4 < 5 mg/dl), positive ENA (Ro/SSA), proteinuria and hematuria, and a slight lymphocytopenia. In February, on the basis of these considerations, the patient was hospitalized. In addition to the hypocomplementemia, ANA and anti-DNA (85 IU/ml) positivity, proteinuria (1.13 g/dl), cryoglobulins, slight RCP increase (2.81 mg/dl), increased erythrocyte sedimentation rate (71) and D-dimer positivity (3122 mg/dl, nv < 200), were also detected during the hospitalization. The total serum IgE were 2 IU/ml. The ophthalmologic examination confirmed conjunctival hyperemia without uveitis.

Taking all these elements was finally diagnosed systemic lupus erythematosus (SLE), so urticaria was only an epiphenomenon of SLE. According to the American Rheumatism Association (ARA), four criteria such as renal abnormalities (proteinuria >0.5 mg/dl), lymphopenia <1,500/mmc in two determinations, high titer ANA and anti-DNA positivity were detected in our patient. To ARA criteria we could therefore add urticaria as optional criterion. The treatment with prednisone 1 mg/kg/day induced a rapid resolution of manifestations of urticaria and proteinuria, as well as a general improvement and a fair resolution of ocular hyperhemia.

The case here reported is of particular interest for some considerations. The more spontaneous and natural one is that urticaria, with or without angioedema, often is not an IgE-mediated disorder. Therefore UAS should not be considered a disease of the allergist only. Other considerations could be speculative and critical, but we should not dwell.

In conclusion we want to underline urticaria with or without angioedema can represent an epiphenomenon of other diseases, as demonstrated by our previous reports. In our case the occurrence of autoimmune disease was to evaluate, considering that a cousin was suffering from SLE, even if the history of urticaria, rhinitis and bronchial asthma during its childhood and adolescence could be misleading. The co-existence of allergic and autoimmune disorders in the same subject is more and more increasing. The idea of a common pathophysiological background between allergic and autoimmune diseases is very speculative and intriguing, as reported recently by J. Bartůňková et al. (2009), "Allergy and autoimmunity: parallels and dissimilarity the yin and yang of immunopathology".

Metabolic syndrome and psoriasis

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Psoriasis is an inflammatory disease, with a chronic-relapsing course and multifactorial pathogenesis, affecting both sexes, with a prevalence of 3 %. It is often associated with psoriasic arthritis, which represents the main comorbidity, but it also associates with metabolic syndrome, which consists in: diabetes, hyperlipidemia, hypertension, obesity and coronary heart disease. According to ATPIII criteria, diagnosis of Metabolic Syndrome is done when at least three of the following are present: TGL >150 mg/dl, HDL <40 in women and 50 in men, glycemia >110 mg/dl, waist >88 cm in women and 120 cm in men, and blood pressure >130/85 mmHg. It is not still clear the role of genetics in the two conditions, but it is well known that metabolic syndrome affects 30–40 % of people suffering for psoriasis, while in general population it has a prevalence of 20 %.

Psoriasis and metabolic syndrome are strictly linked because they both share a systemic, chronic, inflammatory substrate. In fact the high levels of inflammatory cytokines (TNF-α, IL-12, 23) found in active skin lesions, serum and synovial fluid of patients suffering for psoriasis, are also found in patients suffering for MS. Particularly, TNF-α has an important role in the regulation of the metabolism of lipids, insulin, hypertension, atherosclerosis and obesity.

We selected a total of 50 patients among those followed towards Our Dermatologic Department, affected by moderate-severe psoriasis and Metabolic Syndrome too.

The aim of this study is to evaluate the efficacy of Anti TNF-α therapy and the modifications of parameters of Metabolic Syndrome after 12 and 24 weeks of treatment.

In the preliminary results we observed an improvement of some of the metabolic parameters and Psoriasis Area and Severity Index (PASI) score.

Polymyalgia rheumatica and giant cell arteritis after influenza vaccination: update of a systematic case-series with a new case of 'Asia Syndrome'

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Introduction: Giant cell arteritis (GCA) and Polymyalgia Rheumatica (PMR) are inflammatory rheumatic disorders occurring in elderly people and having genetic complex features: the association with HLA-DRB1*04 alleles has been consistently detected in GCA patients and in those presenting a relapse of 'pure' PMR. About the co-existence of precipitating environmental factors, actually direct evidences of active viral or bacterial infections in temporal arteries biopsy or in the synovial tissue are lacking. Recently, a new syndrome termed 'ASIA' (autoimmune/inflammatory syndrome induced by adjuvants) has been described [1]. It includes post-vaccination phenomena such as arthritis, neuronal damage, fatigue, encephalitis and vasculitis.

Case Report: A 69-year-old Caucasian man with a history of chronic obstructive pulmonary disease (COPD) was admitted to our Department because of persistent fever (T_{max} 39 °C) with a serotine trend, associated with shivers, night sweat and a progressive development of *claudicatio intermittens* of lower limbs and bilateral edema of the ankles. Before coming to our attention, he received a preliminary diagnosis of 'steroid-sensitive fever of unknown origin in patient with COPD and pansinusitis', and he was treated with steroids (methylprednisolone 16 mg/day, progressively tapered) and antibiotics (ciprofloxacin 500 mg/day for a week), with transient disappearance of the clinical picture. Few days after the complete tapering of steroid therapy fever reappeared with the same trend, while *claudicatio intermittens* and edema of lower limbs worsened. A careful clinical examination revealed that 15 days before the beginning of the symptoms the patient underwent influenza vaccination. On admission, laboratory tests revealed a mild normocytic anemia (Hb 11.2 g/dL), an elevation of erythrocyte sedimentation rate (ESR 61 mm/h) and C-reactive protein (CRP 48 mg/dL); bacterial and viral screening

tests (hemocultures, urine culture, HIV, HCV and HBV screening, Quantiferon TB Gold test) were negative, as well as immunological tests (rheumatoid factor, ANA, p-ANCA, c-ANCA) and tumor markers. Chest and abdomen CT scans were also unremarkable. An arterial Doppler US of extremities showed a diffuse bilateral parietal thickness of femoral-popliteal axis. To confirm the hypothesis of a lower extremities vasculitic process associated with PMR, a fluorodeoxyglucose (FDG)-PET scan was performed, and revealed metabolic activity interesting C7 spinous process, the chest wall muscles (particularly at the left subscapularis muscle level) and bilateral femoral arteries.
The patient was treated with steroids (methylprednisolone 4 mg/day) and methotrexate (7.5 mg i.m/week) as a steroid-sparing agent, because of the detection of altered glucose tolerance, with prompt improvement of clinical symptoms.
Discussion and Conclusion: This case has been added to our systematic analysis of GCA and/or PMR case-series, conducted since 2005 to detect the possible role of influenza vaccination (Inf-V) in the pathogenesis of 'ASIA' syndrome. Over a 6-year period (2005–2010) we found that 10/20 cases of previously healthy subjects admitted to Periodic Research Fever Centre of Catholic University of Sacred Heart, who received a diagnosis of PMR and/or GCA, developed the disease within 3 months of Inf-V, with a frequency of 1:2 cases and a median of 2 post-immunization cases/year. We compared our case-series with a literature survey of 12 isolated cases of GCA/PMR following Inf-V, obtained through a PubMed/Medline search from 1978 to 2011 [2]. Combining the analysis of the literature and our case-series a period of over 30 years is encompassed: while the Inf-V viral components vary from year to year, a restricted number of adjuvants have been used for decades and could play the major role in post-vaccine immunization, causing the 'ASIA' syndrome. The suggested criteria of 'ASIA' syndrome include the previous exposure to external stimuli (such as infections, vaccines, silicone, adjuvants), the appearance of 'typical' clinical manifestations (myalgia, arthralgia/arthritis, muscle weakness, fever), a typical biopsy of involved organs, a specific human leukocyte antigen (HLA). We are typing the HLA of our patients in order to detect the genetic susceptibility and high-risk individuals. Finally, we recommend a systematic research of previous vaccination in patients with recent onset of GCA/PMR and a strict observation after Inf-V for subjects at higher risk of developing GCA/PMR, such as females at a susceptible age, and for carriers of already known autoimmunity markers, in order to identify genetic markers of high-risk individuals and to avoid potential immunizations/reactivation of a latent disease [3].

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A rare case of idiopathic acquired haemophilia A

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A 75-year-old woman was referred to our emergency department because of lumbar pain and dyspnea. In her history the patient reported type II Diabetes Mellitus and Horton Disease in treatment with low dose of steroid (Prednisone 2.5 mg/die) and antiplatelet therapy (Aspirin 100 mg/die). She referred a minor lumbar trauma about 30 days ago.
Laboratory findings showed a severe normocytic anaemia (Hb 7.2 g/dl), marked increase of LDH (886 U/L) and a moderate increase of activated partial thromboplastin (aPTT 32 s). The other routine coagulation studies (platelet count and prothrombin time) were normal. The abdominal TAC showed a large right iliopsoas haematoma. The patient was transfused with 3 units of red blood cell and we suspended antiplatelet and steroid treatment based on evidence of absence of signs and symptoms of active Horton disease.
A few days after the patient experienced a large spontaneous hematoma in the right forearm.
Ultrasound examination showed a subcutaneous blood effusion.
Haemoglobin value was stable but activated partial thromboplastin time was greatly increased (aPTT 96.2 s.). The mixing study showed a prolonged activated partial thromboplastin time not corrected by incubating a sample of her blood with equal volumes of normal plasma at baseline and after 2 h.
Functional activity of factor VIII was very suppressed (0.6 %) and the research of factor- VIII-inhibitors was positive (77 Bethesda Units). The investigation for autoimmunity and malignancy diseases was negative.
Based on this data, we diagnosed Idiopathic Acquired Haemophilia A. We started therapy with recombinant human coagulation Factor VIIa (rFVIIa) in association with suppressive treatment (prednisone 1 mg/kg) with prompt resolution of "acquired haemophilia".
Acquired Haemophilia A is a rare bleeding diathesis caused by autoantibodies directed against clotting factor VIII. It was associated with an increased morbidity and mortality. This disease occurs most commonly in the elderly, and although it may be associated with a variety of underlying pathological conditions, up to 50 % of reported cases remain idiopathic.

Primary antiphospholipid syndrome: diagnostic challenges and new therapeutic options

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Background: Primary antiphospholipid syndrome (APS) is a risk condition for arterial and/or venous thrombosis and pregnancy complications. Long-term anticoagulant therapy is nowadays considered the most effective therapeutic option but despite this some patients may develop thrombotic events resulting in complex, severe and intricate clinical presentations.
Clinical Case: We describe a 37 years old man with APS treated with anticoagulants for a previous thromboembolic event occurred 4 years before. He came to our attention because of a new deep venous thrombosis in his left leg. During diagnostic work-up a thoracic computed tomography (CT) showed a new pulmonary embolism and multiple lung hyperdense nodules of uncertain origin demonstrating hypermetabolism when studied with position emission tomography (PET). A tissue sampling of the nodules couldn't be obtained because of their peripheric position and the small dimension. During hospital admission acute abdominal pain occurred and an abdominal CT pointed out hemorrhagic infarction of the left adrenal gland.
Discussion: The case gives to us the chance to discuss about:

- differential diagnosis of pulmonary nodules;
- adrenal infarct as a rare cause of acute abdomen;
- therapy of patient with APS refractory to anticoagulant therapy.

A literature review with sensible strategy was made and results will follow. In extreme synthesis:

- In patients with APS, pre-test probability evaluation together with thoracic CT features are enough to make pulmonary infarcts diagnosis and PET does not add relevant diagnostic informations;
- Adrenal hemorrhage is a rare but not exceptional cause of acute abdomen in patients with APS;
- Among the proposed treatments for patients refractory to anticoagulant therapy, with low quality of evidence, hydroxychloroquine, rituximab and other immunosuppressive therapies are worthy to be remarked.

Clinical Cases for the Gymnasium Session

A case of destructive infective endocarditis

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A previously healthy 25 year-old man was admitted to the emergency department of another hospital due to shivering fever and abdominal pain, arose through the previous 12 h. Physical examination was significant for abdominal tenderness, fever (41 °C) and tachycardia. Labs showed Hb 13 g/dL, WBC 22080/mcL (Neu 18920), C-reactive protein 17.5 mg/dl, AST/ALT 1.4/1.5xULN, LDH 957 U/L and bilirubin 1.9 mg/dL (dir 0.5). The electrocardiogram revealed sinus tachycardia. The patient denied any therapy, use of illicit drugs, smoking or alcohol consumption. His family and past medical history were unremarkable.

Because of suspected intra-abdominal infection, he was admitted to the Surgery Unit and started on empiric antibiotic therapy with tigecycline. No clinical improvement was observed during the following days.

On the third day of hospitalization, the patient reported dyspnoea and chest pain. A chest and abdomen computed tomography scan revealed bilateral pleural effusion, multiple pulmonary nodules with central cavitation, hepato-splenomegaly and mild ascites. A 2–3/6 systo-diastolic cardiac murmur was heard. A transthoracic echocardiography (TTE) revealed an echogenic, mobile mass on the aortic valve between right and noncoronary cusps. The patient was then transferred to our Hospital. On admission, four blood cultures were drawn and a 3D-TTE and a trans-esophageal echocardiography (TEE) showed an aortic vegetation (2.4 × 0.8 cm), a moderate aortic valve regurgitation, an aortic-right atrial fistula, a large pericardial effusion and a mild left ventricular (LV) disfunction (EF 48 %). The acute course, severe structural heart involvement and evidence—at history taking—of a prior skin wound occurred 3 weeks before hospitalization, suggested a staphylococcal endocarditis complicated by paradoxical septic pulmonary emboli. Thus, a combination of amoxicillin/clavulanate 2.2 g iv q4 h and linezolid 600 mg iv q12 h was chosen as initial empiric therapy, associated to digoxin, ramipril and furosemide. Despite of medical treatment, the patient rapidly deteriorate due to worsening pericardial effusion and progressive hemodynamic decompensation, and underwent open heart surgery. A massive bloody pericardial effusion was found. The aortic vegetation was removed from the right atrium, the aortic valve was replaced with a mechanical prosthesis and the noncoronary sinus was replaced with a triangular Dacron patch. Tricuspid valve repair, debridement and reconstruction of both atrial roofs with pericardium patches were also performed. A post-operative 3rd degree atrio-ventricular block required an epicardial pacing lead placement, that was followed by an intravascular permanent pace-maker implant due to high epicardial device stimulation thresholds and no recovery of spontaneous rhythm. Anticoagulant therapy with warfarin was started with a target INR of 2–3. Blood, vegetation and epicardial tissue cultures were positive for methicillin-sensitive Staphylococcus aureus. A blood culture performed before pace-maker placement was negative. Amoxicillin/clavulanate was continued for 6 weeks. Due to pleural and pericardial effusion with persistent dry cough, colchicine 1 mg/day and low dose prednisone were started and the ACE-inhibitor withdrawn. Blood transfusions were needed. Serial TTEs revealed complete resolution of residual aorta-to-right atrium shunt, with a full systolic function recovery. Laboratory, radiologic and clinical improvement allowed patient discharge 1 month after admission.

Two weeks later, the patient returned because of worsening cough and left shoulder pain. On re-admission, inflammatory markers were normal, and blood cultures, viral serologies as well nasal/pharyngeal swabs for respiratory viruses were negative. Rhino-pharyngo-laryngoscopy and allergy prick tests resulted negative. Ultrasound of the pacemaker pocket failed to show any collection. A pulmonary angiography ruled out further embolisms but revealed an irregular atrial luminogram with turbulent flow near surgical sutures. A TEE detected an aortic peri-prosthetic collection and multiple masses (largest 2.4 × 1.3 cm) attached to the right atrium patch. This finding, compatible with endocarditis persistence/relapse, was not consistent with patient clinical status. Also, TEE could not differentiate abscess from periprosthetic hematoma and infected vegetations from sterile thrombi. The lack of new periprosthetic leaks or intracardiac shunts suggested a conservative approach to be safe. We added to warfarin both acetyl salicylic acid and high dose daptomycin. Both 'vegetations' and 'abscess' disappeared on TEE. At 1 year follow-up, the patient remains in NYHA class I with no leaks nor infection recurrence and normal heart valve function.

An unusual cause of hypoglycemia

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A 79 years old woman presented to our Emergency Department because of impairment of consciousness. Few hours earlier her son noticed the onset of slurred speech. The physical exam revealed a reduction of breath sounds in the left and upper right hemithorax and a complete absence of breath sounds in the medium and lower right hemithorax. The blood glucose test revealed a severe hypoglycemia (26 mg/dl), the blood gas analysis performed in room air pointed out: pO_2 55 mmHg, pCO_2 62 mmHg, oxygen blood saturation 85 %. A chest X-ray showed the presence of hypodiaphaneity in the medium and lower right lung field "as for massive pleural effusion associated with lung atelectasis/thickening". Nine years before the patient experienced a tumble and reported a right rib fracture; in the subsequent years she took 2 chest X-rays as follow-up, with evidence of "a progressive elevation of the right diaphragm". The patient was admitted in our unit on antibiotic therapy. During the first night of hospitalization the patient experienced another severe hypoglycemia (16 mg/dl). She was not on hypoglycaemic drugs. To exclude the

presence of an insulinoma or an iatrogenic cause of hypoglycemia we ran a basal dosage of insulinaemia and c-peptide, a serial glycemia and insulin dosage during prolonged fast and a pancreatic MRI, no abnormalities were found. A new chest X-ray was performed which pointed out the presence of an elevation of the right diaphragm, this time no pleural effusion or atelectasis or thickening were described. A chest CT was performed to clarify the pulmonary findings with the disclosure of the presence of a bulky (15 cm × 10 cm × 16 cm), solid, capsulated mass in the posterior right emithorax which was in contact with the mediastinic and the postero-lateral costal pleura, with evidence of compression phenomena on cardiac atria and omolateral diaphragm; no pleural effusion was described and no signs of local infiltration as well as secondary localizations were found. The patient underwent a needle biopsy of the mass that suggested the histological and immunohistochemical diagnosis of Solitary Fibrous Tumor of the lung. The patient's Insulin Like Growth Factor-1 (IGF-1) serum concentration resulted decreased. Serum samples are stocked at −80 °C for future dosage of Insulin Like Growth Factor-2 (IGF-2) and IGF-binding proteins. Considering the data in our possession we stated the diagnosis of Doege–Potter syndrome. The removal of the mass is the only curative therapy in this syndrome. Radiotherapy and chemotherapy have limited curative value. Selective embolisation is an option to reduce the tumor mass and consequently the hypoglycemia. Treatment with low dose of corticosteroids has been used to control hypoglycemia. In our case the chest surgeons advised against the mass removal because of patient's age, general conditions and poor nutritional status. We requested a clinical nutritionist's visit and discharged the patient on parenteral nutrition via nasogastric tube, with a good control of glycemia levels even during the night. In addition we prescribed to the patient Non Invasive Ventilation cycles to treat the hypercapnic respiratory failure. Weeks after discharge we received a reply from patient's family confirming the good control of the symptoms.

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A dry and persistent cough

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A 45 obese woman, smoker of about twenty cigarettes a day, was admitted to the Emergency Room of "A. Cardarelli" Hospital in Naples for a dry and persistent cough arose 2 weeks earlier, that didn't worst with position or physical activity. The cough appeared unexpectedly during the day. The patient referred that the cough had a gradual and spontaneous resolution in a few hours. She didn't found a benefit with dextromethorphan. She also referred that she had lose her weight (about 5 kilos) and that she had a stubbing pain in the right armpit few days earlier and fever 48 h before the admission. There were not significant illness in her medical history, except for a candidiasis of her mouth treated with nystatin. She denied hypertension and metabolic disorders, but she referred a family history of cardiovascular diseases. In Emergency Room her vital signs were normal: the ECG showed a sinus rhythm, tending to tachycardia, with right atrium overload. The patient was in eupnoea at rest (RR = 16 breath per minute). The blood gas analysis in air room showed a normal pH with normocapnia and hypoxemia, and with an oxygen saturation of 94 %. The patient was alert and collaborative at the clinical exam. The heart sounds were low pitched; the breath sounds were low at the lung basis and expiratory wheezes were present at the apices. The abdomen was tender at the deep palpation and there was not peripheral oedema. The chest X-ray showed an accentuated vascular plot; blood exams were normal. A chest-CT and then an HRCT were performed: they showed the presence of some nodules of five centimetre maximum diameter, some of which excavated, in both lungs especially to the upper lobes. Because of the symptoms and the chest CT images, a diagnosis could be a lung cancer in smoker patient, even if there were not pleural effusion, hemoptysis nor Bernard-Horner Syndrome, conceivable for upper lobes involvement. A bronchoscopy was made too, and it didn't point out endobronchial lesions while the cytological analysis of the fluid (BAL) showed bronchial inflammatory cells, a lot of macrophages and neutrophils. Cytoimmunological analysis of the bronchoalveolar lavage fluid highlights many pigmented macrophages anthracosis-like, some of which positive to Perls coloration for the presence of ferrous intracytoplasmic residues, a modest neutrophils count growth with a reversal of CD4/CD8 ratio and with a percentage increase of CD1A+ Langerhans cells. The patient also made a spirometry exam that pointed out a modest involvement of the small airways like an early obstructive lung disease. On the basis of the performed examination, our diagnosis directed towards a granulomatous disease: the Langerhans cell histiocytosis.

Conclusions: The pulmonary Langerhans cell histiocytosis is a rare disease found in smoker patients in the third-fourth decade of life, especially in females. The upper and middle lung lobes are a typical localization of this disease. The patient was treated with oral corticosteroids but the stabilization of the disease and the resolution of cough were obtained in particular with smoking cessation, also useful for the increased risk of bronchogenic carcinoma in patients suffering from Langerhans cell histiocytosis.

Fatigue, dyspnea and non pitting peripheral oedema: a case of eosinophilic fasciitis

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A 51-years-old woman presented to our Department of Internal Medicine complaining about fatigue, dyspnea for mild exercise, joint stiffness, muscle pain and non pitting oedema. The oedema was reported for the first time one year before, initially involving only the lower third of the right leg and the ankle. Subsequently, the oedema spread to the left leg and to both forearms, sparing either fingers and toes on each side.

The patient had a medical history of Hashimoto's thyroiditis, currently treated with hormone replacement therapy and a lymphocytopenia of undetermined origin.

A chest X-ray, previously executed for the study of dyspnea, showed hilar enlargement, without any sign of fibrosis.

The physical examination confirmed a thick symmetrical non pitting oedema, involving skin and subcutaneous tissue of forearms, legs and, on a minor extent, ankles. Both hands and feet were spared and radial as well as tibial pulses were present bilaterally.

A small lymph nodal mass, around 1 cm in diameter, was present over the left collarbone.

Differential diagnosis: (1) hypothyroidism myxoedema, (2) systemic sclerosis, (3) morphoea, (4) lymphoproliferative disease, (5) nephrotic syndrome with hypoalbuminemia and oedema, (6) eosinophilic fasciitis.

Laboratory exams showed total white blood count at 4,690/mm^3 with only a mild lymphocytopenia (25.2 %).
The haemoglobin levels (12.4 g/dl), systemic flogosis indexes (ESR 13 mm/h, CRP 0.1 mg/dl), plasma albumin (3.8 g/dl) and CPK (43 U/l) were normal. Also thyroid, liver and kidney function tests were within normal range.
ANA, ENA and rheumatoid factor, already tested in an out-of-hospital setting, were negative.
T and B lymphocyte subset assay confirmed a mild lymphocytopenia without pathological significance.
A CT scan of the neck, chest and abdomen did not report lymphadenopathy or pulmonary fibrosis and pulmonary function testing was normal.
The echocardiography showed no cardiac causes of dyspnea.
Finally an MRI of both legs was performed, showing subcutaneous oedema, thickening and increased signal intensity of the fascia, all signs suggestive for eosinophilic fasciitis.
Deep tissue biopsy of the upper third of the right leg confirmed the diagnosis, showing perivascular lymphocytic and plasma cell infiltration of the fascia.
We subsequently discovered that few months before the admittance to our hospital, the leucocyte count had shown a mild eosinophilia (722/mm^3).
The patient was treated with prednisone at a dose of 0.5 mg/kg daily, with progressive improvement of the clinical signs (thick symmetrical non pitting oedema) and of the symptoms (fatigue, joint stiffness, muscle pain).
After one year the patient is receiving prednisone 5 mg daily and she has no oedema, fatigue or joint stiffness. All the laboratory exams are normal.

Electrolyte imbalances: are all the same?

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Introduction: We present the case of a 72 year-old woman admitted with a diagnosis of diverticulitis in April 2012 to our surgical department for severe diarrhea. An abdominal CT scan confirmed a diverticular disease of the sigmoid colon with multiple protrusions, inflammatory imbibition of perivisceral fat and mesenteric lymphadenopathies. Later the patient developed vomiting, weakness with postural instability, and cachexia with weight loss of 9 kg. For the progressive worsening of her clinical conditions she was transferred to our Internal Medicine Department, in the critical care area.
History: The patient was affected by systemic hypertension and chronic kidney disease (CKD) with moderate secondary normochromic anemia. She was submitted 13 years before to left nephrectomy for renal carcinoma and, 12 years before, to hemicolectomy for ascending colon cancer. She was taking angiotensin receptor blockers (ARBs), allopurinol, statins, D vitamin and subcutaneous erythropoietin. She wasn't currently taking any proton-pump inhibitor (PPIs).
Laboratory: At the admission to our department, we observed a neutrophilic leukocytosis, mild normochromic anemia, renal failure, increased indices of inflammation and hyperuricemia; liver and thyroid function were normal. Urinary electrolytes were at the lower limit. Vidal–Wright reaction, ruling out Salmonellosis and Brucellosis, was negative as well as a stool cultures, occult fecal blood and the research of parasites and *C. difficile* toxins. However, the presence of a faecal calprotectin >300 and the presence of persistent diarrhea and increased ESR and CRP raised the suspicion of an inflammatory bowel disease, having excluded a celiac disorder.
Following Procedures: Colonscopic examination with biopsies showed only signs of inflammation in preanastomotic area due to edema, and chronic nonspecific signs of inflammation at the biopsy. After the colonoscopy, the patient presented stupor, and tonic–clonic seizure with fever. An electrolyte imbalance was suspected as a possible cause of this complication: severe hypomagnesemia (0.4 mg/dl), hypocalcemia (5.9 mg/dl) and hypokalemia (2.9 mEq/l) were found. The immediate administration of intravenous $MgSO_4$ (4 g e.v. in 24 h) and liquids allowed the complete resolution of neurological symptoms. We also observed a normalization of diarrhea and electrolytes in the following days. Therefore, the diarrhea has assumed a dual role: as cause and effect of an electrolyte imbalance. The patient was discharged in good general conditions with calcium and magnesium oral supplements.
Conclusions: This case highlights an often underestimated, often misleading clinical entity, such as electrolyte imbalances. On this subject there is very little in the literature. Electrolyte homeostasis is integrated and the normalization of a parameter can not be obtained without the infusion of another electrolyte. In our case, hypomagnesemia and hypocalcemia. Acute hypomagnesaemia the less frequent imbalance, often diagnosed with delay (magnesium is not routinely evaluated). In addition, it rarely occurs as an undeferrable urgency or with a definite clinical picture, as in this case; symptoms are often non-specific and common to many other diseases. Chronic hypomagnesemia is closely related with hypocalcemia, which is caused by impaired parathyroid hormone (PTH) secretion or the refractoriness of bone and renal tubules to PTH. The dominant mechanism of acute-onset, hypomagnesemia-induced hypocalcemia is currently unclear [1]. Another cause of hypomagnesemia is the adverse effects of long-term proton pump inhibitor therapy, but our patient was not taking PPIs [2]. The guidelines, algorithms, protocols, show us the way forward, and are a good "cookbook", but remember that the patient is always need of a thinking chef.

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Fatal hemophagocytic syndrome in a patient with peripheral T cell lymphoma and interferon therapy for HCV-related chronic hepatitis

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We describe a 53 year man admitted on May 2012 with antibiotic and steroid-resistant Fever of Unknown Origin from 9 weeks, associated

with liver impairment, disseminated intravascular coagulation (DIC) and pancytopenia. Blood tests showed: anemia (Hb 7.7 g/dl), thrombocytopenia (14,000/mmc), leukopenia (540/mmc), extreme hyperferritinemia (29,000 ng/ml), conjugated hyperbilirubinemia (10.6 mg/dl) and transaminitis (AST 182 U/l, ALT 236 U/l), hypoalbuminemia (1.9 g/dl), hyponatremia (129 mEq/l), elevated lactate dehydrogenase (1,170 U/l), isolated hypertriglyceridemia (229 mg/dl).

Medical History: HCV-related chronic hepatitis treated with PEG-interferon and ribavirin (Oct 2011–Feb 2012); recent increasing of splenic volume with multiple focal hypodense lesions (eco and CT-scan). Bone marrow biopsy (March 2012): normal expression of the three cell lines with reactive T lymphocytes.

Because of inconclusive findings a diagnostic (and therapeutic?) splenectomy was proposed. However, the rapidly deteriorating clinical conditions urged the anesthesiologists to postpone surgery.

A bone marrow biopsy was therefore repeated. It showed hyperplastic bone marrow, with a mild T- lymphocytic infiltrate. Furthermore the pathologist pointed out the presence of large histiocytes CD68+ actively phagocytizing erythroblasts cells. The immunohistochemistry characterization showed a pattern suggestive for peripheral T cell lymphoma. An interim diagnosis of EBV reactivation in peripheral T lymphoma was formulated. However hepatic failure, DIC, hyperferritinemia and resistance to steroid appeared difficult to explain. A review of the literature induced us to consider the diagnosis of Hemophagocytic lymphohistiocytosis (HLH). The HLH-2004 diagnostic criteria of America Society of Hematology were indeed completely fulfilled. This is a very rare (incidence 1, 2 cases/million), potentially fatal, hyper-inflammatory condition caused by highly stimulated but ineffective immune response, that can be a primary (genetic and pediatric) or an acquired condition. In our patient HLH could have been triggered by cooperation of the T-lymphoma, the EBV reactivation, and the iatrogenic insult (PEG-interferon), although literature about this last possible correlation lacks of consistence. HLH therapy needs to be promptly instituted to prevent irreversible tissue damage, with the main aim of defusing the hyperinflammatory condition. After that, the underlying lymphoma should be treated. Proposed therapies consist of combinations of immunosuppressive therapy and pro-apoptotic chemotherapy, such as high dose dexamethasone, etoposide, cyclosporine A, antithymocyte globulin and intrathecal methotrexate in patient with central nervous system involvement. Our patient was treated with Rituximab, dexamethasone and etoposide, but he died because of an intractable tumor lysis syndrome after 2 days.

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	Main findings collected during initial diagnostic work-out	
HYPOTHESES	*PRO*	*CON*
Sepsis with splenic abscesses	Remittent fever with shiver High pro-calcitonine levels (9.1 mg/dl) Positive circulating EBV DNA (1600 /ml) Reactive bone marrow	Resistance to several lines of empiric antibiotic therapies Negative cultures (blood, urine, bone marrow), Negative tests for CMV-DNA, HIV, Parvovirus B19, HCV-RNA and Leishmania
Lymphoproliferative disorder (splenic marginal zone lymphoma with bone marrow substitution, acute leukemia)	Severe pancytopenia Elevated LDH Progressive splenomegaly Focal solid splenic abnormalities, with "target pattern" on Abdominal Nuclear Magnetic Resonance (MRI)	Steroid-resistant high fever No clinical or radiological evidence of enlarged lymphonodes (thoracic/abdominal CT and MRI) No evidence of blastic cells on peripheral blood smear or mononuclear cell immunological typing
Iatrogenic damage (PEG-interferon, antibiotics)	Pancytopenia and fever possible adverse effects of PEG-interferon Acute liver impairment described in patients receiving fluoroquinolone	Clinical worsening despite treatments withdrawal

Fig. 1 Initial diagnostic workout

Intermittent claudication and numbness of the upper limbs

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Case Presentation: A 78-year-old Italian man was referred to our institution for the evaluation of a six-month history of worsening numbness and bilateral hypoesthesia in his distal upper limbs associated with episodes of claudication. His previous medical history was unremarkable, except for moderate hypertension under control with combined therapy. He did not smoke. No fever or weight loss was referred by the patient. Only a 2/6 systolic murmur was found at physical examination. Radial pulses were present and symmetric bilaterally. Blood test revealed an increase of the erythrocyte sedimentation rate (ESR, 52 mm/h) and a slight elevation of ferritin (405 ng/ml) suggesting a chronic inflammatory state. Complete blood count, biochemistry and coagulation findings were normal.

Differential Diagnosis: Compression of nerve roots such as in the case of severe arthrosis; cervical spinal stenosis or localized demyelinating neuropathy could explain the numbness but not properly the claudication of the upper limbs. Claudication associated with numbness was suggestive for a vascular-occlusive disease, but the patient's medical history was not evocative for arthrosclerosis. Subclavian steal syndrome could explain this presentation, but it is unusual for this syndrome to occur bilaterally. Thoracic outlet syndrome was unlikely for the same reason, and it usually affects younger people. We took into consideration the large-vessel vasculitides such as Takayasu Arteritis, which did not seem probable because of the patient's age, sex and race; and the aortic arch involvement of Giant Cell Arteritis (GCA), which accompanies 10 or 15 % of temporal arteritis. Systemic diseases, as hypothyroidism, were unlikely. Finally we hypothesized an anti-phospholipid antibody syndrome or an alteration in the coagulation system.

Clinical Management: To rule out the GCA we interrogated the patient for symptoms suggestive of this disease (headache, scalp hyperesthesia, jaw claudication) but he denied. The evaluation of the temporal arteries revealed a normal temporal pulse and no tenderness on palpation. Testing for anti-cardiolipin antibodies, IgG and IgM anti-beta2 glycoprotein I, Leiden V factor and prothrombin mutations were negative. C protein, S protein, activated residual C protein and homocysteine levels were normal. TSH levels were tested and resulted within the normal range. In order to investigate a possible compression or a demyelinating neuropathy, electromyography and electroneurography were performed but they resulted normal. To study a possible brachial or subclavian occlusion, arterial Doppler studies of the upper extremities were performed showing bilateral occlusion of brachial arteries with collateral vessels sustaining the distal flow. A computed tomographic angiography confirmed these findings. Fluorodeoxyglucose positron emission tomography (FDG-PET) showed areas of focally increased FDG uptake in the brachial arteries bilaterally, confirming an active inflammatory process [1].

Diagnosis and Treatment: The diagnosis was compatible with a rare form of GCA with peripheral involvement, in absence of typical temporal and relatively frequent aortic-arch inflammation. In the case described, extracranial GCA was similar to Takayasu arteritis in its anatomical localizations and clinical presentation however the arterial obstructions had remained asymptomatic due to a sufficient collateralization [3]. Only few works describing cases of peripheral artery GCA without temporal and aortic involvement are present in the literature for a total of 79 patients affected [2, 4].

The patient was treated with tapering doses of oral prednisone (starting at 25 mg daily) with progressive reduction of claudication and numbness and normalization of the inflammatory indexes [2]. A FDG-PET performed after 7 months was negative.

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Intermittent high fever, anterior uveitis and mild abdominal pain

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Case Report: A 20-year-old woman was referred to our center for intermittent prednisone-responsive fever since 4 months. The fever peaked in the night, reached 41 °C and used to terminate with profuse sweating. Extensive serological investigations (including HIV, HBV, HCV, CMV, Salmonellae, Brucella, Toxoplasma, Leishmania, Rickettsiae, Borrelia, Bartonella, Plasmodium spp., along with autoimmune serology), a total body CT-scan, a brain MRI and a biopsy of the bone marrow excluded most infectious and malignant aetiologies. Beside fever at presentation she only complained of a mild abdominal pain. Clinical history was unremarkable, with the exception of a recent vaginal uncharacterized lesion. Serological tests were completed with the search for anti-*Saccharomyces cerevisiae* antibodies (ASCA), which scored positive. An eye examination revealed a mild anterior uveitis. A 2 mg/day colchicine trial was performed for a week for a possible Familial Mediterranean Fever (FMF): a reduction of the recurrence and degree of the fever was observed. Meanwhile a last-ileal-loop-targeted ultrasonography revealed a thickening in the wall of the last ileal loop. The patient subsequently underwent colonoscopy, which resulted in the identification of an area of edema, congestion of the local vasculature and mucosal hypotrophy at the level of the last ileal loop. Genetic tests were performed in parallel in order to exclude the presence of HLA-B51 and mutations of the MEFV gene (which encodes for pyrin, a fundamental regulator of the NALP3-inflammasome and the key pathogenic factor in FMF).

Differential Diagnosis and Clinical Management: A diagnosis of adult Still's disease was excluded because of the absence of significant neutrophilia, hyperferritinemia, LDH or transaminase elevation and the lack of clinically relevant lymphadenopathy or arthritis. Despite the atypical clinical scenario (absence of arthritis, myalgia or evidence of serosal involvement at previous imaging studies) a diagnosis of FMF could be suspected since the good response to colchicine [1]. On the other hand the endoscopic findings [2] and the association with high fever, anterior uveitis and ASCA positivity clearly suggest a diagnosis of Chron's disease (CD). However Behçet's disease (BD) with prominent gastrointestinal involvement should also be taken into consideration on the basis of the frequent similarity with CD in terms of clinical and endoscopic findings [2] and because of the history of a previous genital uncharacterized lesion the known good response of BD to colchicine [1,2] and the frequent association with uveal inflammation.

Diagnosis and Treatment: Histopathologic examination of multiple biopsies from ileum and colon revealed the presence of multiple foci of chronic inflammation which were suggestive for CD. Genetic tests were performed in parallel and revealed the absence of HLA-B51, which made the diagnosis of BD less probable. A presumptive diagnosis of CD was made on the basis of endoscopic and histopathologic findings and the association with high intermittent fever [4], ASCA positivity and anterior uveitis. The patient was started on mesalazine plus 25 mg oral prednisone, which was slowly tapered until suspension, with good clinical response. Finally homozygosis for R202Q mutation of the MEFV gene was detected. This finding besides supporting the rejection of a diagnosis of FMF [3,5], possibly provides an explanation for the good response to colchicine and the marked signs of systemic inflammation at presentation [1,3].

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Relapse of disease or what else?

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Case Report: A 19-year-old boy was referred to our Department with a history of chronic diffuse lymph-node enlargements. The patient reported a 24 kg decrease of his body weight during the last 2 months and recurrent nocturnal fever. On admission he also complained of bilateral knees and shoulders pain which appeared severely stiff, tender at palpation but with no sign of joint effusion. He had regularly been vaccinated for mumps. Laboratory tests revealed a mild leukopenia, a slight rise in LDH, ESR and hyperferritinemia. Serology for HIV, HSV 1,2, CMV, EBV, HHV 6, HHV 8, Toxoplasma, Borrelia, Brucella, Parvovirus, Leishmania were negative for active infections. Quantiferon®-test was negative. A CT scan confirmed the diffuse involvement of submandibular, laterocervical, supra-clavear, mediastinal, axillary, coeliac, perisplenic, lumboaortic, porto-caval, iliac and inguinal lymph-nodes. An inguinal lymph-node was biopsied and histopathologic examination led to the diagnosis of Kikuchi–Fujimoto's disease (KFD) [1]. Moreover autoimmune serology revealed a strong positivity of ANA (>1:640 with speckled pattern), positivity of SS-A, antiDNA (ADNA), anti Sm, anti RNP antibodies and low complement (C3 and C4) values were also found. The patient thus fulfilled 4 of the 11 ACR criteria for the classification of SLE (ANA positivity, immune alterations, hematologic involvement, arthritis). The patient was diagnosed with KFD possibly overlapping SLE [2] and he was started on 75 mg/day of oral prednisone, subsequently tapered. Azathioprine 100 mg was then introduced as steroid sparing agent. Four months thereafter, after an initial benefit the patient was re-admitted to our Department for subjective vertigo, tinnitus, fever with shivering and vomit from 3 days. Laboratory test revealed anemia (Hb 10.2 g/dl), leukopenia (WBC 2.000.000/mcL with

700,000/mcL neutrophils), platelets 74×10^9/l, CRP 150 mg/l, Fibrinogen 707 mg/dl, Creatinine Kinase 653 mcg/L and a significant rise in hyperferritinemia (5,500 ng/ml). Neurologic and Ear-Nose-Throat evaluation resulted negative. Mild splenomegaly was detected by abdomen Ultrasonography.

Differential Diagnosis: Considering the clinical condition, the most probable diagnosis were bacterial sepsis or virus reactivation (e.g. CMV) due to the immunosuppression condition; Azathioprine hypersensivity's syndrome [5]; a relapse of SLE or macrophage activation syndrome (MAS).

Diagnosis and Treatment: Suspension of azathioprine and introduction of empiric antibiotic therapy with Levofloxacin didn't result in clinical improvement and ruled out drug hypersensitivity and most bacterial systemic infections. Extensive cultural tests were negative, with the exception of a low grade CMV and EBV replication. Relapse of disease is a diagnosis of exclusion, so to rule out MAS we performed a bone marrow aspiration and biopsy, with the histological evidence of haemophagocytic lymphohistocytosis.

5 of 8 diagnostic criteria for MAS were thus fulfilled (histological evidence of haemophagocytosis, fever, splenomegaly, ferritin >500 ng/mL, peripheral cytopenia in 2 or more lines: platelets <100,000/mcL, neutrophils <1,000.000/mcL). A diagnosis of MAS complicating KFD and possible SLE was made [3, 4]. Therapy with high dose Dexamethasone for 1 week was started, with rapid improvement of clinical conditions and laboratory parameters (resolution of pancytopenia, reduction in hyperferritinemia and flogosis indexes). Maintenance treatment with cyclosporine and oral prednisone slowly tapered was started.

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Ventricular thrombosis during sorafenib therapy for advanced hepatocellular carcinoma

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Introduction: Sorafenib is today the gold standard for the treatment of advanced hepatocellular carcinoma (HCC). Elevation of blood pressure is a common side effect of this drug. Data from clinical trials reported also an incidence near 3 % of congestive heart failure and acute coronary syndromes. Furthermore sorafenib predispose both to thrombosis and, more frequently, bleeding, reflecting the variety of actions of VEGF on vascular walls and coagulation system.

Case Presentation: A 66 years old men, bearing ischemic dilated cardiomyopathy (NYHA class I) and an alcoholic cirrhosis (Child A6, MELD 12) presented with multinodular HCC. The computed tomography (CT) showed a total of 7 nodules, the largest 25 mm on diameter, with a typical contrast enhancement pattern; no evidence of portal vein thrombosis. The AFP was 25 ng/ml. There were no varices at endoscopic evaluation. The performance status was 0. The echocardiogram showed a significant dilatation of left ventricular with akinesis of infero-lateral wall, a low ejection fraction (33 %) and a severe diastolic dysfunction ($E/e' = 17$); a moderate to severe mitral regurgitation secondary to retraction of the leaflets was also present. Nonetheless this unfavourable cardiac condition, treatment with sorafenib 400 mg/d was started. Three months later, the patient presented with asthenia, anorexia, diarrhea, weight loss, hypertension and hepatic encephalopathy. CT showed stable liver disease according to mRECIST criteria, but noticed the presence of apical thrombus in the left ventricle. At follow-up echocardiography a left ventricular apical mural thrombus measuring 24×19 mm appeared. Treatment with sorafenib was stopped and enoxaparin was started. Four months later, the patient had clinical recovery and echocardiography showed complete disappearance of intracavitary thrombosis.

Conclusions: Ventricular thrombosis has never been reported during treatment with sorafenib. In this case we believe that both presence of ventricular dysfunction and cirrhotic-related and cancer-related coagulopathy played a role in determining the occurrence of this peculiar side effect during sorafenib treatment. The case shows that caution and close monitoring should be reserved for HCC patients with ventricular dysfunction who need sorafenib therapy.

A case of association between antiphospholipid syndrome and inflammatory pseudotumor of the liver

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Introduction: Inflammatory pseudotumour of the liver is a rare benign condition which may mimic malignant liver tumors. It is associated with several diseases including Crohn's disease, diabetes mellitus, Sjögren's syndrome, gout, chronic ascending cholangitis, primary sclerosing cholangitis, acute myeloblastic leukemia, HIV infection and autoimmune pancreatitis.

Case Presentation: On January 2011, a 37 years-old woman, nurse, with an history of primary antiphospholipid antibody syndrome with recurrent pulmonary embolism and hypothyroidism, underwent an abdominal ultrasound (US) in order to rule out a possible renal involvement of her thrombophilic syndrome. The scan revealed multiple oval hypoechoic liver lesions (mean diameter 10–20 mm) on the right hepatic lobe. During Contrast-Enhanced UltraSound (CEUS), lesions displayed centripetal arterial enhancement and an early wash out. She denied symptoms. Her current medications included levothyroxine 100 mcg/d and warfarin. Liver function tests were normal, as well as tests for HBV and HCV infections and autoimmune hepatitis. Erythrocyte sedimentation rate was 73 mm/h and Protein C reactive was 39 mg/l. Magnetic Resonance Imaging (MRI) of liver showed multiple T2-hyperintense lesions with a restricted diffusion on Diffusion-Weighted Imaging. The vascular phase of the study demonstrated a peripheral arterial enhancement with delayed central uptake. No enhancement was observed during the hepatospecific phase. Liver biopsy showed fibrovascular tissue embedding biliary ducts and infiltrated by lymphocytes, plasma cells and granulocytes. During a quarterly follow-up, the MRI showed that some lesions spontaneously were reduced or even disappeared, when others were enlarged or new ones appeared. A final diagnosis of an inflammatory pseudotumor of the liver was made. On March 2012, patient started treatment with pentoxifylline 1200 mg/d orally and since then remains asymptomatic.

Conclusion: Here we report a case of peculiar association of inflammatory pseudotumor of the liver and antiphospholipid syndrome.

A mime who comes from Japan

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A 46-year-old woman, with history of secreting adrenal adenoma treated with surgical excision in 2011, was admitted to our Department because of the onset of arthromyalgia predominately localized to the scapular and pelvic girdle that began 1 year earlier and progressively worsened over the past 2 months with onset of continuous fever (max 39 °C), profuse night sweats and arthritis of knees, ankles, feet, wrists and hands accompanied by severe functional impairment apparently unresponsive to corticosteroid therapy. Her physical examination was unremarkable except for fever (38 °C), palpable axillary and pelvic lymph nodes and swelling of both knees, while laboratory tests showed normochromic normocytic anemia (Hb 9.4 g/dl) and increase of erythrocyte sedimentation rate (ESR) C-reactive protein (C-RP) (77 mm/h and 26.4 mg/dl respectively) and D-Dimer (2796 ng/ml) values. Before the admission, the patient had also performed hands and spine X-rays, which resulted negative. During the hospitalization seriate blood cultures, urine culture and autoimmune screening were performed with negative results. Moreover chest X-ray and echocardiogram, transesophageal echocardiogram showed no abnormalities.

Considering the worsening of the symptoms Mantoux test, HBV, HCV, CMV, EBV, HSV, HIV, Leishmania serology, Widal–Wright e Weil Felix reactions, antibodies anti Borrelia and Chlamydia, rubeo- and toxo-test, pharyngeal, urethral and vaginal swabs and stool tests and cultures were carried out with no positive results; even oncomarkers were negative. Thus antibiotic therapy was started (at first Clarithromycin, then teicoplanin and Piperacillin/tazobactam) with any improvement of the fever. Esophagogastroduodenoscopy, colonoscopy, orthopanoramic X-ray venous ultrasound of the legs and brain MRI were also performed and resulted negative.

For the persistence of fever (up to 40 °C) despite antibiotic therapy, further diagnostic tests were required: lymphocyte immunophenotyping revealed a reduction of all populations with preserved T4/T8 ratio and the peripheral smear showed a slight anisocytosis of erythrocytes total nodes ecography evidenced "fusiform lymphadenopathy with preserved echotexture laterocervical and submandibular (<1 cm); axillary and inguinal lymphadenopathy with abundant fatty hilum, increased central vascularity, cortical thickening, hypoechoic." and abdomen CT scans revealed left hepatic lobe hypertrophy and slight splenomegaly; some nodes of the maximum size of 13 mm. Bone marrow biopsy and smear resulted negative, whereas PET–CT scans confirmed some enlarged lymph nodes (the largest in left axillary region had a maximum diameter of 3.8 cm).

An histologic exam of left axillar node, was therefore performed which resulted in "multiple foci of necrotizing hystiocytosis with nuclear karyorrhexis and cortical activation"; we finally diagnosed the Kikuchi–Fujimoto disease (KFD) and we started a corticosteroid therapy, obtaining a prompt resolution of the fever.

Conclusion: KFD is a rare disorder which usually presents with fever and lymphadenopathy and may mimics malignancies, infective, and immunological disorders, systemic lupus erythematosus (SLE) above all. The disease is benign and usually subsides spontaneously. Since the diagnosis is of exclusion or/and histo-pathological we would emphasize the importance of an early histological examination for a correct therapeutic approach.

Follow the heart…and live(r) too!

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C.V. is a 64 year-old man with history of diabetes, arterial hypertension, cryptogenic liver cirrhosis (likely NASH) determining portal hypertension (spleen diameter of 20 cm) with previous complete (currently partial) portal thrombosis and non-hyporegenerative thrombocytopenia. He had an active lifestyle and worked as a cook in a restaurant; his home medication included atenolol, amlodipine and insulin. He complained of dyspnoea on moderate exertion from about 2 months; an ergometric test was performed which resulted positive to moderate workload, without angina. Coronarography showed a three-vessel disease. He was thus admitted to the medicine ward where on esophagogastroduodenoscopy (EGDS) he was found to have three esophageal varices with red spots and an isolated gastric varix in the fundus (IGV1). Problem finding: (1) symptomatic coronary artery disease (CAD) in a diabetic patient. The Duke prognostic treadmill score estimated a five-year survival rate of 90 %. (2) Advanced liver cirrhosis (class B8 Child–Pugh) carrying an high mortality risk (one-year and two-year survival rates of 80 and 60 % respectively) and limiting the suitable therapeutic strategies for CAD. 3. Bleeding risk: severe thrombocytopenia (18–25,000/μL), liver failure (INR 1.5) and reported one-year risk of variceal bleeding of 33 % (deFranchis, R, N Engl J Med 1988; 319:983). Standing all these factors affecting the patient's outcome, we decided to apply a methodological evidence-based approach which, according to Sackett, is nothing but the conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient. It means integrating individual clinical expertise with the best available external clinical evidence from systematic research. CAD-related therapeutic options: 1. Aorto-coronary by-pass and lifelong anti-platelet therapy. According to the modified MELD score, however, this procedure carried a 90-day mortality rate of 19 %. 2. Percutaneous coronary intervention with drug-eluting stent (specifically indicated in this case due to the extension of the stenosis) followed by double anti-platelet therapy for 6 months to 1 year, then shifted to lifelong therapy with a single anti-platelet agent. We couldn't find any study evaluating the bleeding risk during double anti-platelet therapy in populations with the same comorbidities as our patient's. There was only a small case–controlled trial that enrolled cirrhotic patients who underwent orthotopic liver transplantation during double anti-platelet therapy showing a 12.5 % risk of fatal variceal bleeding [J Clin Gastroenterol. 2012;46:339–344]. (3) Medical therapy with an anti-platelet drug and targetted beta-blocker therapy. Several meta-analyses supported this strategy since none of them showed a significant difference in mortality and incidence of acute myocardial infarction when compared to revascularization procedures [Lancet. 2009;373:911–18]. (4) Beta-blocker therapy only, since the introduction of even a single anti-platelet drug increased the bleeding risk [Gut. 1999;44(2):270–3]. Therapeutic options for liver disease: (1) Orthotopic liver transplantation: unfeasible for the patient's age and the presence of two absolute contraindications (portal thrombosis and CAD). (2) Transjugular intrahepatic portosystemic shunt (TIPS): not indicated for the primary prevention of variceal bleeding and relatively contraindicated because of portal thrombosis. (3) Endoscopic variceal ligation: currently indicated as primary prevention procedure only in presence of an absolute contraindication to beta-blocker therapy and unable to achieve a complete therapeutic goal in this case anyway, because IGV1 are not endoscopically treatable. (4) Medical therapy with non-selective beta-blocker directed at lowering portal

hypertension, assessed with hepatic vein-portal pressure gradient (HVPG) test. Since the available evidence in literature was inconclusive regarding the most appropriate clinical management, we excluded the dangerous options and tailored the feasible ones for each of the patient's problems (heart- and liver-related) in order to pursue a bidirectional benefit. We performed an HVPG test before and after propranolol infusion, which resulted effective in reducing the hepatic vein-portal pressure gradient. Hence, as for the liver disease we opted for beta-blocker therapy with propranolol (20 mg bid) in order to reduce splenomegaly and increase the platelet count; this would provide a reduction in the bleeding risk just sufficient to allow us the introduction of acetylsalicylic acid (75 mg od) thus achieving a CAD therapy based on beta-blocker and an anti-platelet agent.

Hungry for air

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A 61-year-old woman was admitted to our department because of a 10-month history of anorexia, nausea and diarrhoea. She had lost about 18 kg in weight in the last year. 4 months ago she had an episode of deep vein thrombosis (DVT) of the left lower limb. She was on prophylactic treatment with warfarin but she didn't do any diagnostic investigation. She reported having a 10 years history of chronic obstructive pulmonary disease (COPD)—she was a heavy smoker- treated with bronchodilators. On examination, the patient was afebrile, cachectic (BMI 12.8 kg/m^2), pale and severely dehydrated. Vital recorded showed a pulse rate of 126 bpm (ECG showed sinus tachycardia), a blood pressure of 80/50 mmHg and oxygen saturation 96 % on room air. The chest auscultation demonstrated bilateral wheezing. The abdominal examination was unremarkable. Routine laboratory data revealed neutrophilic leucocytosis (WBC 23,360/mm^3, NEUT 90.6 %), a severe electrolyte imbalance (hypopotassemia, hyponatremia, hypocalcemia and hypomagnesemia) and an important malnutrition (total protein 3.1 g/dL, albumin 1.9 g/dL). Chest X-ray showed panlobular emphysema and it was negative for pleural effusion or pulmonary consolidation. Patient was managed with intravenous rehydration, infusions of electrolyte and albumin, and vitamin supplementation. Moreover, the second day, because of the persistence of anorexia, parenteral nutrition was started. The culture of the feces demonstrated *Clostridium difficile* toxins A and B while parasitological examination was positive for *Giardia lamblia*. The patient was commenced on Metronidazole 250 mg tris in die. On the fourth day of hospital stay she developed hypochromic microcytic anemia, peripheral edema, profound weakness and fever up to 38 °C. Over the next 24 h the patient had a syncopal episode and she developed dyspnea with acute respiratory failure. Differential diagnosis at this point includes four groups of disorders: refeeding syndrome (RFS) with cardiac failure, pulmonary embolism also in relation with her hystory of DVT, COPD exacerbation and pneumonia. Arterial blood gas analysis showed hypoxemia and respiratory alkalosis. D-dimer test measured by ELISA method was negative. Chest X-ray demonstrated a marked enlargement of cardiac silhouette, prominent bronchovascular markings and bilateral pleural effusion. Colour Doppler ultrasound of the lower limb deep vein system didn't reveal any sign of DVT. Ultrasound examination of abdomen showed the presence of moderate ascitic fluid. Echocardiogram revealed marked dilatation of the right heart chambers with severe hypokinesia of the right ventricle wall and mild pericardial effusion. In order to exclude pulmonary embolism, a CT pulmonary angiography was performed. It didn't demonstrate any filling defects of the pulmonary arterial stump but it showed bilateral pleural effusion and interlobular septal thickening with some areas of ground glass opacity. We focused our diagnostic hypothesis on RFS with acute right heart failure in a patient who was very probably affected by chronic pulmonary heart disease. Biochemistry investigations revealed a decrease in phosphate levels to 0.9 mg/dL and the persistence of hypopotassemia and hypomagnesemia despite adequate electrolyte therapy. The parenteral nutrition was temporarily stopped. Intravenous rehydration was continued. Electrolyte infusions, thiamine and vitamin B complex supplementation were increased. Furosemide and potassium sparing diuretics were added to her treatment, initially administered intravenously and then changed to oral route. There was a gradual improvement in the patient's conditions, with clinical resolution of the RFS in about 10 days.

The essential features of the RFS are rapid falls in plasma levels of phosphorus, potassium and magnesium, and sodium and water retention leading to fluid overload. This syndrome is characterized primarily by cardiac, neurological, muscular and hematological changes. Clinically, signs of heart failure after initiating feeding should suggest the possibility of this syndrome developing and they indicate the feeding should be stopped temporarily. In our patient the fluid overload caused by RFS had got worse pulmonary hypertension secondary to COPD and it had produced acute right heart failure.

A widespread eruption of bullae

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Case Presentation: A 68-year-old man was admitted to our hospital because of a widespread eruption of itchy vescicular-bollous lesions, localized especially in the palms and soles.

The patient suffered from psoriasis vulgaris since he was 30 years old. He had been treated with topical corticosteroids and emollients and he had been in remission for the last year. He was allergic to ceftriaxone (angioedema). In 2008 he underwent a CT scan for a sudden worsening of the dyspnea. The exam disclosed the presence of a small lung nodule in the upper left pulmonary lobe and mediastinal lymphoadenopathies with a positive PET scan. He then had a surgical treatment consisting in upper left lobectomy and mediastinal lymphoadenectomy. Histological examination was compatible with a G2 mixed lung adenocarcinoma with mucous BAC staged pT1 pN0. His oncological follow-up was negative.

His body temperature was 38.5 °C. Pressure was 120/70. He was eupnoic. Skin examination disclosed the presence of tense bullae on erythematous area, urticarial plaques and some papules. The bullae were full of serous and pustulous fluid. They were localized especially in the palms, soles and groin where some of them were already ruptured giving rise to bleeding erosions. Lower limbs also showed sharply marginated erythematous papules with a silvery-white scale. Scales were lamellar, loose, and easily removable by scratching so they were interpreted as psoriasis vulgaris. Some of them coalesced in a serpinginous pattern. Only one bulla was present in the oral mucosa. The remaining findings were normal, except for the presence of conjunctival jaundice. Leukocyte count was 13,000 cells per microliter, with 7 % of eosinophils.

Erythrocyte sedimentation rate was 5 mm/h and C-reactive protein was 17.9 mg/dl (normal values <6 mg/L).

Urine analysis and a biochemistry panel (including liver and renal function tests) revealed a small increase in the indirect bilirubin

(3.78 mg/dL), which was considered compatible with Gilbert's disease.
Total immunoglobulin E level was 126 UI/mL (normal values 1–100). Specific IgE for Cefaclor revealed a borderline value (IgE 0.11). Serological tests for syphilis, hepatitis B and C virus resulted also negative.
Differential Diagnosis: The patient had already been evaluated by a dermatologist in another center when the manifestation started. The colleague suggested that the skin manifestation was dyshidrotic eczema and he prescribed a topical treatment with potassium permanganate as antiseptic plus emollients and topical corticosteroids, that the patient had used for almost 10 days. Moreover, in the first 3 days the patient had autonomously used oral prednisone (25 mg). Because the manifestations had extended after the patients had interrupted the treatment on the tenth day, he went to our Emergency department. In E.R. an abdominal ultrasound was performed secondary to the presentation of abdominal pain and increased indirect bilirubin. No abnormalities were found on examination. The history of corticosteroid treatment, abruptly discontinued, in a patient affected by psoriasis was compatible with a severe pustular psoriasis (von Zumbusch), which usually follows short courses of corticosteroid therapy. Hepatic abnormalities are also present in this disease and it is a life-threatening condition [1]. Our second possible diagnosis was paraneoplastic bullous pemphigoid. The clinical manifestation was highly evocative and the history of lung neoplasm was the other element we took into consideration. To determine the precise nature of the lesion the patient underwent a skin biopsy. The microscopic analysis disclosed the presence of orto and para-hyperkeratosis compatible with the known psoriasis vulgaris and an intraepidermic bulla; its lumen was full of serous fluid and eosinophils. The direct immunofluorescence showed linear deposits of IgG, C3c in the dermo-epidermic junction compatible with bullous pemphigoid. We rapidly started an oral corticosteroid treatment with prednisone 50 mg which resulted in rapid improvement of the patient's clinical conditions. To evaluate the possible paraneoplastic origin of the manifestation, a total body CT scan was performed and it showed no abnormalities, our final diagnosis was Lever's disease (primary bullous pemphigoid) [2].

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A temporal nodule

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Case Presentation: A 41-year-old man presented to our hospital with a painless, fast-growing nodular lesion in the region of the left superficial temporal artery. He reported the occurrence of a similar, controlateral lesion one month previously. His past medical history was unremarkable. He had been smoking 25 pack years. He reported no traumas involving the head, fever, myalgia, or headache.
The general examination disclosed the presence of two subcutaneous pulsating nodules located in the temporal region, more prominent on the right side. No ophthalmological or neurological signs were detected.
Leukocyte count of 7,700 cells per microliter, with 17 % of eosinophils. Erythrocyte sedimentation rate was 5 mm/h and C-reactive protein was negative. Urine analysis, serum electrophoresis, liver and renal function tests were normal. Total immunoglobulin E level was 2,015 UI/mL. Tests for antinuclear antibodies, anti-cardiolipin antibodies, and anti-neutrophil cytoplasmic antibodies were negative, C3 and C4 levels were normal. Serological tests for syphilis, hepatitis B and C virus resulted also negative.
Clinical Management: To evaluate the nature of the nodules we performed an ultrasonography with color-Doppler study of the temporal regions which disclosed a bilateral thickening of temporal arteries, determining a significant reduction in the blood flow in the right side. To better identify the nature of the nodules an high-resolution magnetic resonance angiography was then performed. It showed a thickened right temporal artery with marked enhancement in the vessel wall and in the perivascular region. The vessel wall of the left temporal artery was also enhanced. These findings were consistent with a more recent inflammatory process. In order to exclude other possible vascular involvements, a total body magnetic resonance angiography was also performed, and resulted negative.
Differential Diagnosis: Hypereosinophilic syndrome (HES) was ruled out because of the limited extension of the manifestations and because the number of eosinophils (1300/microliter) did not fulfill the criteria [1, 3]. Giant cell arteritis was easily excluded because of the patient's age and the complete lack of symptoms [8].
We took also into consideration the hypothesis of Kimura disease [5–7] because the presence of a painless nodule, hypereosinophilia and increase of IgE. Our last differential diagnosis was the Juvenile temporal arteritis [2–6]. This rare arteritis, affecting young people with an history of eosinophilia, is completely asymptomatic if we exclude the formation of small nodules in the temporal region.
Diagnosis and Treatment: A biopsy of the right temporal artery was then performed. Histologic analysis disclosed a non-granulomatous panarteritis with eosinophilic infiltrate and several lymphocytes and monocytes. A lymphomonocytic infiltrate was also present in the perivascular connective tissue. The intimal wall was thickened and the internal elastic lamina was severely disrupted. No necrosis, giant cells or luminal thrombosis could be observed. This elements were compatible with a diagnosis of juvenile temporal arteritis. Consistent with the recommendation in the literature, the patient underwent surgical excision of the involved section of the artery [2–6]. Unfortunately this was not curative, so corticosteroid therapy (prednisone 37.5 mg per day) was started and then gradually tapered over a period of 5 months, with decrease of the vascular lesion and a reduction in the eosinophils count. At the end of this period, the patient complained the involvement of left retroauricular artery associated with a rise of peripheral eosinophilia (WBC 7,600 cells/microliter with 13 % of eosinophils). Methotrexate (20 mg/weekly) was then added as a steroid sparing agents resulting in good disease control.

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Postpartum-acquired haemophilia A: rituximab. A new promising therapy?

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A 33-year-old primigravida woman delivered a male baby at the 40th gestational week, without bleeding. The pregnancy was uncomplicated until 1 week before delivery when she developed hypertension, solved with delivery.

Three months after delivery, macrohaematuria without fever occurred, with mild uretero-nephrosis without kidney stones, so she was admitted to another hospital, The hypothesis was hemorrhagic cystitis.

She has a family history of systemic lupus erythematosus, she underwent tonsillectomy when she was child and she was allergic to sulfamidic antibiotics and to acido acetylsalicylic acid.

Because of she complained macrohematuria and she also developed a haematoma in her right thigh (5 × 5 cm) and in her right forearm (3 × 3 cm) she was transferred to our hospital. On admission blood chemistry tests did not revealed anaemia (Hb 13.5 g/dl), but showed a prolonged aPTT (aPTT ratio 2.85 aPTT 73.6 s). Initial 1:1 mixing of the patient's plasma with normal plasma resulted in only partial correction of the activated partial thromboplastin time. On incubation of the mixed plasma, the aPTT remained prolonged. FVIII activity was tested and it was severely decreased (FVIII:C 1.3 %) and a high-titer inhibitor directed against human FVIII (1.7 BU/ml). The plasma was also mildly positive for lupus anticoagulant. An abdominal NMR revealed neither signs of urinary tract infection nor uretero-nephrosis. Actually this is a case of postpartum-acquired haemophilia A. To eradicate the inhibitor, the patient received immunosuppressive therapy with corticosteroids (methylprednisolone 1 mg/kg bw per day) and because of persistent macrohematuria therapy with intravenous recombinant activated FVII (rFVIIa) was started at a dose of 90 μg/kg every 6 h for 2 days and by continuous infusion for the other 3 consecutive days and hematuria gradually disappeared. The day after rFVIIa stopping, macrohaematuria started again and new small haematomas appeared in her right hand and in her right calf. Even if Hb was stable, we decided to administer again the infusion of rFVIIa at the same dose for one day, and the haemorrhagic manifestations were again under control. Transfusion of packed red blood cell was not necessary. After 4 days methylprednisolone was replaced with prednisone (1 mg/kg bw) and she was discharged with normalized coagulation tests and decreased inhibitor directed against human FVIII (0.42 BU/ml), while FVIII was increasing (9 %).

Management of this disease should be aimed at stopping the haemorrhage, raising endogenous FVIII levels and reducing the inhibitor levels. Treatment consists of blood products to replace the blood loss, coagulation factor and immunosuppressants. The choice of the product for the control of acute bleeding depends on the clinical severity and on the FVIII inhibitor titres. According to the majority of authors, medications of choice in bleeding's inhibition in acquired haemophilia patients are activated prothrombin complex concentrates (aPCC) and rFVIIa. In all patients with acquired haemophilia, the immunosuppressive medications used in the inhibitor elimination, apart from corticosteroids, included cyclophosphamide (CTX), azathioprine, cyclosporine A. For the first-line treatment in pregnant or puerperium women with acquired haemophilia A, a corticosteroid monotherapy or a combination with high dose intravenous immunoglobulins or azathioprine is recommended. The findings concerning the great efficacy of rituximab, administered in monotherapy or in combination with corticosteroids or CTX, seem to be very promising [1].

The patient continued to be followed and after one month new small haematomas appeared in her arms and legs: aPTT was prolonged again (ratio 1.49), FVIII:C was low (12 %), with increased inhibitor directed against human FVIII (0.64 BU). Steroid was tapered off because she had developed Cushing's syndrome, so the haematologist decided to introduce rituximab. At the time of writing, she is still taking immunosuppressive therapy. This is an interesting case because of the rarety of acquired haemophilia and because its management is based only on case series and limited prospective data.

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A case of hypereosinophilia post-hemorrhagic stroke

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Medical History and Clinical Presentation: A 75 years old man, smoker, affected by blood hypertension and dyslipidemia, is transported to the Emergency Department (ED) for comatose state secondary to cerebral hemorrage; during the observation in the ED, there was a seizure, with teeth-grinding and sphincter incontinence. Vital signs at the entrance were: blood pressure (BP) 145/90 mmHg, Heart Rate (HR) 98 bpm, respiratory rate (RR) 18 apm, body temperature (BT) 36.7 °C, SpO_2 92 % in room air. The patient was then treated in Urgency Medicine, where he started therapy with dexamethasone, 18 % mannitol, fluids, ceftriaxone, phenobarbital (100 mg im) and clonidine. On the fourth day we witness onset of fever, hypotension, sinus tachycardia and oliguria; the fifth day onset of erythroderma with exfoliative dermatitis associated; in the sixth day the patient showed a dramatic deterioration of the exchange parameters (pO_2 48 mmHg, SpO_2 83 % with O_2-therapy at 2 LPM), whereby ventilation with CPAP in Boussignac Mask became necessary.

Biohumoral Framework: Samples for urine culture and blood culture were performed, but resulted negative. Laboratory tests showed leukocytosis with eosinophilia ($\geq 1.5 \times 10^9$/L), marked increase in transaminases, LDH and CPK, variable increase of myoglobin and bilirubin (mainly direct) and hypoalbuminemia.

Methods: A number of clinical conditions can lead to eosinophilia, which is defined as blood eosinophil counts exceeding 0.5×10^9/L. Three levels of severity of eosinophilia have been defined as follows: mild ($0.5–1.5 \times 10^9$/L), moderate ($1.5–5 \times 10^9$/L), and severe ($>5 \times 10^9$/L). The term "hypereosinophilia" refers to eosinophil levels above 1.5×10^9/L (eosinophilia which may intrinsically cause tissue and organ damage, regardless of underlying etiology). We performed a search of the literature (key words: Drug rash-Eosinophilia-Systemic symptoms), resulting in about 200 papers related to the DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) syndrome, a drug-related adverse reaction, potentially fatal, described in 1996 by Bocquet. So, it was carried out anti-HHV6 antibody, tested positive, interrupted phenobarbital and administered isotonic fluids and corticosteroid.

Results: Six days after, the patient showed a marked improvement of vital signs (BP 140/85 mmHg, HR 80 bpm, RR 16 cpm, BT 36.7 °C, SpO_2 99 % in room air), with regression of the rash and initial normalization of laboratory parameters.
Conclusions: Several drugs are associated with DRESS syndrome, but the main are anti-epileptics and allopurinol, whereby the first step of treatment is their discontinuation. A number of mechanisms has been proposed to explain its pathogenesis and, among these, the main are a defect in detoxification processes with formation of immunoreactive secondary metabolites and, recently, the herpesvirus HHV6 reactivation. Some medications may induce hypogammaglobulinaemia and promote virus reactivation: while the expression of immune response is repressed under normal circumstances, viral reactivation could trigger recognition of drugs as antigens, impair the negative regulation and promote an adverse reaction.

Echocolordoppler and CEUS in the diagnosis of portal vein thrombosis

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We report the case of a 68-year-old woman admitted in September 2011 to our Unit with pain in the dorsolumbar region, hypochondrium and right flank. She had a history of type II DM. In April 2011 she had been hospitalized for hematemesis and discharged with a diagnosis of bleeding esophageal varices and subsequent ligature in a suject with uncompensated cryptogenic liver cirrhosis. In June 2011, abdominal CT control was normal.
At our Unit, blood chemistry tests showed: AST 38, ALT 66, alkaline phosphatase 220, γGT 174, ESR 23, PCR 0.2, FBG 269, D-Dimers 3.69, PLT 100,000.
Intravenous NSAIDS therapy was scheduled and abdominal US showed an increased volume and dyshomogeneous echostructure of the liver, otherwise normal. Due to persistence of the pain, abdominal-pelvic CT was performed without and with contrast medium, showing a defective opacity referable to partial thrombosis of the right, left and main branches of the portal vein and mesenteric vein. Autoantibodies panels and thrombophilia tests were negative. In view of the discrepancy between the US and radiological findings, echocolordoppler of the portal system was performed, showing signs of portal hypertension but no hemodynamically significant thrombosis of this venous system.
The patient underwent CEUS showing: "normal opacity of the portal vein. No foci in the arterial, portal and late phases." The echocolordoppler controls at 1 and 2 months were similar.
In the literature, US is the primary imaging method for studying the liver parenchyma and vascular system. The study by Rossi demonstrated that CEUS has a greater sensitivity than conventional US and echocolordoppler in the diagnosis and characterization (benign/malignant) of a thrombus in the hepatic venous system. The choice of CEUS, a simple, low cost imaging method with minor invasiveness, allowed us to make a firm diagnosis and rapidly draw up a therapeutic plan.

An eye to the past to discover what hides diarrhea

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A 29-year-old man was admitted to the Department of Internal Medicine of Fondazione Policlinico San Matteo (Pavia, Italy) because of the recent appearance of asthenia, lower limb edema with ecchymotic patches and red papules, and worsening of chronic diarrhea. During the last 5 years, indeed, he lost 50 kilos of body weight due to recurrent episodes of diarrhea for which he underwent hospitalization and extensive diagnostic workup without a definitive diagnosis. Specifically, 2 years ago, he was admitted for malabsorption syndrome and follicular purpura at the legs, but all the laboratory and instrumental exams, including serological screening for celiac disease, vasculitis and autoimmune enteropathy, stool exams for occult blood and pathogens, and both upper and lower endoscopy with biopsy sampling, resulted unremarkable. The edema was successfully treated with diuretics which were continued at home due to the relief of hypertension (diastolic blood pressure value >95 mmHg). The subsequent therapies with mesalazine, antibiotics and steroids produced only transient benefit. No psychiatric or chronic illnesses, no drug abuse, nor alcohol intake were reported.
At present admission, blood pressure was 150/100 mmHg and hearth rate 80/min. Skin examination revealed multiple petechial lesions, ecchymotic patches and red nonscaling papules of the lower extremities, mainly on the calves, with edema and muscle wasting. At a careful inspection, perifollicular hemorrhages and corkscrew hairs were evident, whilst the skin of the rest of the body showed a normal appearance. Also the gums, tongue and oral mucosa had regular aspect, and no peripheral lymphadenopathy was found. At blood tests, a moderate anemia (hemoglobin 9.0 g/dl, red cell count 2.6×10^6, mean corpuscolar volume 95.7 fl), slight lymphopenia (850 cells/ul), ipo-γ-globulinemia, and a mild increase of the erythrocyte sedimentation rate (34 mm/h) with normal levels of folic acid, vitamin B12 and iron pool, were detected. All the other exams concerning systemic and organ-related autoantibodies, viral and bacterial tests, cryoglobulins, complement levels, and coagulation state were within normal range, with fecal occult blood test and calprotectin negative. A further serological screening for celiac disease and autoimmune enteropathy was confirmed negative, but the D-xylose test resulted positive. After upper endoscopy showing polyps of gastric mucosa due to glandular cystic dilation, a wireless capsule endoscopy was carried out with the evidence of several lymphangiectasie scattered in the middle part of the small intestine consistent with the clinical picture of protein-loosing enteropathy, and a slow transit time (4 h 21′) probably expression of the phenomenon of 'ileal brake'.
To explain skin lesions, the dosage of clotting factors and a Doppler ultrasound scan of the legs were firstly carried out following the suspicion of a coagulopathy, and gave normal results. The consultant dermatologist, then, suggested a skin biopsy to ascertain the presence of scurvy due to chronic deficiency of vitamin C. The histological examination showed a sparse, focal perifollicular and perivascular lymphocytic inflammatory infiltrate, with perifollicular extravasation of erythrocytes and an overlying follicular hyperkeratosis, consistent

with the diagnosis of scurvy. Unfortunately, the determination of serum level of vitamin C was not performed because unavailable in our hospital. Following a specific query, the patient admitted the lack of any fresh fruit and vegetable in his diet since several years to tentatively reduce bowel movements. Intravenous supplementation of vitamin C (1 g bid), therefore, was established with a rapid and critical disappearance of skin lesions within the first 2–3 days. The treatment was prolonged for 2 weeks and then continued per os (1 g/die) for further 4 weeks when also the ecchymoses and petechial lesions disappeared.

The present report shows that scurvy still exists even in Western countries when extreme diet restrictions are inadvertently overrun, since malabsorption syndrome *per se* does not cause vitamin C deficiency. Humans are unable to synthesize their daily need of ascorbic acid, then a regular intake of citrus fruits (oranges, lemons, limes, grapefruits) and vegetables (potatoes, broccoli, spinach, Brussels sprouts, red peppers) is mandatory. Vitamin C deficiency causes the synthesis of an abnormal collagen which, in turn, leads to capillary fragility, perivascular edema and red cell extravasations. However, despite the presence of these typical features, our case lacked of evocative risk factors, such as poor socioeconomic conditions, alcoholic abuse, food allergies, cancer, psychiatric disorders, and feeding difficulties. This case also implies that a multidisciplinary approach with dermatologists and experts in the field of hemostasis may be more helpful than unnecessary laboratory tests for patients carrying skin lesions. Undoubtedly, early recognition of scurvy is hard because symptoms are vague and mimic a variety of more common systemic conditions, but mostly it is a forgotten disease.

Subclinical cardiovascular disease: new hypothesis for predictive factors

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Cardiovascular disease is the most common cause of death in developed and developing countries. The Framingham risk score has been used as a prediction tool in patients with coronary risk factors, although recent research has shown that it underestimates or misclassifies cardiovascular risk in a subset of population. In particular, it is not well established which patients should undergo invasive evaluation of coronary disease (i.e., angiographic evaluation). Therefore, we tried to define predictive factors of atherosclerotic lesions in a case-control cohort of hypertensive patients and no symptoms of cardiac ischemic disease. We examined 14 consecutive patients (2 women, 12 men, mean age 56 ± 9 years) with grade I-II essential hypertension and at least 3 coronary risk factors (among age, family history for CAD, smoking, overweight, hypercholesterolemia, hypertriglyceridemia, insulin resistance). The patients were in antihypertensive therapy with beta-blockers and/or ACE inhibitors and/or ARBs and/or diuretic. We also measured the following parameters: systolic and diastolic blood pressure in supine and upright position, systolic and diastolic blood pressure in tilt up, heart-rate, height, weight, BMI. In all patients we evaluated the plasma glucose, creatinine, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides and, to rule out secondary causes of hypertension, measured: renin in supine and upright position, aldosterone in supine and upright position; 24-h urine collection for determination of metanephrines, normetanefrine, vanillylmandelic acid. All patients underwent ECG and echocardiography (ASE guidelines). According to the last guidelines for the appropriate use of cardiac computed tomography (CCT), patients were scanned with low-dose-gated multislice helical computed tomography angiograms of the chest. As results, we detected in 7 out of 12 the presence of coronary plaques. Among the glycometabolic and clinical parameters evaluated, we found that only overweight ($p = 0.003$) and Left Ventricular Hypertrophy (LVH; $p = 0.009$) were independent predictors of coronary lesions. In conclusion, our study showed that in patients with low-to-intermediate risk of cardiovascular disease, the presence of overweight and/or LVH should encourage a more invasive evaluation of coronary circulation.

An unusual diagnosis for a common symptom

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Case Presentation: A 54-year-old woman was admitted to our ward for a 3-month history of progressive dyspnea without other associated symptoms. As with all undifferentiated symptoms, a carefully taken history and physical examination are important because this approach yields clues, if not the actual diagnosis, in many cases. The patient reported 50 cigarettes/day from the age of 14 and she was on treatment with ACE inhibitors for hypertension. The physical examination on admission revealed only clubbing. Taking in account that the most common organic causes of dyspnea are cardiac and pulmonary disorders, a diagnostic work up was performed. Electrocardiogram and echocardiogram did not disclose significant alterations. The respiratory function tests, instead, showed mild mixed ventilatory deficit, reducing the spread of the alveolar-capillary CO. Laboratory examination revealed only hypoxemia. Plain radiograph showed diffuse interstitial pattern of reinforcement of the reticulo-nodular type. High-resolution computed tomography imaging of the chest revealed diffuse and marked thickening of the pulmonary reticulo-micronodular in appearance with multiple cystic cavities some of which show thicker and thinner walls and multiple nodules in a predominantly upper lobe of both lungs, suggestive of Pulmonary Langerhans' cell histiocytosis (Figure 1). The bronchopulmonary lavage, to test other alternative diagnosis for interstitial lung involvement, revealed the presence of 9 % CD1a-stained cells that confirmed the diagnosis. Pulmonary Langerhans' cell histiocytosis is a rare disease strongly correlated with smoking and besides quit smoking a specific therapy is not yet available.

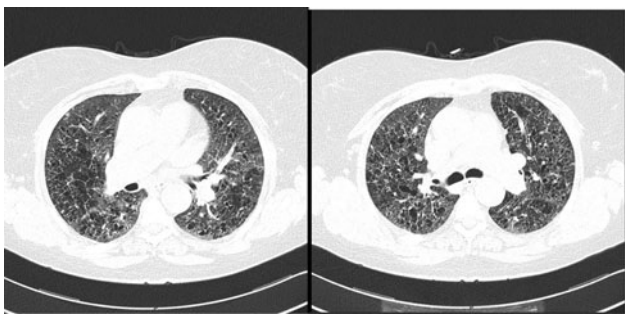

Fig. 1 High resolution computed tomography scans of the chest show multiple small, irregularly-shaped, cysts of varying sizes with thin walls scattered throughout the lungs but predominantly seen in the upper lung fields

A patient with pulmonary embolism presenting as non-ST elevation acute coronary syndrome

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A 81-year-old woman was admitted to the Department of Internal Diseases at Second University Hospital in Naples on account of mild chest pain unrelated to physical activity and accompanied with fatigue and difficult breathing. These complaints follow up to an episode of acute dyspnoea with central chest tightness occurred 3 days earlier and treated at home with oxygen therapy, bronchodilators and diuretics. She had smoked 10–15 cigarettes a day for the preceding 65 years and her medical history was significant for longstanding hyperlipidemia, hypertension, and renal insufficiency. Moreover, she had been diagnosed with deforming arthritis and COPD.

On admission her blood pressure was 115/85 mmHg, pulse 78 beats/min and regular, respiratory rate 30 breaths/min, and body temperature 37.5 °C. Her mental status was alert and cooperative. Cardiac examination revealed a grade 2 to 3 early-peaking systolic murmur at the lower left sternal border. No jugular venous distension was noted. Chest wall was clear bilaterally on auscultation. Findings from the abdominal examination were unremarkable. The patient's extremities were warm with normal pulses. Ankles were mildly swollen and tender. The 12 lead ECG showed subtle ST elevation ($\sim$ 1 mm) in the leads V2 and V3, and inverted T waves in the right precordial and inferior leads.

Laboratory data revealed near-baseline serum electrolyte and CPK levels and unremarkable complete blood cell count.

Creatinine level was mildly elevated (2.1 mg/dL), Troponin I was 0.07 ng/mL (cut off of normal range 0.06), myoglobin 100.1 ng/mL (normal range 0–70) and LDH 745 U/L.

On the basis of clinical presentation, ECG changes, and blood tests, non-ST segment elevation acute coronary syndrome was diagnosed and arrangements were made for emergency cardiac catheterization and primary coronary intervention.

Looking forward, a bedside echocardiogram detected some features of right ventricle pressure overload: right ventricle dilatation (41 mm), displacement of the interventricular septum towards the left ventricle, functional tricuspid valve regurgitation (grade II/III) and significant pulmonary hypertension (62 mmHg). There was no regional abnormality in left ventricular contraction but a global impairment of systolic performance (ejection fraction 48 %). With our surprise the echocardiographic image was suggestive of pulmonary embolism. The diagnosis was confirmed by contrast-enhanced CT pulmonary angiogram which demonstrated enlarged pulmonary trunk and multiple contrast defects in the lumen of the left and right pulmonary arteries extending into the lobe arteries.

Arterial blood gas analysis while breathing 4 L of oxygen via bi-nasal catheter showed pH 7.516, carbon dioxide pressure of 29.3 mmHg, oxygen pressure of 53.6 mmHg, bicarbonate concentration of 25.5 mmol/L and saturation of 89.7 %. Ultrasound of lower extremity veins revealed partially organised thrombi in both popliteal veins.

Intravenous unfractionated heparin was administered as a 5,000 U bolus dose followed by an infusion of 1,000 U/h. Partial thromboplastin time was measured after 1 h, and the infusion was adjusted according to a previously established nomogram. After continuation of intravenous heparin therapy, the patient's condition stabilized. During the remainder of hospital stay she was hemodynamically stable and, apart from the day of admission, did not complain of chest pain. Five days after presentation, a second echocardiogram revealed reduction of the right ventricular cavity size and a decrease in estimated pulmonary artery pressures. Likewise, all cardiac enzyme markers normalized and the anterior ST-T interval changes resolved without the occurrence of pathologic Q waves.

In a few days heparin infusion was substituted with warfarin and, once the INR was in the therapeutic range, the patient was allowed to go home and was advised to continue on warfarin for 6 months. A follow-up electrocardiographic and echocardiographic examination was advised after 3 months.

Necrotizing fasciitis caused by *Pseudomonas aeruginosa*

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Introduction: Necrotizing soft tissue infections (NSTIs) are a group of diseases characterized by acute inflammation of skin, dermis and subcutaneous tissue, often associated with systemic symptoms such as fever, illness and shivers. NSTIs include necrotizing cellulitis, adipositis, fasciitis and myositis/myonecrosis. Group A beta-haemolytic *Streptococcus* (GABHS) is the most common aetiological agent; however, a wide spectrum of other organisms have been recovered, such as *Staphylococcus* spp, *Pseudomonas*, *Bacteroides*, *Clostridium*, *Peptostreptococcus*, enterobacteriaceae, coliforms, *Proteus* and *Klebsiella*. We present the case of an old man with upper lip necrotizing fasciitis due to *Pseudomonas aeruginosa*.

Case Report: A 70-year-old Italian man with gastric adenocarcinoma treated with surgical intervention (Billroth II gastrectomy) and adjuvant chemotherapy with 5-fluorouracil (5-FU) and folinic acid (AF) was admitted in August 2011 to the Internal Medicine Department of our hospital with a history of severe chemotherapy-induced nausea and vomiting.

Six days after admission, the patient showed a pustular skin lesion on the left upper lip, perioral erythema with local edema, and necrosis of floor of the mouth, hard palate and gums; he also complained about exhaustion, drowsiness and increasing pain over the left upper lip.

A presumptive diagnosis of necrotizing fasciitis was made, and the patient was immediately administered with intravenous ciprofloxacin and clindamycin as empirical treatment, a lip swab and an urgent facial skeleton computed tomography were required. The lip swab grew *P. aeruginosa*, which was sensitive to levofloxacin, ciprofloxacin, clindamycin, gentamycin, tobramycin, amikacin, cefapime, ceftazidime, colistin and piperacillin/tazobactam. The computed tomography revealed diffuse soft tissue imbibition of submandibular and malar regions bilaterally, including the root of the nose.

The patient was controlled closely; the following day, the body temperature returned normal and the face deflated. In view of the clinical improvement in his local and systemic condition, the patient was continued on antibiotic therapy with ciprofloxacin and clyndamicin for other 5 days instead of changing to a different culture-sensitive antibiotic and medications with 2 % aqueous eosin solution on the external necrotic lesions. Five days later, another lip swab was made and it showed the persistence of *Pseudomonas*, which was sensitive only to colistin; the patient, therefore, was started on an intramuscular colistin bolus.

After 16 days by the admission, the patient refused to undergo emergency wound debridement for removing the necrotic areas (which is mandatory in these cases), and decided to discharge against the doctors' advice.

Discussion: Monomicrobial necrotizing fasciitis due to *Pseudomonas aeruginosa* is extremely rare; up to now, thirty-seven cases are described in the literature, with an overall mortality rate of 30 %. Perineum and ocular adnexa are affected in the most of cases, but the infection can develop in any part of the body. The most reported risk

factors are diabetes, alcoholism and malnutrition in adult patients, congenital immunodeficiency and chemotherapy for malignant haematological neoplasms in children.
Early diagnosis and prompt aggressive medical and surgical therapy are indispensable for the management of this potentially fatal disease and the combination of both approaches appears to reduce the mortality rate.

"Noli me tangere": a cardiac mass not suitable for the surgeon

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A 75 year-old woman was referred to our ambulatory of cardiovascular prevention for metabolic syndrome. Her clinical history was remarkable for high blood pressure since 1993 on current treatment with irbesartan 150 mg and amlodipine 10 mg. Physical and laboratory findings are summarized in Table 1.
To better characterize her subclinical organ damage, electrocardiogram, carotid doppler ultrasound and echocardiogram were performed. An unexpected finding was revealed by transthoracic echocardiography (TTE): a disomogeneous mass of approximately 20 × 20 mm, with echogenic border, localized just behind the atrial side of the posterior mitral leaflet, without significant mitral regurgitation, was shown. Other remarkable echocardiographic findings were: septal hypertrophy (13 mm) and first degree diastolic disfunction.
To better characterize the mass a transesophageal echocardiographic examination (TEE) was performed. The exam confirmed the presence of a disomogenous, pedunculated mass in the postero-lateral left atrial wall, just above the posterior mitral valve ring. The diagnosis was atrial myxoma and the patient was referred to the surgeon for removal.
Nevertheless two echocardiographic findings were not very consistent with the diagnosis of atrial myxoma:

1. Postero-lateral left atrial wall is not a typical site of atrial myxoma, usually localized in the interatrial septum.
2. Distinct echogenic border due to calcification is not a common finding in atrial myxomas.

The patient was thus sent to another referral center for echocardiography and cardiac surgery. TTE 2-D and 3-D were performed. The mass was described as a large (23 × 21 mm, 5 ml of volume), round mass of disomogeneous echodensity with sharp borders, with a central echofree area partially surrounding the posterior mitral annular ring (Figs. 1 and 2). The mass was described as fixed. The diagnosis was "Caseous calcification of mitral annulus (CCMA)". Echocardiographic follow-up every 6 months was scheduled; at the first control the mass resulted unchanged.
CCMA is a rare and benign echocardiographic finding, variant of the very common mitral annular calcification. Differential diagnosis is with other cardiac masses such as malignant tumors, thrombi, myocardial abscesses and, of course, myxomas. An accurate diagnosis is critical because CCMA, unlike most cardiac masses, doesn't need any therapy unless it is associated with severe valvular dysfunction. Current literature data suggest that TTE is essential for the diagnosis; the use of TEE for a better characterization of the mass is controversial; cardiac magnetic resonance has recently been proposed as effective diagnostic tool.

Table 1 Physical and laboratory findings

BMI	40.2 kg/m^2
CV	116 cm
TC	174 mg/dl
LDL	98 mg/dl
HDL	44 mg/dl
TG	159 mg/dl
PA	140/85 mmHg
Glu	100 mg/dl

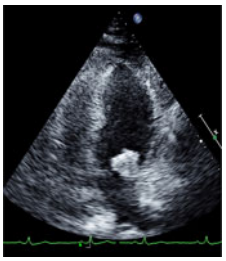

Fig. 1

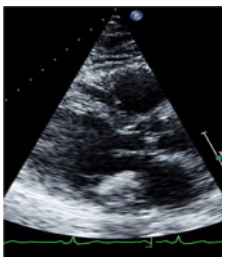

Fig. 2

Balint's syndrome in subacute HIV encephalitis

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Case Report: The patient was a 65 year old schoolteacher with AIDS stage IV who had already suffered from two opportunistic pneumonias a year ago, but who had not previously experienced any neurological sequelae. She had been infected through unprotected sexual intercourse and had never used intravenous drugs. Therapy with zidovudine was initiated only 10 days before admittance. She was a heavy smoker with 80 pack-years. She was admitted because of visual disturbances. She had already felt a progressive weakness of her right arm for 3 weeks, when she noticed an inability to perceive the properties of standing objects or persons some days before admittance. She had first realized this when she recognized only

moving objects on television. In daily life, she could not distinguish between people and objects if they did not move. However, she still recognized familiar people, even though she was puzzled by not being able to see specific features, such as the colour of their hair or eyes or hairstyle. She thought she remembered newly introduced people mainly through such hints as their walk or voice. She was totally unable to read anything, even large newspaper headlines. When walking she often did not perceive obstacles on either side and repeatedly walked into them, especially into glass doors. The patient was able to walk without aid but preferred to go along the walls to orient herself. She found her way around in the hospital but was unable to find her bedroom as she could not read the room number. Thus a plastic bag was attached to the door which she would search for. She could eat by herself but could not cut the food because she could not find it with the knife. She could pour coffee into a cup without spilling it but had to adjust the positions of the cup and the pot carefully with tactile control before pouring. On neurological examination, there was a right homonymous hemianopsia both in the upper and lower quadrant with preserved perception of movements of the whole hand of the examiner, but not off line movements such as the fingers. Her gaze seemed void in that her eyes moved around in search of eye contact with the examiner or when trying to fixate an object. Once she had fixed an object, her eye movements were full and she could smoothly follow it with her eyes. However, when trying to "catch" an object in her visual field with her eyes, the saccades were severely dysmetric to both sides (ocular apraxia). No other disturbances of cranial nerves were observed. There was a slight weakness of the right arm, both for proximal and distal muscles. Sensibility of the right arm and especially the right hand was diminished for all qualities, and she did not recognize objects put into her right hand. There was no upper limb ataxia on either side in the finger-to-nose trial with closed eyes. However, with visual control, she displayed severe ataxia of both arms when trying to point to an object with her index finger (optic ataxia). With both arms, this was more pronounced in the right hemispace. Muscular strength and sensibility of the legs were intact. Tendon reflexes were normal and symmetrical, and the plantar response was flexor on both sides. On mental status examination this left handed woman was oriented for space and time. Language functions such as spontaneous speech, auditory comprehension, repetition, word list generation, comprehension of words spelled out to her, and naming of environmental sounds were intact. Oral calculations were correct. There was no ideomotor apraxia of the face or the arms and no finger agnosia. Verbal immediate and short term memory were intact. In a line cancellation test, she did not show hemispatial neglect, that is, she succeeded in marking all lines despite great difficulty in adjusting the position of the pencil to the lines. Her problems were primarily visual: she wrote with correct sequences of letters with both her right and left hand but had great difficulties in aligning the letters. If she briefly interrupted the writing she could not find the end of what she had written previously and therefore could not keep to one line. There was no prosopagnosia: the patient knew most of a series of famous people on photographs and recognized the examiner after several hours even though he was wearing different clothes from those during the examination and was neither moving nor speaking. Facial emotions on photographs were recognized. She could distinguish, match, and name colours, even though sometimes she misjudged their brightness. She recognized drawings of single thin straight lines or a circle. However, if the drawing consisted of several lines that were crossed or if the lines were dashed (needing mental completion), she was totally incapable of identifying any form or of following it with a pencil. A CT scan revealed a hypodensity in the parieto-occipital region on the left side without contrast enhancement. An MRI showed extensive lesions, which involved mainly the white matter, in the occipital lobes with extension into the temporal and parietal lobe on the left side and into the temporal lobe on the right side. Furthermore, a small subcortical lesion was seen in the area of the Rolandic fissure on the left side. The lumbar tap yielded a slight pleocytosis with 12 cells per mm3, mainly lymphocytes, while the protein content was normal. Serologic and microbial studies were negative for cytomegalovirus, toxoplasmosis, cryptococcosis, and mycobacteria. The patient continued to receive zidovudine. On a follow up examination 2 months later, her visual perception had significantly improved and she was now able to recognize correctly all the items. Her ability to read was still much impaired but she succeeded in reading in a letter-by-letter fashion a whole text. The patient received a Balint's Syndrome diagnosis. Further follow up was not possible.

Congenital portal systemic encephalopathy misdiagnosed as vascular dementia

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Case Report: The patient, an 86-year-old man, developed cognitive dysfunction approximately 3 years earlier. He received a diagnosis of vascular dementia. His medical history included previous transient loss of consciousness, which has been interpreted as transient ischemic attacks.

The patient was admitted to our Department with a left femoral neck fracture caused by a fall, and bipolar hemiarthroplasty was performed. Speaking with physicians, the patient's family reported that the frequency of these transient loss of consciousness had gradually increased in recent months. The patient had no history of abdominal surgery. On examination, he tended to be somnolent, his pulse rate was 76/min, his blood pressure was 140/74 mmHg, his respiration rate was 25/min, and there were no abnormalities of the chest or abdomen. Brain computed tomography (CT) showed age-appropriate cerebral atrophy, but there was no evidence of lesions such as cerebral hemorrhage or cerebral infarction that might cause disturbance of consciousness. There were no electrocardiogram anomalies. Blood tests performed at the time of admission revealed mild anemia (hemoglobin, 12.0 g/dL) and hypoalbuminemia (albumin, 3.1 g/dL), but there were no electrolyte or blood glucose abnormalities that might be the cause of the disturbance of consciousness. On blood gas analysis, there was no hypoxemia, carbon dioxide narcosis, or acidosis. The only abnormal finding was elevation of the serum ammonia level to 187 μg/dL. Hepatic encephalopathy was suspected, but Hepatitis B s antigen and Hepatitis C virus antibody were both negative, and total bilirubin (0.8 mg/dL), prothrombin activity (85 %), cholinesterase (277 IU/L), aspirate aminotransferase (15 IU/L), alanine aminotransferase (12 IU/L), alkaline phosphatase (295 IU/L), gamma glutamyl transpeptidase (35 IU/L), as well as the platelet count (17.7 × 104/mm3) and type IV collagen 7S (5.2 ng/mL), were all within their normal ranges. Thus, there was no evidence of chronic hepatitis or liver cirrhosis. Upper abdominal enhanced CT showed mild atrophy in both lobes of the liver, but the surface of the liver was smooth and showed no morphological changes suggestive of liver cirrhosis. The umbilical part of the portal vein was narrow, there was no clear splenomegaly, and there were no findings indicative of portal hypertension. In addition, there was no evidence of intrahepatic or extrahepatic shunt that could have caused encephalopathy. Therefore, lower abdominal enhanced CT was performed to screen for possible extrahepatic shunts in the lower abdomen, and a shunt connecting with the inferior vena cava was found in the lower right abdomen.

That site was diagnosed as an extrahepatic portal systemic shunt, and it was concluded that the disturbance of consciousness seen in this patient was actually encephalopathy that was caused by this extrahepatic shunt. Conservative therapy was carried out by administering branched-chain amino acids and lactulose, but there was little improvement in the patient's level of consciousness or serum ammonia level. On superior mesenteric arteriography, the portal vein was not well-visualized, and the meso-caval shunt that had been seen on CT was visualized in the venous phase, and the inferior vena cava was subsequently enhanced via the right gonadal vein. On the other hand, using a retrograde approach from the inferior vena cava, the shunt was partially enhanced via the right gonadal vein, and BRTO was performed for this shunt. A total amount of 17 mL of 5 % ethanolamineoleate with iopamidol was gradually injected into the shunt. The inflated balloon catheter was kept in place for 3 h. Enhanced CT performed after the BRTO showed no shunt and confirmed that good blockage had been achieved. The serum ammonia level decreased markedly to 77 μg/dL within 24 h after this treatment, and the level of consciousness also improved. The shunt was successfully thrombosed by balloon occluded retrograde transvenous obliteration on lower abdominal enhanced CT (circle) was discontinued. The cognitive dysfunction that had been observed earlier also disappeared, the patient's dietary intake improved, and there was improvement in both the anemia and the hypoalbuminemia. The patient was then followed for more than 1 year, and there were no further episodes of loss of consciousness.

Presenile dementia: a case of Hashimoto's encephalopathy

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Case Report: A 57-year-old woman presented in 2012 with generalized seizure. She had a medical history of thyroid disease, for which she was taking thyroxine supplement after radioactive iodine treatment, and an insidious onset of dementia from the age of 51 years, resulting in her early retirement 2 years later due to deterioration in work performance. Her family history was notable as her elderly mother also had dementia. At the age of 53 years, she received medical attention for cognitive impairment, and scored 22 of 30 in the Mini- Mental State Examination (MMSE). Dementia workup revealed normal blood test results, including thyroidstimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4). Computed tomography (CT) of the brain showed atrophic changes over the frontal region, while electroencephalogram revealed non-specific findings. She was diagnosed with AD and was treated with rivastigmine 3 mg twice a day. However, her global cognitive function continued to decline rapidly, with a decrease in MMSE score to 19 in 6 months, and her dependency for activities of daily living and self-care increased. She also demonstrated gradual personality changes from outgoing and sociable to withdrawn and apathetic. About 6 months prior to the index hospital admission, her motor function and activities of daily living became disturbed, with gait abnormality that confined her to a wheelchair and she was mentally dull with akinetic mutism. Her feeding was poor and she became incontinent of urine. The patient was admitted to the Department of Cardiovascular, Respiratory, Nephrological and Geriatric Sciences, "Umberto I" Policlinico di Roma after the generalized seizure, and a thorough examination and investigations for encephalopathy started. Magnetic resonance imaging (MRI) revealed deep white matter ischaemic changes and mild cortical atrophy. The high thyroid autoantibody titres (antithyroglobulin, 1:1,280; antimicrosomal, 1:1,600) supported the diagnosis of HE, even though the patient was clinically and biochemically euthyroid. She started steroid therapy and showed a satisfactory response in subsequent weeks, being seizure-free and regaining ambulation and better interaction and awareness of her surroundings. Longer follow-up is needed for longitudinal observation on the progress of her cognitive function.

Discussion: This patient was initially diagnosed with early-onset AD for its compatible manifestations, including insidious pattern of onset, progressive deterioration over time, clinical presentation of cortical dementia, and the unremarkable findings of the preliminary organic workup. The emergence of motor impairment (gait abnormality), change in consciousness level (mental dullness and akinetic mutism), and the episode of seizure showed the clinical picture of encephalopathy, which initiated further investigations. Early-onset AD often runs in families. For this patient, the absence of a family history of early-onset dementia, plus the lack of response to the cholinesterase inhibitor, complicated the diagnosis of early-onset AD. Thyroid disease has a well-known detrimental effect on the neurological system, and hypothyroidism is a cause of reversible dementia. In this patient, thyroid screening (TSH, T3, and T4) was performed as part of the routine dementia workup, but the results were normal. Such negative findings might lower the index of suspicion for biochemical euthyroid conditions, resulting in a delay to investigation for HE. Given the links between past history of thyroiditis, female sex, and HE with investigation negative early-onset dementia, these authors suggest performing antithyroid antibody assay to include or exclude HE at an earlier stage of illness. The aetiology and pathogenesis of HE remain unclear. There is no evidence to suggest that the antithyroid antibodies have a pathogenic role and their levels do not correlate with the clinical course or response to treatment. Several different hypotheses have been suggested, including localized cerebral oedema, autoimmune vasculitis, toxic effect of thyrotropin-releasing hormone, and an immunopathological basis similar to relapsing acute disseminated encephalomyelitis. In retrospect, the atypical features of rapid progression and motor involvement could have indicated HE at an earlier stage of illness. Most patients respond to treatment with steroids. Initial treatment with high-dose steroids in the form of oral prednisolone 1 mg/kg or intravenous (IV) methylprednisolone 1 g/day has been suggested. This patient was diagnosed to have HE which, despite delayed treatment for some years since the onset of neuropsychiatric symptoms, has shown some reversion of cognitive impairment. In conclusion, HE should be considered a differential diagnosis in female patients presenting with presenile dementia, especially in the presence of a history of thyroid disorder.

Tricuspid valve endocarditis complicated by septic pulmonary embolism in an intravenous drug user

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A 34-year old male with a history of heroin intravenous drug use, was admitted to the Internal Medicine ward of our hospital complaining of chest pain, cough and dyspnoea. On physical examination, body temperature was 39 °C, blood pressure was 70/40 mmHg, pulse was 104 beats/min. The lung auscultation revealed basal bilateral inspiratory crackles, no murmur was audible over the precordium, abdominal and neurologic examinations were normal. The electrocardiography showed a S1Q3T3 pattern, chest X-rays revealed

multiple bilateral patchy opacities. Laboratory findings included a D-dimer of >2,000 ng/ml, an ESR of 100 mm/h and leukocytosis (WBC 9,400/μl, 92 % neutrophils); platelets count was 13,000/μl. Transthoracic echocardiography showed a mass at the septal leaflet of the tricuspid valve associated with moderate tricuspidal regurgitation. A presumptive diagnosis of infective endocarditis complicated by septic pulmonary embolism was made. Two sets of blood cultures were positive for *Staphylococcus aureus*. After a 6 week course regimen with intravenous ampicillin/sulbactam plus gentamycin, chosen initially as an empiric approach and later on as the treatment based on susceptibility tests, the patient recovered uneventfully.

Right-sided endocarditis accounts for only 5–10 % of cases of infective endocarditis and is overwhelmingly a disease of injection drug users. It has long been hypothesized that repetitive bombardment with particulate matter present in injected material may damage cardiac valves, particularly the tricuspid valve, the first one to screen intravenously injected substances and that addictive drug itself may cause endothelial damage, priming a valve for endocarditis; besides, drug-induced pulmonary hypertension may cause increased pressure gradients and turbulence leading to right-side valves disfunction and subsequent damage to valve leaflets. The presenting clinical features of right and left sided endocarditis are different: in right sided endocarditis immunologic and peripheral vascular phenomena are characteristically less common; rather, symptoms and complications arise from the involvement of the pulmonary vasculature by multiple septic pulmonary emboli. Hence, dyspnoea, chest pain, cough and haemoptysis may be presenting features; moreover, it should be pointed out that right side murmurs are more difficult to detect and that injection drug use and septic pulmonary embolism are listed as minor criteria in the Duke scheme. It could then be argued that this important diagnostic features are somewhat underweighted in this particular setting. Thus, in drug users, the conjunction of fever, respiratory symptoms and multiple pulmonary infiltrates on chest radiography, even in the absence of heart murmurs, should always prompt a search for right side endocarditis.

Fever and pain on walking

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A 61-year old male patient suffering from dyslipidemia treated with statin and suffering back pain, abdominal pain, high fever and fatigue presented to the Department of Clinical Medicine at the University Federico II of Naples. He had undergone a TRUS-guided prostate biopsy a week before because of high serum prostate specific antigen levels (PSA 10.7 ng/mL). Antibiotic prophylaxis (ciprofloxacin 500 mg) had been performed a day before the procedure. The histopathological features of 12 biopsy specimens had shown benign prostate tissue.

High fever started with shivers 1 day after the prostate biopsy and the back pain a few days later. He had been treated with analgesic drugs and antibiotic (nebicine) for a week.

On physical examination he complained of severe pain at the level of L2–L4 spinal column associated with muscle cramps in legs and abdominal pain on palpation; neurological examination was negative except for a positive Lasègue bilaterally, particularly on the right. The patient still had septic fever.

Laboratory tests showed neutrophilic leucocytosis (white cells 12,400/mL and neutrophils 9,900/mL), high levels of C- reactive protein (CRP 17.8 mg/dL) and the value of CPK was at the higher limits (205 U/L). Serological tests for *Brucella*, *Salmonella* and PPD, blood and urine culture were normal.

Chest X-ray and echocardiography were negative. Lumbo-sacral spine X-rays showed marked reduction in the height of the L1–L3 discs.

Abdominal ultrasound showed abscesses in the middle third of the right ileopsoas muscle (36 × 34 × 51 mm) and in the proximal third of the left ileopsoas muscle (35 × 20 mm) concomitant with hypoechogenicity of the middle lobe of prostate. At entry in the hospital, clinical presentation and laboratory analyses were typical of an acute infection.

The first diagnostic hypotesis was a septic fever after TRUS-guided prostate biopsy complicated to abdominal abscesses and spondylodiscitis. Other possible diagnoses were: neoplastic infiltration of the bone, degenerative disk disease, intra-osseous disk herniation, high levels of CPK after use of statins. These hypothesis were excluded on the basis of clinical, laboratory and radiological findings.

To support our first diagnostic hypothesis the patient, thereafter, underwent MRI, with contrast enhancement, of the lumbo-sacral spine. Pre and post-contrast multiplanar images obtained by T1-T2 weighted turbo spin echo and STIR sequences showed widespread impregnation of the upper portion of L3 and the lower portion of L2 involving the epidural anterior tissue and lateral recesses bilaterally, compressing the spinal roots as well as the psoas muscle where abscesses were detected.

These findings were consistent with diagnosis of spondylodiscitis L3–L4. Medical interventions may lead to iatrogenic spondylodiscitis either directly by inoculation or indirectly by hematogenous dissemination.

Patient denied his consent to the biopsy of the column L3–L4 (it was the Gold Standard for the diagnosis).

A broad spectrum antibiotic therapy, using Rifampicin 600 mg iv, ceftazidime 2 g twice a day iv, teicoplanin 400 mg iv, was thereafter started for 6 weeks. Patient started also to wear a metallic girdle.

Fever remitted in 24 h after starting antibiotic therapy. Fifteen days later patient repeated ultrasound abdominal ultrasound that showed resolution of abscesses in the right and left ileopsoas. Inflammatory markers (CRP, white blood cells and neutrophils), controlled bi-weekly, declined over time. Also abdominal pain, back pain and leg pain were gradually reduced.

After 6 weeks of intravenous antibiotic therapy with negative PPD and TIBI test, patient started treatment with ciprofloxacin 500 mg orally twice daily and teycoplanin 400 mg fl i.m. for 6 months: liver enzymes, renal function and inflammatory markers were monitored at weekly intervals.

At the end of the antibiotic treatment patient was asymptomatic and laboratory tests showed normal levels of white blood cells and of C-reactive protein. MRI of the lumbar spine performed again revealed stabilized outcome of the previous infectious episode showing signs of spondylosis associated with structural irregularities of the cortical bone of L3–L4. The discs included in the section L1–L5 had undergone to degenerative process.

The thirsty and sleepy young athlete

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We have studied an 18 yr old man admitted for development of polyuria (7,200 mL/24 h), polydipsia (6,000 mL/24 h) with nocturia. He referred recurrent otitis infections in infancy, treated with amoxicillin and clavulanic acid. Since May 2011 patient started

competitive sport (athletics) and in November 2011 appeared abrupt thirsty and polyuria, initially supposed to be related to sport activity. Polydipsia (6 L of water/24 h with water requirement also during the night) and polyuria (about 6–7 L/24 h) persisted despite discontinuation of sport activity in April 2012, forced by degenerative lumbar protruding disc disease with water tone reduction. Nocturia 8–10 voiding/night, sleeping discontinuation and daytime drowsiness also developed, associated with a reduction of appetite and consequent weight loss (BMI 17.6) due to the large amount of water introduced. He did not refer drugs assumption (FANS, anesthetics, nephrotoxic drugs) neither surgical intervention nor trauma. At admission in May 2012 he presented BP 120/70 mmHg and HR 72 bpm, he was apyretic, dehydrated in appearance with no evident neurologic deficit. The major laboratory parameters showed: RBC 4.690 $\times$ 10^3/mm^3, WBC 5,690/mm^3, Hb 14 g/dL, Ht 41.6 %, glycemia 72 mg/dL, creatinine 0.95 mg/dL, BUN 14.5 mg/dL, uric acid 4.9 mg/dL, Na 144 mEq/L, K 4.2 mEq/L, Cl 105 mEq/L, Ca 9.7 mg/dL, Mg 2.4 mg/dL, urinalysis: pH 7, specific gravity (uSG) 1002, glucose absent. The 24 h urine volume was 5.4L. Furthermore ipothalamic hormones, TSH, FT3 and FT4, ANA, c/p-ANCA, ds-DNA, ENA antibodies, IgG/A/M, C3 and C4 resulted in normal range. Mantoux test was negative. Polycystic kidney disease was excluded by ultrasonography. Normal values of glycemia, glycosuria and HbA1c 5.1 % excluded the hypothesis of Diabetes Mellitus, firstly considered. Simultaneous measurements of serum osmolality (305 mOsm/kg), urine osmolality (180 mOsm/kg) and serum electrolyte were the initial step to diagnosis of Diabetes Insipidus (DI). Polyuria, polydipsia with nocturia associated with a urine osmolality lower than plasma osmolality and increased serum sodium were indeed suggestive of DI, excluding primary polydipsia.

Results of fluid test deprivation are showed in table, associated with a weight reduction <5 %. BUN, uric acid, Hb, Ht, Na and Ca showed a gradual increase during the test, in agreement with a state of hemoconcentration.

Fluid deprivation did not achieve a urine concentration >700 mOsm/kg, supporting the diagnosis of DI, but the increased urine concentration >300 mOsm/kg suggested a partial type of DI, supported by the diuresis amount <10 L/24 h. A low dose of desmopressin administration (5 μg) resulted in immediate disappearance of nocturia, decrease in diuresis to 1.04 mL/min daytime and uSG increase. These results proved the diagnosis of partial type of central DI. The contrast-enhanced brain MRI study subsequently requested, did not reveal masses, granulomas or other evident lesions.

Central DI occurs by 5–6 years old of age but may manifest as late as the third decade. Our case seems to be central form DI that is considered idiopathic in 25–30 % of cases. The partial form is more rare but we cannot exclude a role for the sport activity as cause of mild and unrecognized cerebral trauma. Anti-diuretic hormone (ADH) assay would be the gold standard but is not routine examination and it's hardly viable. Fluid deprivation test is considered accurate for the diagnosis.

Table 8-h test of water deprivation showed

Time (h)	0	1	2	3	4	5	6	7	8
Urinary volume (ml)	0	450	500	350	300	100	200	100	100
Serum Osmolarity (mOsm/kg)	285	291		295		297	295		298
Urinary osmolarity (mOsm/kg)		113		129		234	283	279	353
Specific gravity	1,002								1,015

A metabolic syndrome with recurrent syncopal episodes

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Caucasian male, 60 years old

Family history: the mother underwent to surgery for brain neoplasm at 46 years also numerous intervention for dental treatment. Physiological history: negative. Occupational history: numerous injuries at work.

Distal medical history: metabolic syndrome (obesity, diabetes mellitus, arterial ipetensione, hypertriglyceridemia, hypoalphalipoproteinemia), hypertensive heart disease with atrial fibrillation (AF) paroxysmal (coronary arteries with a previous coronary angiography examination), bleeding from a peptic ulcer, many syncopal episodes never investigated.

Recent medical history: admitted to the ward after prolonged orthostatic syncope, without prodrome, with urinary and anal sphincterial incontinence and AF with high ventricular response.

Objectivity at the entrance to the ward: obesity with a prevalent visceral manifestation, facies characterized by frontal bossing, hypertelorism, and teeth in poor condition, high ventricular rate in AF, toe systolic murmur 2/6, hepatomegaly at 6 cm from the right rib, ulceration on the right foot, macular lesions as capillaritis on lower parts of limbs, high blood pressure 170/105 mmHg.

Blood chemistry: col. tot./HDL/Trig. 334/21/929 mg/dl, GGT 129 U/l, glucose 434 mg/dl, hemoglobin A1c 14 %.

Laboratory tests: ECG: AF at average ventricular rate;

CXR: negative echocardiogram: left ventricular concentric hypertrophy with preserved global contraction; Abdomen sonography: liver enlarged and brilliant as massive steatosis;

The clinical picture was therefore compatible with the presence of metabolic syndrome with diabetes mellitus type II uncompensated, dyslipidemia, blood pressure hypertension with hypertensive heart disease.

The study of recurrent syncopal episodes was completed by performing brain CT scan: marked calcification of the falx and the tentorium, moreover lytic bone lesions were detected in the right mandibular branch.

Further diagnostic CT scan of the massive facial: confirmation of lytic bone lesions with numerous lesions borne by the cortex of the maxillary and also with mandibular multiple keratocysts.

Diagnosis of Gorlin syndrome or NBCCS (Nevoid Basal Cell Cancers) was suspected [1].

The measurement of head circumference was 60 cm.

For the diagnosis confirmation was sent a blood sample to perform the genetic test at a specialized laboratory. The molecular analysis with PCR amplification was positive with the identification of the affected gene on chromosome 9 PTCH1.

It is an autosomal dominant genetic disorder with a high degree of penetrance (approximately 97 %).

The cause is a germline inactivating mutation involving the human homolog of the Drosophila PTCH1 (patched) gene, which is located on chromosome 9q22.3 [2].

We decided for the metabolic syndrome and cardiac rhythm treatment and follow-up for the Gorlin syndrome after family members alert (son and sister).

The possible evolution of genetic disease could be treated with a new drug recently approved by FDA, vismodegib (GDC-0449) an oral inhibitor of the hedgehog pathway that has been used for patients with NBCCS. Resolution of odontogenic keratocysts has been reported in a patient treated with vismodegib [3].

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An atypical case of constrictive pericarditis

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A 23 years old man came to the Emergency Department complaining lower limbs edema, abdominal distension and dyspnea. Five months before, he had had an acute thoracic pain and 1 month later he had developed puffy ankle. He started furosemide 25 mg daily without benefits. Two months before hospital admission he complained exertional dyspnea and palpitations. In the past history some attacks of questionable asthma in infancy was recorded. He was admitted to an other hospital, where chest X-ray showed bilateral basal pleural effusion and abdominal ultrasound sowed ascites and inferior cava distension, whereas cardiac ultrasound documented a paradoxical movement of intraventricular (IV) septum, dilated hepatic veins, normal Pulmonary Artery Systolic Pressure and systolic function. Pericardial effusion was not present. Thoracic CT scan did not show pulmonary emboli. Endoscopy showed F1 esophageal varices. Hearth failure was diagnosed and higher doses of diuretics were started (furosemide 100 mg and spironolactone 100 mg daily), with a reduction of lower limbs edema. Because of symptoms persistence, he was admitted to our hospital. He was alert, afebrile, tachycardic, with normal level of arterial pressure, respiratory rate at rest and oxygen saturation of 95 %. On examination he had puffy ankle, hepatomegaly, jugular vein distention, crackles on right pulmonary base. Blood cell count showed a mild lymphopenia (0.61×10^9/l; CD4 30 %, CD4/CD8 1.58, CD19 30 %). Inflammatory indexes, aminotransferase, alkaline phosphatase and renal function were normal. Brain Natriuretic Peptide was normal (204 pg/ml), but Gamma-glutamyl transferase was elevated (214 UI/l), with lupus anti-coagulant (dRVV 44.60 s) and E Immunoglobulin (IgE) (3,540 UI/ml). Abdomen ultrasound showed hepatomegaly, inferior vein distention (29 mm), normal resistivity index of hepatic artery and a phasic flux of hepatic veins, which excluded Budd–Chiari syndrome. A new echocardiogram confirmed a hypokinetic right ventricle, paradoxical movement of IV septum, bulging of interatrial septum. In differential diagnosis with constrictive pericarditis we performed a heart Magnetic Resonance (MR): pericardium was very thickened. The cardiac catheterization, during volume expansion, confirmed constrictive pericarditis. Searching for the etiology, TBC was excluded (BK was never found in urine, sputum and bronchoalveolar lavage) as viral myocarditis and sarcoidosis. Searching for high IgE levels, neither *Aspergillus* or other fungal species were present. Autoantibodies were all normal. We lastly looked for Mediterranean fever gene mutations, considering the geographical origin (Calabria) and parents' consanguinity: a single E148Q mutation was found. We concluded for idiopathic constrictive pericarditis; therefore the patient underwent to pericardiectomy, with resolution of all symptoms. At present, 12 months after surgery, patients is asymptomatic.
Conclusions: The diagnosis of constrictive pericarditis may be difficult and it can simulate heart failure. The role of E148Q MEFV mutation must be discussed; in spite of Tel Hashomer criteria were not fulfilled for FMF diagnosis, where usually fever and recurrent serositis are present. Since recently cases of chronic effusive pericarditis has been described in FMF, and the phenotype 2 FMF includes only symptoms of chronic inflammation as amyloidosis, a role for the MeFV mutation cannot be excluded in the pathogenesis of the constrictive pericarditis of this patients without previous pericarditis attacks.

The lower (not always) the better

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The Case: A 38-years-old man was referred to our clinic for hypocholesterolemia and thrombocytopenia. His blood tests showed a total-cholesterol (TC) of 53 mg/dl, high-density-lipoprotein-cholesterol (HDL-C) of 1 mg/dl, triglycerides (TG) of 202 mg/dl, Apolipoprotein A1 (ApoA1) 10 mg/dl and a low platelets count (72,000/μl). He reported erectile dysfunction and no family history of cardiovascular disease. His clinical examination was normal. Ultrasonography showed mild hepatomegaly and steatosis (Hamaguchi Score: 4/6).
History: He reported tonsillectomy and splenectomy due to spontaneous rupture. Splenic histological examination showed the presence of foamy histiocytes and megakaryocytes in the red pulp, suggesting the diagnosis of lipidic thesaurismosis. A bone biopsy and bone-marrow aspiration had been performed, showing a 50 % foamy cells infiltration and a mild hypoplasia, respectively. The lysosomal-enzymes activity tested was normal.
Diagnostic Hypothesis: Lipids levels and past medical history were highly suggestive of a genetic form of HDL deficiency. Two diagnosis were plausible: the presence of Lechitin cholesterol acyltransferase (L-CAT) deficiency or Tangier Disease (TD). Concerning LCAT deficiency, kidney and corneal involvement, typical features of the disease, were investigated and excluded (creatinine plasma levels 0.7 mg/dl, eGFR 126 ml/min/1.73 m^2; 24 h urine collection for proteinuria absent). These findings led us to exclude homozygous and heterozygous L-CAT deficiency.
On the other hand, HDL-C and apo A1 levels were strongly suggestive of an homozygous form of TD Tonsillectomy and hepatomegaly are reported in about 90 % of TD patients and splenic and bone-marrow findings similar to our case have been found in TD, as ABCA1 is expressed in human platelets. Lipid values of the proband's father, sister and two siblings were measured and resulted suggestive of an heterozygous form of TD. To confirm diagnosis, genetic analysis looking at ABCA1 gene-mutation was planned and is still ongoing.
Decision-Making: If TD diagnosis will be confirmed by genetic analysis, should we consider our patient at a higher cardiovascular risk because of the very low levels of HDL-C? How should we follow up the patient and his family members? To date, available therapy targeting HDL-C levels have not been shown to be effective in decreasing cardiovascular risk. There is still uncertainty about mechanisms underlying protective effect of HDL-C, and attainable therapeutic targets are lacking.

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Anomalous skin pigmentation: unmasking a rare syndrome with relevance for the internist

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A 39-year-old, 196-cm-high man, came to our observation with pigmented lesions in lips, gingival mucosa and perioral skin, with otherwise unremarkable clinical history. Peutz–Jeghers Syndrome (PJS) was suspected based on his characteristic pigmentation.
PJS is a rare autosomal dominant disorder, characterized by multiple pigmented macule affecting skin and oral mucosa, as well as by the pathognomonic presence of hamartomatous polyposis in the GI tract. The patient was subjected to instrumental examination in order to confirm PJS diagnosis. Pancolonscopy evidenced no anomalies. Multiple hypo-echogenic nodules were disclosed by thyroid echography which were characterized by FNAB as adenomatous lesions. In the light of these findings, and of the patient's tall stature and skeletal features, the patient was referred for endocrinological examination and appropriate hormonal assays. Hormonal quantitation showed increased levels of growth hormone (GH) and Insulin-Growth-Factor-1, reduced testosterone values, and normal prolactinaemia. Based on these observations, diagnosis of acromegaly was then suspected, which prompted for a contrast-enhanced cerebral MRI.
Brain MRI detected a pituitary adenoma, which led us to suspect Carney Complex (CC) disease. To confirm such diagnostic suspicion, we investigated the eventual presence of myxomatous lesions, by echocardiography. Two independent echocardiographic examinations revealed the presence of a left atrial myxoma.
Clinical diagnosis of CC is confirmed by the presence of two or more major criteria or by one minor criterion with concomitance of a first-degree affected relative. Mutations in the PRKAR1A gene are responsible for this disorder.
Our patient had 4 major criteria: spotty skin pigmentation with typical distribution, cardiac myxoma, acromegaly as a result of GH-producing adenoma, hypo-echogenic nodules on thyroid ultrasound. Therefore, clinical diagnosis of CC could be conformed in our patient. Mutational screening in the PRKAR1A gene is on way.

Neck mass of undetermined nature

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We report a case of 36-year-old that was 10th gestational week in a triple pregnancy at the time of this hospitalization. The patient reported a history of recent in vitro fertilization (IVF) for primary infertility.
She was referred to the local Emergency Department complaining pain and swelling in the right supraclavicular region, thus she underwent an US exam of the neck recording a lymphadenomegaly close to the right sternocleidomastoid muscle, then she was immediately discharged and her care was returned to the general practitioner. Two days later, due to persistence of symptoms, she was evaluated by a gynaecologic specialist. In the suspicion of infectious or haematological disease the patient was admitted to our Hospital to underwent some serologic laboratory test (EBV, Parvovirus B19, CMV, thyroid function tests), an hematologic and endocrinologic consultation.
At admission the pain was in the right side of the neck and it did not limit the cervical range of motion. Palpation revealed a painful induration and erythematous area under the anterior edge of the sternocleidomastoid muscle. The neck showed venous distention on the right side and a small mass of undetermined size in the supraclavicular region.
Examination revealed a patient with normal vital signs.
She had no fever or night sweats. Blood pressure was 110/70 mmHg and oxygen saturation was 98 %. The patient was not tachypneic. Laboratory investigations were within normal limits with the exception of an elevated reactive C protein and mild anaemia.
Obstetric ultrasonography revealed three healthy fetus with normal cardiac activity.
Thus we performed cervical color-doppler sonography disclosed an image consistent with external jugular vein (EJV) thrombosis.
Therefore she has received low molecular weight heparin by sc injections in weight-adjusted doses (100 units/kg BD).
Thrombosis of the external jugular vein is a rare entity with the potential for serious consequences (most of the reported cases have occurred in internal jugular vein). This clinical condition is frequently associated with central venous catheterization, head and neck infections, intravenous drug abuse and compression at the affected site [1].
Most cases of thrombosis after ovarian stimulation with gonadotrophins are a complication of Ovarian Hyperstimulation Syndrome (OHSS) [2]. A hypercoagulable state is created due to haemoconcentration as a result of the escape of intravascular fluid into the third space. There is a rise in blood viscosity and the coagulation factors become concentrated [3]. A hereditary hypercoagulable state is also a risk factor for thrombosis, e.g. activated protein C resistance, antithrombin deficiency and protein C and S deficiency, but our patient was screened for hereditary hypercoagulability and was negative.
While OHSS may be important factor in the pathogenesis of thrombosis it does not precede all cases, may be exist other predisposing factors act to precipitate thrombus formation.
We report a case of unusual and serious thrombosis of the external jugular vein following IVF-ET, indicating the importance of vigilance on the part of all physicians caring for patients who have undergone fertility treatment and the possibility of considering thrombosis of the EJV such another lesion in the extensive differential diagnosis of a mass in the lateral neck.

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A case of hypertensive encephalopathy

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A Caucasian 45-year-old woman was admitted to emergency department for recent onset of progressive deterioration of visual acuity. At admission bilateral papilledema was found, blood pressure was 200/140, heart rate was 76 beats/min, and oxygen saturation was 100 % at ambient air. Physical examination was normal. Ophthalmological examination was normal except for blurring of central vision. Laboratory tests revealed acute renal failure (creatinine 3.5 mg/dl), thrombocytopenia (101,000/mm^3) without anemia (Hb 14.9 g/dl), LDH markedly increased (1,059 U/l) cholestasis signs absent (total bilirubin 1 mg/dl) and normal coagulation tests with an increased d-dimer (1.63 μg/ml). ECG showed sinus rhythm with left ventricular hypertrophy. Brain contrast-enhanced CT of the head showed signs of cerebral edema.

The woman was a smoker with a history of autoimmune hypothyroidism and frequent inter-menstrual headaches. Home therapy included levothyroxin, oral contraceptives and nimesulfide if needed. Because of the acute renal failure associated to mild thrombocytopenia, thrombotic thrombocytopenic purpura was supposed but blood smear analysis did not demonstrate any schistocyte and ADAMTS-13 activity was normal. Furthermore no evidence of hemolysis signs was found. The hypothesis of acute nephritis was considered in the light of the moderate proteinuria which was detected (2 g/24 h) but antiglomerular basement membrane antibodies were negative. Renal ultrasound revealed normal kidney size with hyperecogen cortical. Nor immediate renal biopsy, neither treatment with steroids was indicated. Immunological screening was also negative and laboratory tests confirmed the hypothyroidism. Other major causes of secondary hypertension were excluded by urinary metanephrines measurement, renin-angiotensin-aldosterone system evaluation, renal artery Doppler. Echocardiography showed ventricular hypertrophy and a mild dilatation of the ascendent aorta. An intra-cranial angio-NMR was performed: it confirmed the absence of focal lesions or ischemic areas and it showed brain edema according to hypertensive encephalopathy. Firstly the contraceptive pill was stopped then, after initial anti-edema treatment with mannitol and dexamethasone and an attempt to control blood pressure with clonidine, the patient was treated with continuous infusion of labetalol. Symptomatology improved during hospitalization (almost complete resolution of visual acuity deficit despite alterations in visual evoked potentials persisted) as well as the cerebral edema while creatinine stabilized around 2.2 mg/dl.

The switch to the oral treatment required polytherapy (atenolol, doxazosin, amlodipine, furosemide, and potassium canreonato). The use of polytherapy permitted to reach a good blood pressure control. These findings led to the diagnosis of malignant hypertension with organ damage at presentation (hypertensive encephalopathy, renal failure, hypertensive heart disease) probably associated with intake of oral contraceptives, which may be a common cause of hypertension in women of childbearing age, who generally require two or more drugs to control blood pressure as well as the stopping of contraceptive treatment [1].

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Thrombotic thrombocytopenic purpura: is fresh frozen plasma infusion alone still an option in selected patients with atypical presentation?

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A Caucasian 64-year old woman was admitted in emergency department because of ecchymosis and petechiae diffused to arms, legs and trunk. The patient had been in her usual health until approximately 3 weeks earlier, when she developed irritative urinary symptoms without fever associated with mild migraine and soonafter she noted non traumatic petechiae and ecchymosis in her legs.

On examination at admission blood pressure was 140/80, heart rate was 90 beats/min, respiratory rate was 16/min, oxygen saturation was 99 % at ambient air; pulmonary, abdominal, cardiovascular and neurological examinations were normal, while ecchymosis were seen at legs, arms and trunk. Laboratory tests revealed severe piastrinopenia (Ptls 22,000/mcl) and normocytic anemia (hemoglobin (Hb) 10.8 g/dl, MCV 89 fl) with signs of hemolysis (LDH 1,071 UI/L, indirect bilirubin 2.7 mg/dl, haptoglobin <3 mg/dl). Coagulation tests and creatinine were normal. Consulting hematologist reviewed peripheral blood smear, with evidence of few reticulocyte and no schistocyte. Empiric therapy with ceftriaxone was started for urinary tract infection.

The woman had a history of obesity (BMI 34), essential hypertension, dyslipidemia, alopecia areata and autoimmune hypothyroidism. Home therapy included levothyroxine, simvastatin and ramipril.

Principal differential diagnosis were then considered. Evans syndrome was supposed but direct antiglobulin test and antiplatelet antibodies were negative; vitamin B12 and folate deficiency was excluded; normal coagulation tests were not consistent with a disseminated intravascular coagulation; lymphoma with bone marrow involvement was excluded at bone marrow biopsy (that revealed megakaryocytes and red cells hyperplasia). Thrombotic thrombocytopenic purpura (TTP) with a non typical earlier presentation was then supposed, but 2 different blood smear analysis couldn't demonstrate any schistocyte. During admission we assisted to a progressive worsening of anemia (Hb 7.7 g/dl) and a new blood smear finally showed schistocyte. Mild proteinuria (200 mg/dl) was detected with normal renal ultrasound. Very low ADAMTS13 activity level were detected (2 %), but no ADAMTS13 inhibitors were found. The patient was given immediate 1,000 ml of fresh frozen plasma infusion (PI) and high-dose methylprednisolone (1 mg/kg/die), with striking rapid increase of platelets (22,000/mcl → 36,000/mcl after 2 days) and stability of hemoglobin levels. Giving mild presentation of the disease, clinical stability and the necessity to exclude other causes of thrombotic microangiopathy for a definitive diagnosis, we decided according with the patient not to start immediately plasma exchange (PE). Thoracic and abdominal CT scan excluded occult neoplasia or infective foci. Blood and urine culture were negative, echocardiography showed no vegetations nor valvular alterations. A diagnosis of idiopathic acquired TTP was made. Ptls were 58,000 after 5 days of therapy with PI and steroid; PI was stopped after 8 days, Aspirin 100 mg was started and after 10 days Ptls were 107,000 with LDH 472 UI/L and aptoglobin 32 mg/dl. Prednisone was progressively tapered for 10 months with maintenance of ptls >150,000 and Hb 12 g/dl, during the following 3 months with no therapy. ADAMTS13 activity levels progressively raised, until 63 % at the time of writing (3 months after stopping steroid).

In 1991 Canadian Apheresis Group trial established PE as the treatment of choice in TTP. In this study, however, the volume of plasma administered in the PI group was low compared with those of the PE group (15 vs. 45 mL/kg per day, respectively), and therefore the clear effectiveness of high-dose PI could not be tested. Some authors reported in retrospective studies comparable rates of complete remission and mortality in patient treated with high doses PI or PE. The decision to begin PE is a balance between confidence in the diagnosis and risks of the procedure (catheter insertion complications or obstruction, systemic infection, hypotension, venous thrombosis, death). This case confirms that selected case of acquired TTP with a curable cause (i.e. infections) could be safely managed with high doses PI and steroids alone without relapse and without organ damage. Another open question still remains about acquired idiopathic TTP with no detectable ADAMTS13-inhibitors (IgG presumably autoantibodies). It isn't known whether a transient, severe defect in ADAMTS13 production or survival occurs, or if the test systems that are currently in use fail to detect autoantibodies. Further studies are needed.

A 58-year-old woman with severe refractory thrombocytopenia

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A 58-year-old woman was seen in our hospital because of non palpable purpura, hematomas at upper and lower extremities. Laboratory tests showed severe thrombocytopenia (1.000/mm3), microcytic anemia (11.3 g/dL MCV 81 fL), normal LDH, aptoglobin and white blood cell count. A blood smear showed no schistocyte. The patient was in her usual state of health until 20 days before admission when she accused flu-like syndrome with dry cough, fever (37.5 °C) and headache. Approximately 1 week before the evaluation she noticed purpura lesions at limbs. Medications included a satanic for elevated blood pressure. The remainder of medical history was unremarkable with no history of alcohol, tobacco use or illicit drugs. A transfusion with 5 platelet concentrate units was performed because of epistaxis. During transfusion urticarial rush developed treated with intravenous glucocorticoids. Thrombocytopenia can result from a failure of platelet production, excluded with a bone marrow biopsy showing megakaryocyte hyperplasia and dyserythropoiesis with normal immunophenotype and cytogenetics. Abnormal distribution or sequestration was unlikely because she did not have splenomegaly on physical examination confirmed by echotomography. Destruction of platelets was considered the most probable pathogenetic cause; among infectious diseases we looked for HIV, viral hepatitis, Epstein–Barr virus, CMV, Mycoplasma pneumoniae and parvovirus infections. CMV PCR resulted positive for 700 copies, that couldn't justify a severe thrombocytopenia. A systemic lupus with cytopenias was a concern in this case and immunologic tests showed positivity for ANA (1:640) and AMA (++); however diagnostic criteria for systemic lupus lacked. Therapy with prednisone 75 mg/die per os for 4 days was started followed by intravenous immunoglobulin infusion (0.4 mg/kg/die) for 7 days and intravenous desametasone (40 mg/die) for 3 days without improvement of platelet count. Once excluded HBV infection, rituximab was administered without improvement. A new PCR for CMV revealed virus active replication (19,000 copies). Rituximab was interrupted and foscarnet 90 mg/kg twice daily was administered for 11 days. PCR after treatment showed CMV copies <500. On physical examination only small lymph nodes were palpable in left laterocervical locations that could be correlated to CMV infection but an echotomography of the neck showed multiple deep bilateral laterocervical lymphadenomegaly suggestive for malignancy. Total body CT scan showed bilateral thoracic and left laterocervical lymphadenomegaly with pathological hypercaptation at Positron Emission Tomography.

On the 25th day after admission, anemia (Hb 6.2 g/dL) and fever developed together with an episode of dysarthria lasted 1 h. A cranial CT scan did not reveal hemorrhagic foci. Infectious and inflammatory causes of dysarthria are possible in patients receiving immunosuppressive therapy but a blood smear revealed 5 % of schistocyte; moreover additional laboratory tests revealed undetectable haptoglobin and elevated LDH, which are further evidence of hemolysis. Fever, laboratory findings of microangiopathy hemolytic anemia, thrombocytopenia and neurological symptoms were suggestive of a diagnosis of thrombotic thrombocytopenic purpura (TTP). Treatment with plasma exchange was started with prompt improvement of platelet count, resolution of purpura; then it was performed on alternate days for other 5 days, along with glucocorticoids administration. A lymph node biopsy showed Nodular Sclerosis Hodgkin Lymphoma stage II A (Ann Arbor) and chemotherapy was started. A TTP could be a rare paraneoplastic syndrome in lymphomas.

Endocarditis or not?

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A 31 year-old man was admitted to our hospital with fever and acute renal failure. Two months before, he had been diagnosed with aortic valve endocarditis caused by Methicillin-resistant Staphylococcus Aureus, treated with ciprofloxacin, vancomycin and rifampicin with defervescence and decreasing of inflammatory markers. After some days his condition worsened and a transesophageal echocardiogram showed an erosion and a fistula of the interventricular septum with aortic root dilatation, valve stenosis and insufficiency requiring an urgent valve replacement. Heart surgery was performed without complications and antibiotic therapy with daptomycin and rifampicin was started.

40 days after surgery, he became febrile again and a prosthetic valve endocarditis was suspected. Blood cultures were obtained and they resulted negative. A transesophageal echocardiogram did not reveal new signs of endocarditis. The antibiotic therapy was empirically changed to meropenem, teicoplanin and gentamicin. After 2 weeks the patient developed acute anuric renal failure (creatinine 7.2 mg/dl), so he was transferred to our hospital.

He has a history of commisurotomy for aortic stenosis when he was 7 years old, he suffered from chronic tonsillitis and the tonsillectomy had been proposed; in 2010 a transthoracic echocardiogram revealed a bicuspid aortic valve with a moderate valve stenosis. He was allergic to beta-lattamic antibiotics.

On arrival the patient was febrile without signs of shock. Physical examination showed neither new cardiac abnormalities nor signs of systemic embolization. Blood tests did not reveal leucocytosis, but showed renal failure (creatinine 9.4 mg/dl) and mild elevation of procalcitonin levels (6 mcg/L). A CT scan of his head, chest and abdomen was negative for septic emboli. Transesophageal echocardiogram revealed a normally functioning prosthetic aortic valve with no evidence of vegetations. Blood cultures were negative. Because of the elevation of procalcitonin, fever was considered to be of infectious origin and renal failure was attributed to aminoglycoside nephrotoxicity. Gentamicin was discontinued, antibiotic treatment was changed again (vancomycin, levofloxacin and linezolid were administered) and hemodialysis was started.

In the following days the patient had one episode of severe hemoptysis associated with respiratory failure and blood loss. He required to be transferred to Intensive Care Unit (ICU) and a continuous positive airway pressure (CPAP) therapy was started. A CT scan of the chest showed diffuse alveolar-interstitial infiltrates suggestive of alveolar hemorrhage.
In the light of what was observed (the poor clinical and instrumental signs of an infection, in particular endocarditis—negative blood cultures, mild elevation of procalcitonin, no echocardiography signs of vegetation—, the acute renal failure and finally the severe hemoptysis), a diagnosis of a pulmonary renal syndrome was suspected. Tests for antineutrophil cytoplasmic autoantibodies (ANCAs) was mildly positive and the titer of antiglomerular basement membrane (anti-GBM) antibodies resulted highly elevated (>1,200 KUI/L).
A diagnosis of Goodpasture syndrome was performed. After the evaluation of the risk of an immunoppressive therapy in a patient with a recent severe infection, he was administered prednisone, and rituximab, and underwent a series of 19 plasma-exchange treatments. Untreated the disease is rapidly fatal. Therapy with cyclophosphamide, corticosteroids and plasmapheresis has remained the gold standard for over 30 years. Small numbers of case reports have suggested efficacy with rituximab, whereas other reports of successful outcome with mycophemolate mofetil and cyclosporin in patients unresponsive to or intolerant of standard therapy have been published. Clinical conditions improved, no further episodes of hemoptysis occurred and at the time of discharge anti-GBM antibodies titer resulted undetectable. However the patient became dependent on chronic hemodialysis.

A female with pediatric thymoma and polyglandular autoimmune syndrome: the role of immune system

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A 51 year old woman presented to our department with headache and systemic arterial hypertension (blood pressure 150/100 mmHg). When she was 2 years old, in 1963, was diagnosed with thymoma then treated with radiotherapy. In 1999 she was subjected to surgery for parathyroid adenoma. In 2002, the patient complained of diarrhea and abdominal pain and she was diagnosed celiac disease (tTGAB and EMA negative; HLA BQB1*03 haplotype; resolution of symptoms after gluten-free diet), already evidenced in her mother and sister; in the same year she was diagnosed autoimmune ipothyroidism (treated with levothyroxine 50mcg/die), shown in her sister too. In 2003 occasional survey of hepatitis HCV+ during hospitalization after accident. When she was young suffered of muscle weakness and asthenia, then complicated by dysphagia and rhinolalia. In 2006, she was diagnosed with fibromyalgia and 2 years later, she had been diagnosed to have seronegative myasthenia gravis (Ab AchR negative, non-specific myopathic EMG, treated with pyridostigmine 60 mg; resolution bulbar symptoms but unresolved asthenia). Afterwards, the patient manifested xerophthalmia and xerostomia and she has been diagnosed as having Sicca syndrome (parotid gland's biopsy negative and ENA Immunoblot: SM, RNP, SSA, SSB, SCL70, JO-1 negative excluded Sjogren's syndrome). In the same year was hypothesized diagnosis of mixed connective tissue disease, cause of Raynaud's phenomenon (percutaneous angioscopy indicated autoimmune disease), asthenia (evaluated clinically) and pulmonary fibrosis (shown on CT), cryoglobulinemia, but there was not possible to confirm it, because antibodies anti-U1RNP were negative. In 2007 was performed clinical diagnosis of purpura and orthokeratotic hyperkeratosis dermatitis through biopsy. Cardiac eco-color-Doppler showed fibrosis of the papillary muscles. In 2011, following positive tilt test was diagnosed postural orthostatic tachycardia syndrome (POTS). A diagnostic hypotheses was secondary hypertension: renal Doppler ultrasound excluded renal artery stenosis; abdominal CT and assay of urinary catecholamines ruled out pheochromocytoma; blood assay of aldosterone, renin and cortisol were normal, allowing us to exclude hyperaldosteronism and Cushing's syndrome. Whereas the patient had presented a parathyroid adenoma, we considered the possible presence of multiple endocrine neoplasia (MEN) type1: we excluded pituitary adenoma with encephalic RMN and normal range pituitary hormones; abdominal TC and the dosage of pancreatic hormones allowed us to exclude pancreatic endocrine tumor. We could hypothesize that the development of thymoma, rare in children, may have compromised immune system. Considering complexity of the clinical case, we think that the patient can be affected by polyglandular autoimmune syndrome (PAS), especially by the PAS type III, that includes autoimmune hypothyroidism and various autoimmune diseases such as celiac disease, myasthenia gravis, Sicca syndrome. Given the progressive multi-organ involvement, is appropriate to continue to monitor the patient to evaluate the possible development of other systemic autoimmune diseases such as rheumatoid arthritis, scleroderma and systemic lupus erythematosus (SLE).

Young woman with proteinuria, arterial hypertension and renal failure two months after pregnancy

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We have studied a 41 years old Caucasian woman was admitted of the hospital with proteinuria (1,280 mg/24 h), rapid deterioration of renal function (serum creatinine from 0.8 to 1.2 mg/dL during 2 months). The major laboratory parameters showed anemia with Hb 10 g/dL, RBC $3.560 \times 10^3/mm^3$ and serum iron 100 mg/dL, hypercholesterolemia and hypertriglyceridemia with cholesterol level 260 mg/dL and triglyceride level 300 mg/dL and WBC $5680/mm^3$, Plt $230 \times 10^3/mm^3$, glycemia 84 mg/dL, BUN 14.5 mg/dL, uric acid 5 mg/dL, Na 140 mEq/L, K 4.3 mEq/L, Ca 9.5 mg/dL, P 4 mg/dL, serum protein 6.5 g/dL, GOT 15 U/L, GPT 17 U/L, coagulation test and serum protidogram were normal. Urinalysis: Ph 6.5, specific gravity 1015, red blood cells absent. EGA was normal. The 24 h urine volume was 2 L and the 24 h fluid intake was about 2L. She was apyretic, hydrated in appearance, blood pressure 150/85 mmHg, HR 75 bpm, mild heart murmur and the rest of physical examination was negative. She didn't present any peripheral edema. She referred frequent episodes of epistaxis. She related pregnancy 2 months ago and during that period she didn't present proteinuria but only high blood pressure. She did not refer nephrotoxic drugs assumption. Renal ultrasonography excluded ureteral obstruction and it showed normal size of kidney. We suspected an autoimmune disease but ANA, dsDNA, c/p-ANCA, ENA antibodies, IgG/A/M, C3, C4, were negative. Furthermore TSH, FT3, FT4, markers of hepatitis B and C resulted in normal range. The patient was subjected to renal biopsy which showed the presence of Amyloidosis AL with deposits of light chains k. Subsequently, at the same time, the patient showed a rapid deterioration of renal function with nephrotic syndrome (proteinuria 4 g/24 h, 3 of which albuminuria) and decreased of the liver function with increased indices of cholestasis associated to hepatomegaly. An echocardiogram was negative She was started on chemotherapy,

consisting of bortezomib and dexamethasone. This led to clinical improvement, stabilization of the illness and good tolerance of the treatment. This case is very interesting because rapidly progressive renal and hepatic failure was simultaneously observed, and renal amyloid deposition was restricted to the glomeruli. Moreover the myocardium was not involved. The epidemiology of amyloidosis is not well known and Amyloidosis is a rare entity that is difficult to diagnose. This is because of the unspecific early clinical manifestations of the disease. The hypothesis of amyloidosis is only considered when specific organ failure occurs. This case consisted of primary amyloidosis with involvement of the kidneys as an initial presentation of the disease and its difficulties were shown, going from the clinical approach to the final diagnosis.

A tricky management of comorbidities

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In February 2012, a 75 years-old woman was admitted to our Hospital because of dyspnoea, palpitations and acute confusional state. The patient, affected by breast cancer with bone and pulmonary metastasis, was evaluated 4 days before by an Oncologist for an acute confusional state and, suspecting cerebral metastases, treated with desametasone (8 mg/day i.v.) and diazepam (2.5 mg per os). The patient had a history of right mastectomy in 1984 for an invasive lobular breast carcinoma, in 2003 a cancer recurrence occurred with subsequent lymphonodal, bone and lung metastasis, that required chemo-radio therapy; in November 2011 she underwent a right talc pleurodesis. Despite this history the patient was actively working as a baker until 10 days before admission to our hospital. At admission the patient was febrile (38 °C), collaborating and asthenic. Her blood pressure was 105/60 mmHg, she had sinus tachycardia (105 bpm) and arterial oxygenation was 94 %. On cardiac auscultation there was a 2/6 L systolic murmur, examination of lungs revealed right basilar dull sounds with decreased vesicular murmur. The abdominal and neurologic examinations were normal. There were signs of right mastectomy with lymphedema of homolateral arm. Laboratory test showed WBC 15130/ml (N 13,540/ml), Hemoglobin 10 g/dl, Platelet count 125000/ml, increased serum creatinine (1.5 mg/dl), RCP (9.1 mg/dl). Electrolytes, ALT and ALP were normal. Urine was turbid, with glycosuria, proteinuria and leukocyturia (WBC 4025/μl). Blood, urine and sputum culture were collected. We immediately performed a cerebral CT scan with contrast (on suspicion of CNS replicative lesions → resulted negative) and a Chest X-ray (right pleural effusion). Diagnosis of severe urosepsis was taken into account (possible urinary tract infection + WBC > 12000/mm^3 + HR > 90 bpm + confusion and impaired kidney functions) and treatment with ciprofloxacin (400 mg bid i.v.) was immediately started. Abdominal US revealed hepatomegaly with steatosis, hydropic gallbladder with normal wall thickness, splenomegaly, bilateral pyelocaliectasis (II degree on the left and I degree on the right). 2 days later (urine culture resulted negative), considering the persisting septic fever and the worsening of respiratory function (oxygen therapy become necessary) treatment was implemented with amikacin (750 mg i.v.) and an abdominal-chest CT was performed (right inferior lung consolidation with bilateral wide loculated pleural effusion; left pyelocaliectasis with contrastographic enhancement of the left ureter and periureteral tissue). Clinical conditions did not improve and 5 days after admission different blood cultures, previously collected, resulted positive for *Escherichia coli* ESBL negative. Clinical features, such as fever with chills, heart murmur and splenomegaly, associated with laboratory signs of infection and *E. coli* isolation leaded us to infective endocarditis (IE), therefore we decided to perform a Transthoracic Echocardiography (TTE) that confirmed the presence of flail mitral valve with vegetation and pulmonary hypertension. Thus we stopped ciprofloxacin and started therapy with ceftazidime (2 g tid ev). 2009 ESC guidelines recommended treatment with early surgery in gram negative non-hacek IE. However, although the presence of different predictor of poor outcome (gram negative bacilli and pulmonary hypertension), considering the comorbidities we decided to continue just with medical therapy. After a week septic fever was still present. Guidelines and literature suggest to continue IE therapy for at least 4 weeks, however is not clear when antimicrobial therapy should be considered failed and consequently changed. We decided not to shift the therapy regardless of septic fever supported by improvement of laboratory findings: CRP 9 → 7 mg/dl; WBC 15,130 → 8,900/ml.

5 days later clinical conditions improved with fever resolution and normalization of laboratory findings.

After discharge the patient continued antimicrobial therapy (amoxicillin 1 g tid per os and amikacin 1 g daily i.m.) for further 4 weeks, without relapse of fever for the following weeks but TTE was not performed.

The modified DUKES criteria classifies this case as definitive IE.

IE by *E. coli* is rare (1.8 %) with high mortality rate (24–65 %) and although latest guidelines recommended early surgery to reduce mortality, our report show that, in patients not eligible for surgery, a targeted and prolonged antimicrobial therapy can lead to a resolution of IE.

Loss of weight: observing the patient versus lab tests

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A 25 years-old man was admitted to our medical ward in November 2011 for a diagnostic evaluation for anemia, leucopenia, hypogonadotropic hypogonadism and hypercortisolism in progressive weight loss. The patient had been healthy until 1 year before. He was a regular blood donor since 5 years. In September 2010 blood tests for donation revealed normocytic anemia with increased ALT and AST and reduction of fT3 with normal fT4, TSH and Abs anti-Tg and anti-TPO. At hepatological evaluation in December 2010 laboratory tests showed negative serologic viral tests including Herpes viruses and Abs anti-HIV; auto-Abs and 24-h urine copper test were normal. A reduction of C3 and C4 was detected. The diagnosis of Gilbert syndrome was made because mild unconjugated hyperbilirubin was found. Abdominal CT showed mild hepatomegaly and fluid in the pouch of Douglas. Celiac sprue was excluded by biopsy during EGDS. Physical examination was negative except for bradycardia and weight loss (4 kg in 6 months): weight 63 kg for 172 cm of height (BMI 21). In the suspicion of hyponutrition pre-albumin was measured with normal result. For hypercortisolism, in June 2011 he underwent endocrinologic evaluation in the suspect of Cushing syndrome: no suppression after dexamethasone 1 and 4 mg was observed, while 8 mg of dexamethasone suppressed the level of cortisol (2.72 mcg/dl). Hypogonadotropic hypogonadism was detected with no peripheral signs of hypoandrogenism. Low T3 syndrome was confirmed. From December 2010 to July 2011 he lost 9 kilos

more (weight 54 kg, BMI 18.6) and developed a more severe anemia with neutropenia. For this reason he underwent hematologic evaluation: bone marrow aspirate and biopsy revealed hypoplastic bone marrow with blast 1 %, with suspected toxic dismyelopoiesis or myelodysplastic syndrome; the karyotype was normal (46, XY). Fanconi anemia was excluded by the specific test of breakage frequencies. During these months the patient refused any psychological evaluation. Because of worsening of liver tests he underwent a liver biopsy, performed after coagulation screening because of prolonged bleeding time. Coagulation tests revealed a deficit of FVII (39 %) due to reduced hepatic synthesis. Liver biopsy showed aspecific central lobular lipofuscinosis. PET scan was negative. At the admission in our medical ward the patient was alert, collaborative; blood pressure was 120/80 mmHg, with marked bradycardia (44 bpm); reduction of muscular mass and extreme thinness was observed. He's weight was 47 kg (BMI 16). After the evaluation of the diagnostic iter, we reasonably excluded a neoplastic process. We excluded toxic etiology by the dosage of lead, aluminum, zinc and mercury in urine. Urine was negative for opioids, methadone and cocaine. Polyuria was observed and water deprivation test showed promptly urinary concentration; we concluded for polydipsia. We find out a hyperactive habit, such as jogging around the hospital and doing push-ups. According to the history and the observations during the hospitalization, we suspected an atypical eating disorder. We referred the patient to a center for eating disorders where he's still in follow up. The psychiatric evaluation diagnosed an Atypical Restrictive Anorexia. The patient refused any pharmacological treatment but accepted the psychotherapy. He reached a nadir of 41.5 kg (BMI 14.56) and was hospitalized in a clinic for nutritional rehabilitation, with an increase of 5 kg. During the rehabilitation he developed a thyrotoxicosis related to excess of iodine intake. Actually his weight is 48.8 kg.

Take home message: in the era of imaging exams and molecular medicine we still have to observe, listen and treat the person, not only trust laboratory tests.

	12/10	06/11	11/11	02/12	05/12	06/12
Weight (kg)	63	54	47	41.5	47.9	48.8
Hb(g/dl)/neutrophils ($\times$1,000/mm^3)	12.3/–	10.8/–	11.6/1.2	10.2/–	10.4/1.1	
TSH (mU/l)	2.2	3.9	2.86	0.125	8.41	6.84
fT3/fT4 ng/L	1.6/15.3	1.3/8.9	1.6/13	1.2/18.8	2.1/12.2	–/11.9
CLU (mcg/24 h)		65.7		504	170.8	
Testosterone (ng/ml)		1.1	1.44	12.1	10.64	

A prothrombotic state

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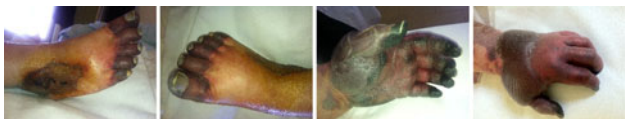
A 47-year old patient was admitted to our hospital because of persistent dyspnoea at rest and unilateral lower limb oedema. Chest X-ray revealed abnormal bilateral fluid accumulation with basal bilateral inspiratory crackles at physical examination and no clinical signs of hemodynamic impairment. A sample for arterial blood gas analysis was obtained with evidence of mild hypoxia and normocapny. In order to rule out a thromboembolic disease, D-dimer test was performed (>2,000 ng/ml) before CT angiography was taken. The radiological report was negative for pulmonary embolism, but revealed diffuse patchy opacities in both lung fields, metastatic focii in the liver and distal deep vein thrombosis. A diagnosis of pulmonary lymphangitic carcinomatosis was made on the basis of the presence of adenocarcinoma cells within the supraclavicular lymph nodes at histological examination.

Anticoagulant therapy with enoxaparin was planned on day 3 to prevent embolic dissemination from distal site, but 7 days later the platelet count fells from an initial 171 $\times$ 10^3/mL to 15 $\times$ 10^3/mL. In the suspicion of rapid onset heparin-induced thrombocytopenia (HIT), anti-platelet factor 4/heparin antibody testing was performed resulted positive. Thus HIT diagnosis was made.

In the next 3 days the patient showed a progressive and rapid decline of her clinical situation. The initial unilateral lower limb oedema involved controlateral one, dyspnoea worsening was documented and skin lesions appeared in the left hand and right foot. A new angio-CT scan was immediately performed, with evidence of bilateral pulmonary emboli complicated by hemorrhagic infarction and progression of the initial unilateral deep vein thrombosis to bilateral lower limbs thrombosis. Skin lesions moved to dermal necrosis with hemorrhagic vesicles covering the left hand, while symmetrical necrosis interested all fingers of the right foot.

The therapeutical approach after diagnosis of HIT, based on once daily subcutaneous somministration of Fondaparinux, a heparin-analog synthetic pentasaccharide, was partially influenced by limited compliance of the patient. Fourteen days after admission, the platelet count was reestablished within physiological values, but no improvement of the thromboembolic and skin lesions disease was observed.

This case report is focused on the acquired prothrombotic state resulting from the combination of several risk factors: deep vein thrombosis as paraneoplastic event of unknown lung cancer in a smoker subject; heparin-induced thrombocytopenia (HIT) with necrotic skin lesions at distance from the heparin injection sites due to intradermal microvascular thrombi as consequence of production of IgG antibodies against heparin–platelet factor 4 complex and subsequent activation of platelets. Furthermore, anamnestic research revealed several miscarriages and previous unilateral limb oedema, unrecognized expressions of a likely anti-phospholipid syndrome.



Outset of Takayasu arteritis as long-lasting fuo: FDG PET scanning diagnosis

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A 65-year-old Italian female came to the hospital with a 5-month history of fever (100.4 °F), dyspnea, high erythrocyte sedimentation rate (ESR), high C-reactive protein (CRP), myalgia and fatigue.

On presentation, her physical examination at the hospital was negative, except for a persistent temperature of 100–104 °F.

Her medical history was significant for mitral valve prolax, colon cancer resection 7-years ago and recent follow-up colonoscopy without endocarditis antibiotic prophylaxis.

The patient was found to be very tired and febrile (temperature 99.5–100 °F). She was treated with fluoroquinolone without beneficial effect and with glucocorticoids with slight benefit.
Initial laboratory work-up showed: CRP 6 mg/dl; ESR 70 mm/h; Hb 11.8 g/dl, PLT 418.000/ml; alfa2 globulin 14 %; beta2 globulin 6.2 %. Three sets of blood cultures taken on different occasions resulted negative. Serology for brucella and salmonella, rickettsia, Toxoplasma, CMV, HSV, HCV, HBV, EBV, HIV was negative. The Mantoux test for tuberculosis was non reactive and the malaria smear was negative. ACA, LAC, AMA, ANA, ASMA, APCA, ENA screening was negative.
We supposed a differential diagnosis between fever correlated with infective endocarditis on mitral valve prolax and rheumatologic disease. We excluded mitral valve endocarditis on the basis of negative blood culture, negative Duke criteria and negative transesophageal echocardiography (TEE).
After 2 months without antibiotic and glucocorticoid therapy the patient had persistent fever. We repeated blood culture that was negative, while immunological panel and p-ANCA and c-ANCA resulted negative. We proposed Fluorodeoxyglucose positron emission tomography (FDG PET) for FUO (Fever of Unknown Origin) that demonstrated increased metabolic activity of the aortic wall, carotid arteries, iliac arteries (SUV_{max} 7.3). Differential diagnosis of large vessels vasculitis is between giant cells arteritis and Takayasu disease. A bitemporal biopsies was negative for giant cells arteritis. Angio RM had not demonstrated significant stenosis of the vessels.
Our diagnosis was Takayasu arteritis and we administered low dose of corticosteroid (prednisone) with a gradual resolution of the fever and decrease of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The acute or pre-pulseless stage of Takayasu arteritis is characterized by fever, high sweats, arthralgias, myalgias, cough, hemoptysis, pleural effusion, anemia and persistent elevation of the ESR. Collagen vascular diseases have been acknowledged as a major cause of FUO since the initial description by Petersdorf [1]. Most authors agree that FDG PET scanning has a role in the diagnosis of Takayasu arteritis, even at an early stage, while stenosis are not yet visible on angiography [2, 3]. Recent studies showed there is no association between FDG vascular uptake intensity and clinical, biologic or MRI assessment of disease activity [4].

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A case of coagulopathy of unclear definition

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A 73 year-old man was admitted in our Unit because of purpura over the whole trunk and ecchymoses on the right ear and the legs, occurred throughout the prior 2 days. He appeared acutely ill and confused. Physical examination showed an asymmetric oedema of the legs (right > left) but no fever, focal neurologic signs or impaired hemodynamic. Initial investigations revealed an haemoglobin of 7.4 g/dL, a white cell count of 17,280/mcL, a platelet count of 6,000/mcL, creatinine 1 mg/dL, prothrombin time 17.6 s, partial thromboplastin time 46 s, fibrinogen 145 mg/dl.
One week before, the patient was admitted to the surgical division of our hospital to undergo colectomy. At the time of initial admission, his platelet count was 116,000/mcL, the prothrombin time was 19.7 s, partial thromboplastin time 44.2 s. His medical history was significant for ulcerative colitis since 7 years. In the first 6 years, the patient had received treatment with both oral and rectal steroids and mesalazine and was followed up with periodic colonoscopy and multiple endoscopic polypectomies. Despite of medical treatment, there had been no meaningful improvement of symptoms, leading the patient to deliberately withdrew all medications. Subsequently, a severe flare of mucous and bloody diarrhea, associated to abdominal pain, occurred, leading to the current hospitalization.
On evaluation by our team, the clinical picture was that of an ulcerative colitis-induced coagulopathy. Chest X-ray, trans-thoracic echocardiography and contrast-enhanced abdominal CT scan did not show abnormalities. The D-dimers were moderately elevated (1,721 ng/mL; normal <200), peaking at 8,022 ng/mL over few days, whilst anti-thrombin, haptoglobin and LDH levels remained normal. A vascular ultrasound and Doppler scan of the lower limbs revealed a thrombotic occlusion of the anterior tibial artery and the posterior medial calf perforators veins, both at the right side. A stool culture was positive for *Clostridium difficile*. The peripheral blood smear showed occasional fragmented and polychromatophilic red cells (schistocytes), many erythroblasts and no atypical cells. A bone-marrow biopsy was also performed and displayed a normal haemopoiethic activity. The dosage of ADAMTS13 was not feasible.
The diagnostic procedure deemed the current coagulopathy compatible with a high probability of Disseminated Intravascular Coagulation (ISTH score = 5, with 2 points for platelet count, 1 point for prolonged prothrombin time, 2 points for moderately increased D-dimers, 0 point for fibrinogen levels), although vitamin K deficiency could have caused prothrombin time prolongation. In light of the very low platelet count, the normal values of antithrombin and the altered mental status, we could not exclude also a Thrombotic Thrombocytopenic Purpura, although there was no renal functional impairment.
Based on this diagnostic assessment, treatment was started via a central venous catheter with fresh frozen plasma (10 mL/kg/day), intravenous immunoglobulins (400 mg/kg/day for 5 days), i.v. metronidazole (1,500 mg/day) and oral ciprofloxacin (1 g/day). The patient was also transfused with 3 units of packed red blood cells and received a total parenteral nutrition. Anticoagulation with heparin was withheld due to the concurrent bowel haemorrhage. Although total colectomy was considered at that time the treatment of choice, we chose to postponed it due to unacceptable surgical risk. Accordingly, the underlying inflammatory bowel disease was treated with high dose steroids (methylprednisolone 1.5 mg/kg/day, subsequently tapered off) and the addition of cyclosporine A (with a target trough level of 300–350 ng/mL).
Patient clinical conditions slowly improved and the patient was discharged after 3 weeks with resolution of the coagulopathy and marked improvement of the bloody stools; the laboratory tests showed an haemoglobin of 10.2 g/dL, a white cell count of 10,100/mcL, a platelet count of 80,000/mcL, prothrombin time 18.9 s, partial thromboplastin time 45.0 s, fibrinogen 259 mg/dL, C-reactive protein 0.5 mg/dL. Sadly, over the next 4 months, the patient developed an overwhelming Kaposi's sarcoma, likely induced by the aggressive immunosuppression, and he eventually died.
In conclusion, this case shows that the differential diagnosis between Disseminated Intravascular Coagulation and Thrombotic Thrombocytopenic Purpura may be a clinical challenge and that a multimodal therapeutic approach may be needed to successfully manage a complex condition of coagulopathy.

Nothing as it seems

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An 82 years old woman presented to Emergency Department (ED) for sudden right ocular deviation, dysarthria, left limbs hyposthenia, impaired attention and apraxya.
Her past medical history was significant for dementia with Lewy bodies and systemic hypertension. Her medications included quetiapina, selegina, zolpidem, escitalopram, acetylsalicylic acid, atenolol, enalapril and amlodipina.
On admission to ED, the patient was alert but confuse with left eminattention, right ocular deviation, left partial vision paralysis deficiency of the VII left cranial nerve, severe hyposthenia of the left hemysoma, Babinsky reflex on the left side, deep pain stimulus extinction on the left side; the NIH Stroke Scale (NIHSS) was 11.
The patient was apyretic, blood pressure was 235/135 mmHg, oxygen saturation 97% in room air, heart rate 95 beats/min, respiratory rate 26/min, plasma glucose 101 mg/dl. The remaining physical examination was normal except for pulmonary bibasilar crackles. Laboratory blood tests, ECG and chest X-ray were normal; the first brain CT-scan performed showed a past lacunar hyschemia on the left thalamic region without evidence of any acute lesions.
In ED, the patient was treated with captopril and urapidil for blood pressure control; due to the patient's agitation, Delorazepam was administered. The patient was admitted to our Internal Medicine division.
At the beginning, the patient was sleepy but awakable, while physical examination was unchanged. Worsening of the state of consciousness was interpreted as a result of the administration of benzodiazepines, hence intravenous hydration was initiated, with partial recovery. Within 24 hours from admission, there was a complete remission of the left hemisyndrome. Surprisingly, the brain CT-scan performed after 48 h was negative for any acute ischemic lesion. Thus we hypothesized a cardiovascular origin of the neurological hemisyndrome and performed a supraortic vessels Doppler ultrasound and echocardiography that resulted negative.
Few days after, to test the hypothesis that the left hemisyndrome could have been due to an ischemic lesion not detectable with CT scan, a brain magnetic resonance (MR) was performed. Few hours before undergoing the MR, the patient complained about right arm hyposthenia and brain-MR showed an acute ischemic lesion in left thalamic-capsular region. Furthermore, an EEG was performed and it showed left slow temporal abnormalities in a context of mild diffuse encephalopathy.
These acute findings were compatible with the latest neurologic feature but did not explain the previous hemisyndrome. Therefore, taking into consideration the rapid improvements of neurological features with a complete neurological recovery within 3–4 days and the negative CT and MR scans for right ischemic stroke, the patient was diagnosed of post-critical paralysis (Todd's paralysis), followed by a left thalamic-capsular ischemia with right arm hypostenia.
The patient showed gradual improvement of the neurological clinical condition, with a mild right arm hyposthenia at the time of the discharge from Hospital.

Not all yellow are Chinese

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A 50 year-old woman came to our attention approximately 2 months after the onset of progressively worsening nausea: vomiting, first food, then bile; episodic abdominal pain and common cramps; worsening jaundice. The patient had no history of disease or surgery worthy of note and was not taking any medications except—on and off-again for about a year—known dietary supplements, herbal teas and herbal extracts. Objectively, the patient presented with marked weakness, anorexia, worsening jaundice, important muscle wasting, postural instability and lively abdominal tenderness on palpation of superficial and deep upper quadrant and right flank.
The patient showed no signs of fever or other symptoms of note. Laboratory testing indicated the presence of predominantly direct hyperbilirubinemia (totoal 23.2 mg/dl, direct 17.7 mg/dl), the absence of alteration in transaminases or alkaline phosfatasi, ggt below normal values; various laboratory results indicated malnutrition. Assuming the patient was suffering from obstructive jaundice, abdominal ultrasound was performed yielding evidence of mild steatosis and the massive presence of gallstone formation about 3 cm in the gall bladder in the absence of dilation of intra and extrahepatic bile ducts. To exclude the involvement of the intrahepatic bile ducts, cholangio-MRI was conducted and proved non-diagnostic. Moreover, in order to exclude causes of extrahepatic cholestasis, abdominal CT was performed showing a hepatic situation similar to previous diagnostic investigations, but with evidence of a hyperdense formation of 2 mm at the uncinate process of the pancreas, behind the second portion of the duodenum. To better characterize the lesion endoscopic ultrasound and a biopsy were performed giving results compatible with simple adenoma, therefore non-diagnostic. Laboratory tests excluded liver disease of other origin (panel expanded autoantibody, profile martial, antiviral profile, ceruloplasmin, cupremia, all negative), and instrumental tests, designed to exclude major diseases (mammography, endoscopy, echocardiogram, Rx digestive above), had normal results. Given the steady increase of bilirubin, in the absence of clear indications of obstruction, a liver biopsy was performed and showed evidence of centrilobular cholestasis and necrosis with a plausible metabolic basis in hypoplasia of the bile ducts. During hospitalization, the patient was treated with ursodeoxycholic acid and steroids. She showed a progressive decrease in bilirubin and a gradual improvement in general condition. One month after discharge, the patient is in good health, with weight gain, normal alimentation and bilirubin values in the norm. We present this case report to emphasize how positive diagnostic test results for apparently probable hypotheses can assist the physician from excluding rare but still possible causes, as in this case, Vanishing bile duct syndrome.

The cryptic "genesis" of a pulmonary embolus

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A 32 year old man was admitted to the trauma ER complaining of knee pain. Suspecting a lesion of the anterior cruciate ligament, the patient was given NSAID therapy, while waiting for MRI scan. Afterwards, he was referred for a muscular echography of the left leg, because of the persistence of the knee pain, associated with mild effort dyspnea. During this examination, a complete thrombosis of the superior femoral vein was accidentally detected, together with the thrombosis of the popliteal vein from the origin down to the gemellar veins. For these reasons the patient was brought to our attention. During history taking the patient did not refer any trauma, recent surgical procedures, known thrombophilia, or family history of any thrombophilic disease. Physical examination revealed mild tachypnea, splitting of the second heart sound and gallop rhythm on cardiac auscultation; spontaneous pain of the left gemellar area was also noticed. The ECG showed negatives T waves on precordial leads from V_1

to V_4. Comparison with the ECGs recorded during the previous ER admissions revealed the appearance of negative T waves and the absence of a $S_1Q_3T_3$ pattern. In contrast, the latter pattern was retrospectively detectable in previous ECGs. Arterial blood gas analysis showed pO_2 31 mmHg, pCO_2 74 mmHg, with a 96 % O_2 saturation. Echocardiography showed right ventricular volume and pressure overload. High resolution CT scan was then requested, showing a picture of massive bilateral pulmonary embolism. Parenteral infusion of unfractionated heparin was started, subsequently combined with oral anticoagulant therapy with a INR goal >2. Given the young age of the patient, the threatening condition, and the possibility of a relapse, we investigated some uncommon factors that could have predisposed the subject to deep venous thrombosis and pulmonary embolism. Particularly, we accomplished a thrombophilic screening that showed only few heterozygous mutations in genes codifying for the V coagulation factor and the MTHFR. We excluded the concomitant presence of occult neoplasm or of lymphoproliferative diseases. Abdomen echo- and CT scans excluded the presence of neoplastic masses, or of other causes of venous compression. Suspecting a testicular neoplasia, the inspection of genitalia was executed, revealing testicular atrophy. Testicular echography showed small gonads, accompanied by pseudonodules and microcalcifications, suggestive of a precancerous condition. Hormonal studies demonstrated hypergonadotropic hypogonadism, a finding that was supported by the absence of thoracic and facial hair. Moreover, the patient was 185 cm tall, nearly 20 cm taller than his parents. On the basis of these findings (sparse piliferous system, tall stature, gynoid distribution of adipose tissue, and hypergonadotropic hypogonadism), the karyotype of the patient was finally analysed, confirming the suspected Klinefelter syndrome (47, XXY). Available literature reports an increased incidence of thromboembolic episodes in Klinefelter carriers, due to the hyperfibrinolytic state, and the hyperagglutination of platelets, in turn secondary to the low blood androgen level, and further aggravated by the association to prothrombotic mutations of coagulation factors. Such a diagnosis can be challenging in the absence of a clearcut patient phenotype.
In conclusion, complex genetic syndromes can appear as proteiform, unusual pictures displaying conditions of internistic interest.

A case of thrombocytopenia: a problem of diagnosis and treatment

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A 79-year Caucasian male was hospitalized in February 2012 for the onset of severe thrombocytopenia not responsive to treatment with steroids at high dose. A medical history revealed hypertension, COPD, primary biliary cirrhosis, previous HBV infection, peritoneal fibrosis with left iliac deep venous thrombosis, antral gastropathy and hyperemic duodenitis. Moreover, about 6 months before, he was hospitalized for syncope with a subsequent diagnosis of A-type aortic dissection. He underwent cardiac surgery to replace ascending aorta and aortic arch with a vascular prosthesis. The post-surgery was complicated by the onset of some complications as parossistic atrial fibrillation successfully treated with pharmacological cardioversion with amiodaron, lymphedema of left upper limb following the intraoperative resection of innominate vein resection, inhalation syndrome with recurrent pneumonia with endotracheal intubation and subsequent tracheostomia, left vocal cord paralysis following left recurrent laryngeal nerve injury; hemoptysis, periprosthetic hematoma and left haemothorax needing blood transfusions. In December 2011 thrombocytopenia occurred in course of therapy with low molecular weight heparin, progressively worsening. At the ward admission, platelets were 7×10^9/L, patient was asthenic with dysphonia, although his vital signs were normal, he had scattered bronchi in pulmonary physical examination and cutaneous bleeding diathesis at upper limbs. He never had major bleeding even with the need of repeated transfusions in order to maintain platelets count greater than 10×10^9/L. Laboratory data revealed neutrophilic leucocytosis and mild macrocytic anemia with high reticulocyte count, folic acid 20 ng/mL, B12 vitamin 581 pg/mL, fibrinogen and prothrombin time normal. Pseudothrombocytopenia was excluded by count with heparin, citrate and EDTA. Heparin-induced thrombocytopenia was excluded by drug discontinuation without benefit and negative antibody heparin-PF4 complex study. Immunological screening was negative too and bone marrow biopsy revealed well working marrow with dyserythropoiesis and myeloid and megakaryocytic hyperplasia. Investigating possible infectious causes, previous HBV infection was confirmed, and HCV, HIV, parvovirus and Mycobacterium tuberculosis infections were excluded. High viral load of CMV appeared and patient started antiviral therapy (Valganciclovir); furthermore serology for *H. pylori* was positive for infection: patient started eradication treatment (PPI, Amoxicillin, Metronidazole). On sputum culture multiresistant *S. aureus*, *K. pneumoniae, P. aeruginosa* e *B. catarrhalis* had been isolated without evidence of pneumonia, but targeted antibiotic therapy was started. Platelet count didn't rise although all these therapies, and it didn't improve with prolonged steroid therapy at high dose. We just observed mild and transient response to therapy with intravenous immunoglobulin. Finally, we hypothesized a diagnosis of refractory idiopathic immune thrombocytopenia. Idiopathic immune thrombocytopenia is a diagnosis of exclusion. The first line therapy is the administration of corticosteroids, intravenous immunoglobulin or, in selected cases, anti-Rho(D). The second line therapy includes splenectomy, administration of rituximab (Ab anti CD20) and therapy with thrombopoietin receptor agonists which includes Romiplostin [1]. Romiplostin is a fusion protein acting as agonist of receptor of thrombopoietin and activating intracellular transcriptional pathways increasing the production of platelets [2]. Taking into account the comorbidity, the risk of infection and the consequent inability to second life approach with surgical splenectomy or anti CD20 Ab, we initiated therapy with Romiplostim [3]. Given the incidence of thrombotic complications, thrombophilia screening was performed with the diagnosis of coagulation protein S deficiency, a condition not constituting contraindication to administration of the drug. Following haematologist's advice, treatment started with a dose of 1 mcg/kg/wk, rising in coming weeks with the response obtained to a dose of 3 mcg/kg/week. The patient was discharged with a platelet count rising and after 60 days platelet count rose to 198×10^9/L.

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Dyspnoea: focus on the chest but don't forget the rest

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A 59 years old woman presented with a 10 days history of mild dyspnoea on exertion, 1 week low-grade fever, backpain treated with

FANS since 3 months, asthenia, hyporexia and loss of weight of 5 kg. Her work was sedentary, her medical history consisted in: anxious depressive syndrome, treated with SSRI; a contact with aTBC case 2 years before treated with prophylactic drug and a history of smoking (39 pack years).Before admission she performed chest X-ray that showed diffuse interstitial thickening and small bilateral pleural effusion and a chest CT that confirmed X ray result and found a flogistic consolidation in left lower lobe. At admission vitals were: ABP 140/80, CR 112, RR 34, $SatO_2$ 93 % aa. Bibasilar crackles, 2 laterocervical enlarged lymphnodes and a systolic 2/6 murmur were found during visit. EKG was normal. ABG showed a respiratory alkalosis with normoxia. Laboratory data showed leukocytosis and increased CRP (3.88 mg/dl) and PCT (0.09 ng/dl), normochromic normocytic anaemia (Hb 8.8 g/dl, MCV 81 fl). Low pseudocholinesterase and albumin without hepatopathy suggested an undernourishment state. CPK were elevated (360 mg/dl). Oxygen and antibiotic therapy for CAP were begun. Microbiological tests were performed (legionella and pneumococcal urinary antigen, *Mycoplasma* pn., *Chlamydophila* pn., *Legionella*, CMV, HIV, EBV serology) all resulted negative. We performed further exams for anaemia: reticulocyte 3 %, normal haptoglobin and bilirubin, iron pattern at low threshold (ferritin 229 mg/dl, transferrin saturation 15 % serum iron 40 mg/dl). Fecal occult blood tests were negative. To investigate the aetiology of interstitial lung disease BAL and sieric ACE level were performed but all of them weren't diagnostic. Autoimmune screening showed only ANA positivity (speckled pattern, 1/320).The patient complained muscles pain but myositis with interstitial lung disease was excluded performing EMG (normal pattern)and sieric anti Jo1 level (in range). After 1 week anemia and dyspnoea worsened, she complained palpitation and she received transfusions. CRP remained high despite antibiotic therapy and she started needing metoclopramide to prevent recurrent vomit episodes. For this new symptom we performed a chest-abdominal CT (she refused EGDS) that showed an increase in bilateral pleural effusion and multiple ground glass opacity. Pathological lymphadenopathy was found in thorax and abdomen. We changed antibiotic therapy starting imipenem and performed a thoracentesis but tests on pleural effusion were inconclusive. An echocardiography showed pulmonary hypertension (PAPs 59 mmHg). PFR revealed restrictive pattern syndrome, DLCO was not performed for patient low collaboration. She gradually increased her need of oxygen therefore anaesthetist controindicated videotoracoscopic biopsy of the lung. We suspected a lymphoproliferative disease and performed PET total body that found a diffuse bone marrow FDG uptake (SUV 19) in the axial skeleton (vertebra, ribs, clavicles, pelvis, sternum) and appendicular one (scapulea, head of the humerus, diaphysis of the right humerus, femurs) and in laterocervical, intrathoracic and subdiaphragmatic lymphnodes. The great diffusion of FDG uptake made diagnosis of hematological disease or diffuse metastatic tumor the most probable ones. Normal breast X-ray, thyroid echography and PAP test excluded these as the primitive tumor site. Meanwhile she underwent a OMB and a neck lymphnode asportation; the histologic exams revealed a metastatic adenocarcinoma and the immunophenotype profile suggested a gastrointestinal origin of the tumor. EGDS showed an antral heteroplastic circumferential mass that extended along the small curve. Multiple biopsy showed a diffuse gastric signet ring cell adenocarcinoma according to Lauren classification. HER 2 neu was positive. Oncologic consult suggested palliative support therapy and steroids were started. After few days CRP had a fast augmentation. Anaemia kept on worsening despite transfusions and a severe DIC developed. Acute respiratory failure developed, she slowly became unconscious and finally died after 1 month of hospitalization. Despite impossibility of performing a lung biopsy, we believe the interstitial lung pattern could be due to carcinomatous lymphangitis non rare pattern of gastric cancer metastasis. The first symptom, backpain, was probably ascribable to bone marrow metastasis of the tumor.

A case of relapsing fever

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A 79 years-old man came to our observation in April 2012, after about 4 months of recurrent fever (up to 38.5° C) without chills and accompanied by headache, sweating and general malaise. He had a history of prostatectomy at 72 years, paroxysmal atrial fibrillation since 1980 (treated with flecainide and sotalol as needed), intolerance to amiodarone for hyperthyroidism and known mitral insufficiency with prolapse of the posterior leaflet.

The first blood tests performed (January 2012) showed neutrophilic leukocytosis with increased inflammatory markers and the chest X-ray showed a pleural haze. He hired levofloxacin for 10 days. After that a defervescence was observed, but with persistence of elevated inflammatory markers in blood tests.

In February 2012 a cycle of steroid therapy was performed on suspicion of polymyalgia rheumatic, without resolution of symptoms.

He also underwent echocardiography with detection of known mitral regurgitation and mild aortic stenosis.

In April 2012, he described an episode of gastroenteritis and fever after a trip to Libya, treated with levofloxacin. There was also a weight loss of 1–2 kg and detection of mild normocytic anemia.

For persisting fever and symptoms at this point he was admitted to hospital.

At admission the electrocardiogram showed sinus rhythm with right bundle branch block.

A PET scan was performed, in order to exclude temporal arteritis and a lymphoproliferative disorder. It gave a negative result. Transesophageal echocardiogram was also performed and showed vegetation on an aortic valve (right coronary cusp) with moderate mitral regurgitation.

On a febrile episode, blood cultures were performed, and turned out positive for Streptococcus sanguinis.

A panoramic radiograph revealed diffuse periodontal disease and polypoid thickening of mucosa in the left maxillary sinus.

He was initially treated with ampicillin (1 g three times daily) and gentamicin (80 mg three times daily) according to antibiogram. Despite an initial improvement, the inflammatory indices increased. So ampicillin dose was raised to 2 g six times a day.

During hospitalization a deterioration of circulatory compensation was also observed, with appearance of interstitial edema and pleural effusion at the bases bilaterally on chest radiographs.

A diuretic therapy was started, with good clinical response.

A new transesophageal echocardiogram showed:

1. marked worsening of aortic valve insufficiency (severe);
2. vegetations extending even to non coronary cusps;
3. slight worsening of mitral regurgitation (without vegetations on mitral valve);
4. normal left ventricular function.

The patient was immediately sent to a cardiac surgery department. After a coronary angiography (which didn't find any pathological

alterations), he was subjected to an aortic valve replacement, using a biological prostheses, and also to a plastic surgery of the mitral valve.

Hemophagocytic lymphohistiocytosis: an internist emergency

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We report the case of a 47-year-old woman with no relevant medical history, who was admitted to the Dermatology Unit for urticaria and then transferred to our Unit for the onset of high fever, mild piastrinopenia and increased inflammatory indexes. On admission, she underwent tests for infectious diseases, autoantibodies panels, chest X-ray and abdominal US, all negative. We started empirical wide-spectrum antibiotic therapy but no benefit was obtained. After a few days, due to the onset of polyarthritis, steroids and anti-inflammatory non steroid drugs were started on the suspicion of Still's disease or alternatively a vasculitis.

Two weeks after admission the clinical and laboratory picture suddenly deteriorated sharply, with the onset of respiratory failure and the appearance of a rash on the face and trunk, peak temperatures of 40.5 °C, anemia, piastrinopenia and neutrophilic leukocytosis, high amino transferase values, a marked increase in ferritin and LDH values, low fibrinogen, and proteinuria: 2 g/24 h. CT scan showed pulmonary thickening, bilateral mild basal pleural and pericardiac effusion, profound lymphadenopathy, signs of portal hypertension with collaterals at the splenic hilum and mild splenomegaly. Early serum CMV antigens and PCR for this virus were positive.

On the suspicion of hemophagocytic lymphohistiocytosis (HLH) secondary to CMV infection, we analyzed peripheral blood smears, bone marrow aspirate and myeloculture, all normal. Lymphocytogram and immunophenotypic analysis of the marrow showed increased CD8, and reduced CD4, B and NK lymphocytes. Despite the negative findings for hemophagocytosis, the fever, dual cytopenia, low fibrinogen, splenomegaly, high ferritin values and reduced NK led us to make a clinical diagnosis of HLH in accordance with the HLH-2004 guidelines. Therapy with Methylprednisolone 1 g/day, Indomethacin and Gancyclovir was started and the fever subsided, the respiratory failure resolved and the erythema gradually attenuated.

The evidence of multiorgan failure developing in this patient, a frequent observation in the natural history of HLH, dictated urgent treatment despite the lack of histological evidence of the disease. The ensuing rapid clinical improvement caused us to refrain from further biopsies. However, some clinical and laboratory aspects remained undefined, and we continue to monitor this patient to complete the diagnostic workup, paying particular attention to the possibility of an underlying immune disease.

Silent renal failure unveiled by hypertension diagnosis in a young "healthy" woman

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During a routine medical check-up, a healthy 35-year-old woman showed blood pressure values of 170/120 mmHg, confirmed during repeated measurements.

She reported no history of hypertension nor of cardiovascular and renal disease. She had no history of renal stones, renal or urinary tract infections and referred regular menstruo, without dysmenorrhea or chronic pelvic pain. A Holter BP monitoring revealed values constantly over 175/100 mmHg. In order to rule out a secondary hypertension, the patient underwent abdominal ultrasound (US) with Doppler study of renal arteries, that showed severe left hydronephrosis and left hydroureter, confirmed by urography (see Fig. 1). Renal scintigraphy with tubular tracer revealed a complete functional exclusion of the left kidney, totally compensated by the right one. Given persistent hypertension, a therapy with Angiotensin Receptor Blockers was instituted with good compensation. Magnetic resonance imaging (MRI) sequences showed a narrowing in the distal part of the left ureter, that was involved and surrounded by a soft tissue-similar mass, which was suggestive for pelvic endometriosis with left ureter involvement.

Left kidney was drained by nephrostomy, but 3 months later, given persistent hydronephrosis, the patient was submitted to the excision of the periureteral neoformation and the ureterolysis of the distal left ureter in combination with double-J stent insertion. Biopsies were sampled around the left ureter, and the histological diagnosis confirmed endometriosis. After surgery, blood pressure values normalized and antihypertensive therapy was withdrawn [1, 2]. Two months later, the patient complained of back pain at the left side. Clinical exam revealed a Giordano Sign positive for the left kidney and the recurrence of high blood pressure. Abdominal US showed recurrence of moderate hydronephrosis of the left kidney, with normal values of serum creatinine. Antihypertensive therapy was reinstituted, while urologist considered the recurrence of hydronephrosis as a consequence of the previous urological procedures. At a 3 months follow up, renal tract US showed resolution of hydronephrosis and cortical atrophy of the left kidney. Accordingly, renal scintigraphy revealed persistent failure of the left kidney and initial loss of function in the right one. At the follow up all creatinine measurements were normal.

Ureteral endometriosis is an unfrequent localization of extragenital endometriosis (less than 1 % of endometriosis cases), that can be complicated by progressive ureteral obstruction resulting in ureterohydronephrosis and silent loss of renal function [3]. The shown case highlights the need to extensively investigate the pathophysiology of hypertension in young women to rule out secondary causes of hypertension. Specifically, if a non-stone hydroureter or hydronephrosis is found, the possibility of endometriosis-induced hypertension must be investigated.

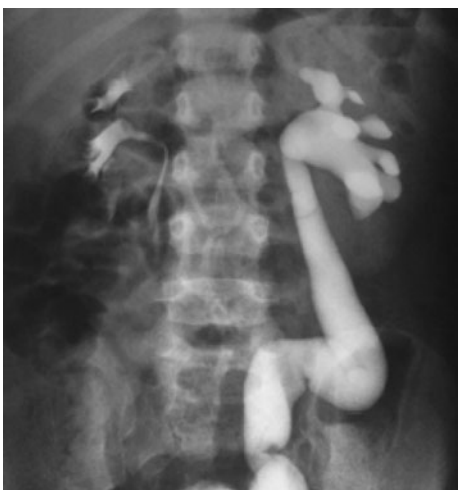

Fig. 1 Urography: left hydroureter nephrosis

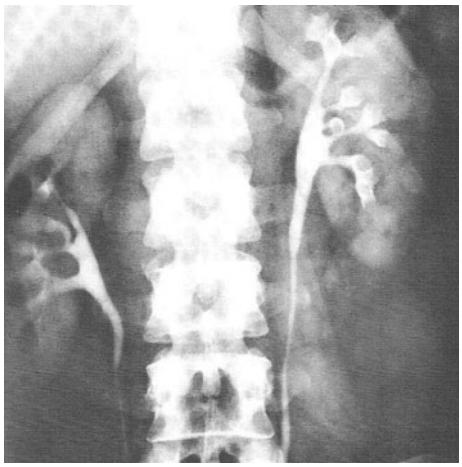

Fig. 2 Urography: normal left kidney

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A simple acute cholecystitis?

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Case Report: A 34 year-old-man, with a history of toxic-degenerative liver cirrhosis, was admitted to our Department for fever, worsening jaundice and abdominal distension. He also complained an intense epigastralgia radiated to the back. Laboratory workout, recently performed in China (where he had been on business), documented an increase of GOT, GPT, gamma-gt, alkaline phosphatase, total and direct bilirubin. The patient reported a recent ingestion of "Yusheng", a traditional Chinese raw fish salad. Objectively, the patient had fever (body temperature 39 °C), tense and globose abdomen, right hypochondrium pain on palpation and positive Murphy's sign. Cardiac and pulmonary examination was intact. The patient was alert and oriented. The laboratory exams, performed during hospitalization, confirmed those carried out in China and showed the presence of elevated ESR, neutrophilic leukocytosis, prolongation of the INR and thrombocytopenia. Electrolytes and renal function were normal. Chest X-ray, performed routinely, was normal. An abdomen ultrasound confirmed the diagnosis of cirrhosis and showed a distended gallbladder (length and A-P diameter 15 × 6 cm, respectively) with thickened walls and lumen occupied by hyperechoic and stratified material, compatible with biliary sludge. In the dependent portion of the gallbladder, a flocculent, nonshadowing and floating group of echos was appreciated. It changed in position in reaction to a light blow with the transducer. The stool examination was positive for *Clonorchis synesis*. These features, together with history, clinical and laboratory data, were suggestive for a diagnosis of acute cholecystitis provoked by parasites. The sonographic aspects (size, appearance and motility) were consistent with previous reports of gallbladder infections by *Clonorchis synesis* [1]. After treatment with mebendazole, the patient became asymptomatic with resolution of the laboratory abnormalities and improvement of the ultrasound features.

Conclusion: The gallbladder involvement by parasites is unusual in our country, but should be considered in the differential diagnosis in the presence of a suggestive history (e.g. recent travel to endemic areas) and typical sonographic features. Early medical treatment is associated with a substantial and rapid clinical improvement, thus avoiding any surgical approach [2].

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Doubtful splenic lesions in a patient with a history of colon cancer

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Introduction: Colon cancer (CC) is the fourth most common carcinoma and the second leading cause of cancer deaths in the United States. In 2009 there were 106,100 new cases with 49,920 deaths [1]. Common sites of metastases are liver, lungs and bones. Splenic involvement is unusual, arising in less than 1 % of all metastases, and may be asymptomatic or manifest with fatigue, asthenia and weight loss. Carcinoembryonic antigen (CEA) level is elevated in 73 % of cases. The sonographic pattern is variable, with prevalence of hypoechoic appearance [2]. Recent EFSUMB (European Federation of Societies for Ultrasound in Medicine and Biology) guidelines suggest Contrast-Enhanced Ultrasonography (CEUS) to characterize suspected splenic lesions on conventional US, pointing out that, based on the current evidence, malignant lesions can show typical findings such as peripheral or diffuse contrast enhancement in the arterial phase, followed by rapid and marked wash-out in the parenchymal phase [3].

Case Description: A 45 year-old woman came to our observation for worsening fatigue, weight loss (10 kg in the last 6 months) left ocular pain and headache. She did not report change in bowel habits. She reported a history of colon cancer undergone previous surgical resection and adjuvant chemotherapy 10 years before. She also reported a history for polycystic ovary syndrome and migraine. The physical examination was normal. A mild laterocervical lymphadenopathy was found. The complete blood count documented a mild thrombocytopenia and lymphopenia, with reduction of CD4 and CD4/CD8 ratio. Neoplastic markers such as Ca 19-9, Ca 125, AFP were normal. CEA was slightly increased. Serological tests for viruses and parasites were negative. Quantiferon test was normal. A baseline gray-scale sonography revealed the presence of splenomegaly with multiple and roundish hypoechoic lesions, in absence of echo color Doppler signal. The liver was enlarged without evidence for focal lesions. As recommended by the Efsumb guidelines, we performed Contrast-Enhanced Sonography (CEUS) with sulfur exafluoride which showed poor and peripheral enhancement of the lesions during the arterial phase and washout in the parenchymal stage with hypoechoic appearance during all the examination. CEUS pattern was highly

suggestive for malignancy. We also performed further diagnostic exams such as chest X-ray, which showed the presence of bilateral hilar lymphadenopathy and CT scan of chest and abdomen, which confirmed the presence of lymphadenopathy and hypodense splenic lesions, also showing multiple little hepatic nodules of non-unique interpretation. Esophagogastroduodenoscopy and colonoscopy were negative. PET-CT documented the presence of tracer uptake by the spleen and peri-bronchial, supra- and under-clavicular and mediastinal lymph nodes. In relation to reported eye pain and headache, we performed an MRI of the brain, which showed an increased size of the pituitary gland with compression of the optic chiasm. Finally, we performed a biopsy of supraclavicular lymph nodes, which revealed the presence of non-caseating and non-necrotizing granulomas.

Conclusions: The clinical and instrumental findings suggested a diagnosis of systemic Sarcoidosis. sACE levels were also increased, but lacked of sensitivity and specificity. In our patient, CEUS behavior posed problems of differential diagnosis with other focal lesions such as metastases or lymphoma. A correct diagnosis of Sarcoidosis is based on the exclusion of other diseases such as cancer, lymphoma or tuberculosis and on the biopsy of an accessible site. The patient improved with corticosteroid therapy. To our experience, CEUS may play a role in the evaluation of focal splenic lesions only if combined with other diagnostic exams, suggested by clinical findings.

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An unusual finding in a patient with headache and previous head injury

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Introduction: Headache is a very common disorder and is traditionally divided into secondary and primary, respectively based on the presence or not of known causes. Secondary findings for headache are unusual. Neuroimaging is expensive and has a low yield in headache patients. Most patients with intracranial pathology have clinical features that would raise a ''red flag''. A new or different headache or a statement that "this is the worst headache ever", maximum severity at onset, new onset after age 50, precipitating factors such as cough, sneeze, bending or with exertion (physical or sexual), worsening over time (months), evidence such as fever, hypertension, myalgias, weight loss or scalp tenderness suggesting a systemic disorder [1], neurological signs or seizures are all signs that raise suspicion of secondary headache and further diagnostic exams are needed.

Case Report: A healthy 61-year-old man presented to our clinic for bilateral high intensity throbbing headache, exacerbated by physical exertion, associated with photophobia and phonophobia but not with nausea and vomiting. The patient reported these symptoms since the age of 13–14 years. His mother suffered from headache associated with the menstrual cycle. The neurological examination was normal. In the last months the patient complained worsening of the number of episodes with unresponsiveness to common analgesics (previously effective). In childhood he had a head injury in the right parietal bone of the skull after an accidental fall down stairs. At palpation, a nodule with soft consistency was appreciated. For all these reasons we performed a Computer Tomography scan that showed the presence of an osteolytic lesion localized in the same site of the previous head injury, with radiopaque sequestration with "button" aspect, attributable to intact bone in the center of a circular area of destruction. An increase in the amplitude of the subarachnoid space below and a severe sinusopatia were also described. The radiological features were typical of eosinophilic granuloma. A brain Magnetic Resonance Imaging with contrast medium confirmed this report. Laboratory tests documented the presence of mild leukocytosis ($10.24 \times 10^3/\mu l$) with increase of neutrophils ($7.59 \times 10^3/\mu l$) and monocytes ($0.89 \times 10^3/\mu l$). A bone scan showed no areas of increased uptake except for the skull lesion. A neurosurgical evaluation did not indicate a need for surgery. The patient performs periodic CT scans documenting the dimensional stability of the lesion. A prophylactic treatment with magnesium, tryptophan and serotonin resulted in a reduction of the number and intensity of the crises.

Conclusions: The red flags listed above (unresponsiveness to analgesics, worsening over time), a history of head trauma and the lesion evident on palpation raised the suspicion of a secondary headache; however, the reported symptoms were suggestive for migraine and did not correlate with the lesion shown on CT. This was especially true because the lesion remained stable over time and the patient found benefit from prophylactic therapy. Eosinophilic granuloma (EG) is a rare benign tumor-like condition characterized by a clonal proliferation of Langerhans-type histiocytes [2]. Usually (90 %) occurs under the age of 15 years and is asymptomatic. Rarely a post-traumatic etiology is described. The incidence is estimated at 0.05–0.5 per 100,000. To our knowledge, this is the first detection of a rare case of post-traumatic eosinophilic granuloma associated with a primary headache (migraine).

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Acute confusional state in a patient with fever and hyperglycemia

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Introduction: Acute confusional state is an extremely common condition, affecting up to 30–50 % of the hospitalized patients older than age 70. It can be defined as a transient disorder of cognition and attention accompanied by disturbances of the sleep-wake cycle and psychomotor behavior [1]. The presence of advanced age and previous cognitive disorders are important risk factors. Common precipitating factors are alcohol and drugs intoxication (e.g. antipsychotics, antidepressants, prednisone, illicit drugs), metabolic disorders (e.g. hyperglycemia with or without diabetic ketoacidosis), infections with high fever (pneumonias, urinary tract infections) nutritional deficiencies (thiamine, vitamin B-12) and organ failure syndromes (COPD with hypercarbia or hypoxia, azotemia, hepatic failure with or without hyperammonemia). Focal brain lesions such as subdural hematomas, strokes and hemorrhages occasionally cause acute confusion.

Case Report: A 65 year-old woman, with a history of type-II diabetes treated with oral hypoglycemic drugs, anxious-depressive

syndrome and personality disorders in treatment, severe obesity and previous thyroidectomy (30 years before) with residual hypoparathyroidism in calcium-replacement therapy, a tracheostomy placement for vocal cord paralysis caused by post-surgical recurrent nerve injury, was admitted to our department of Internal Medicine for the persistence, from a few days, of space–time disorientation, hallucinations, agitation, tremor and fever (body temperature until 39.2 °C). She reported a previous hospitalization for an acute respiratory failure due to tracheal obstruction by a polyp endoscopically removed. The neurological examination excluded the presence of meningeal irritation and focal signs. The remaining physical examination was normal. Laboratory exams documented the presence of high blood glucose levels (400 mg/dl) and neutrophilic leukocytosis. Hemoglobin, creatinine, GOT, GPT were normal. Sodium and potassium levels were normal. The ionized serum calcium was reduced. Ketostix was negative. The arterial blood gas analysis ruled out the presence of respiratory or metabolic acidosis. Due to the detection of elevated blood glucose levels, the hypoglycaemic therapy was temporarily replaced with insulin, with a rapid resolution of the glycometabolic decompensation. The calcium-replacement therapy was enhanced with normalization of serum levels. Because of the persistence of confusion and fever, further investigations were performed, including urine culture, blood culture on three samples, chest X-ray and abdominal ultrasound (all negative). A bronchoscopy with BAL revealed an infection by *Geotrichum capitatum*. Adequate therapy was promptly inserted with resolution of the fever. Despite appropriate treatment, the confusional state persisted. Brain CT scan was therefore performed and documented the presence of diffuse calcifications on both cerebellar hemispheres, basal ganglia and white matter, excluding acute injuries. Based on the reported history and the presence of typical CT features (bilateral striopallidodentate calcinosis), Fahr's syndrome was diagnosed.

Conclusion: Bilateral striopallidodentate calcinosis (BSPDC, also called Fahr's Disease) is an extremely rare (less than 200 cases reported in the literature) sporadic or autosomic dominant disease characterized by calcium accumulation in brain sites such as basal ganglia and dentate nucleus [2]. More common in men (M:F 2:1), it is often associated with neurodegeneration and can be asymptomatic or manifest with movement and/or neuropsychiatric disorders. Symptomatic forms usually manifest in the fourth decade of life. In literature, the association with dysparathyroidism is described [3] and can suggest a major etiopathogenetic link between these two conditions. The treatment is not specific and is based on the amelioration of the clinical manifestations. Our patient was assigned to a neurologist which enhanced the antipsychotic therapy.

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From a vicious circle to a virtuous loop

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We report the case of a 68 year old man who had been suffering from recurrent syncopal episodes for the previous 3 years. These episodes usually lasted about 1 or 2 min, they were associated with diaphoresis and sometime chest oppressive discomfort; they were not related either to exertion or orthostatic position and presented with rapid and spontaneous recovery.

His past medical history was remarkable for *H. pylori* positive gastroduodenitis, unresponsive to eradication therapy and recently diagnosed arterial hypertension. The patient had many cardiovascular risk factors: family history positive for coronary artery disease, hypercholesterolemia, previous smoking. He was under medication with simvastatin 20 mg OD.

In order to investigate the possible cause of the syncopal episodes, the patient had already undergone several examinations as outpatient. A Holter ECG monitoring had demonstrated first degree atrioventricular block (already known at basal ECG), rare supraventricular and ventricular ectopic beats. An echocardiogram had identified only a right ventricle diastolic bulging and an altered compliance of both ventricles, then confirmed by a cardiac MR, thus excluding a major structural cardiac disease. Doppler US of the supra- aortic vessels had not shown any emodynamically significant stenosis, ruling out vertebral-basilar transitory ischaemia. A 24-h ambulatory blood pressure monitoring had revealed high blood pressure (BP) values, with preserved circadian rhythm; significant orthostatic hypotension had not been reported. An electrophysiological study had resulted negative, thus excluding a possible tachyarrhythmic origin of the syncope. In addition, a tilting test, although negative at baseline, was positive after the administration of sublingual nitrate: however, sensitivity and specificity of this pharmacological test is very low, thus this result was not useful for a conclusive diagnosis. At this point, considering that the patient was still complaining about transient chest-epigastric discomfort, apparently not related to gastroduodenitis and persistent recurrent syncopal episodes, to further exclude an arrhythmic origin of the syncope, we decided to place an external Loop Recorder device (Spiderflash, Elamedical). Surprisingly, during four different presyncopal episodes reported by the patient on the diary, ECG traces showed transient, less-than-a-minute, ST segment elevation associated with paroxysmal first and second degree atrioventricular blocks.

The patient was then immediately admitted to our Department and underwent a coronary angiography highlighting a 90 % stenosis in the middle segment of the right coronary artery, which was treated with a bare-metal stent. After the procedure, the patient remained asymptomatic during the whole hospitalization period. However, a subsequent control 24-h Holter ECG monitoring showed brief episodes of ST segment depression. For this reason, we performed an ergometric exercise test, which was positive for residual ischaemia, showing a ST segment depression from leads V3 to V6 on mild exertion, without chest pain, leading us to optimize medical therapy. The patient was discharged with the following therapy regimen: double antiplatelet therapy (acetylsalicylic acid and clopidogrel), ACE-inhibitor, statin, transdermal nitrate and pantoprazole.

There are different possible causes which might explain the patient's syncopal episodes, not necessarily excluding one another. A stenosis of the right coronary artery can be consistent with the occurrence of vagal symptoms such as diaphoresis as well as bradyarrhythmia, suggesting an inferior wall involvement with vagal overactivity. On the other hand, myocardial ischemia could have uncovered a pre-existent sick sinus syndrome.

Considering the residual alterations on Holter ECG monitoring and ergometric exercise test even after revascularization, we might speculate that the patient was affected by a diffuse cardiac disease (perhaps involving the microcirculation). Moreover, the transitory character of the ST segment elevation episodes as well as the occurrence of symptoms even at rest might suggest a vasospastic component.

After 1 month, the patient was admitted again to the emergency department for syncope associated with chest pain. He underwent another coronary angiography with no evidence of intra-stent restenosis or new culprit lesions. In order to prevent both arrhythmic and vasospastic mediated syncope and chest pain, the patient was implanted with a DDD bicameral pacemaker and amlodipine was added to the therapeutic regimen.

Hematology

Can MCP-1 and VEGF be used in the evaluation of first line therapy response in AL amyloidosis?

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Amyloidosis is characterized by an altered conformation of autologous proteins or their fragments. They aggregate into fibrils and are deposited in various organs and tissues in bundles of β-sheet fibrillar protein.
The most common form is light chain Amyloidosis (AL amyloidosis), characterized by a bone marrow plasma cells clonal subset. These produce monoclonal light chains of type κ or λ. The clinical spectrum of AL amyloidosis may involve kidney, heart, liver and peripheral nervous system, alone or in different association. AL amyloidosis is an insidious and potentially fatal disease. AL amyloidosis prognosis is related mainly to hearth involvement. Based on cardiac troponins and NT-proBNP serum values, conventionally AL amyloidosis is classified in three different prognostic panels that consider for the treatment choice.
Aim of the study was focused to evaluate MCP-1 and VEGF role in AL amyloidosis in relation to the first-line treatment also. The choice of these two molecules is related to their significant increase in angiogenic tumor microenvironment.
Peripheral blood samples were collected from 6 patients with systemic AL amyloidosis and from 10 healthy controls to detect serum MCP-1 and VEGF levels. After disease typization and risk stratification, all the patients were allocated to the first line chemotherapy with melphalan and dexamethasone (MDex).
Results were analyzed by Mann–Whitney test and "paired and unpaired t test". Probability (p) values ≤ 0.05 were considered significant.
In the patients, serum MCP-1 levels were significantly ($p = 0.004$) lower than the healthy controls (M ± SD: 333.20 ± 148.80 vs. 379.74 ± 79.20 pg/mL). While serum VEGF values were significantly ($p = 0.03$) higher in systemic disease if compared with those found in healthy controls (M ± SD: 242.50 ± 275.00 vs. 46.23 ± 36.44 pg/mL). After the first cycle of chemotherapy, VEGF values decreased significantly ($p = 0.04$) (M ± SD: 165.40 ± 207.40 vs. 242.50 ± 275.00 pg/mL). While, serum MCP-1 levels resulted significantly ($p = 0.04$) higher evaluated after the treatment (M ± SD: 410.10 ± 159.70 vs. 333.20 ± 148.80 pg/mL). On the basis of the results we can think that the treatment induced the decrease of pro-angiogenic VEGF activity. The MCP-1 increase is to relate to reduction of disease inflammatory activity.
In conclusion in systemic AL amyloidosis, the first-line therapy with MDex is effective in reducing significantly serum VEGF and MCP-1 values, suggesting the use of these substances in the response evaluation to therapy.
Further studies are required to evaluate both the role played by MCP-1 and VEGF in systemic AL amyloidosis, and if these mediators can be considered as markers in the disease management and if there is a relation between VEGF and MCP-1 levels and sFLC (serum free light chain) values.

Delayed diagnosis in global society

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Introduction: Sickle cell disease (SCD) is an inherited chronic haemolytic anaemia whose clinical manifestations arise from the tendency of the haemoglobin to polymerize and deform red blood cells into the characteristic sickle shape due to a single nucleotide change in the β-globin. Vascular occlusion of small and large vessels can lead to chronic damage of multiple organs including brain, lung, bone, kidney, liver, spleen, and retina.
Case Report: A 18 year old Kenyan man arrived to our attention for edema of the legs appeared in the previous 2 weeks. He was not able to speak Italian but in poor english language reported also shortness of breath and fatigue. NT pro BNP was 4126 pg/ml and ECG showed signs of right overload. He had no history of heart disease; in suspected pulmonary embolism, he was subjected to lung TC, but no evidence of pulmonary embolism was found.
Echocardiogram showed enlargment of right chambers with pulmonary hypertension. TSH was normal.
Only after 2 days we knew by boy's father that another son was affected by SCD; we requested hemoglobin electrophoresis that found no abnormalities; hemoglobin was 10.1 g/dl and ferritin was low (16 ng/ml). He was treated with iron ev, but in fifth day he suddenly died; during ALS maneuvers he was initially in PEA.
The autopsy showed endocardial scars.
The results of hemoglobin electrophoresis can be altered by iron status of the patient.
Cardiovascular manifestations of SCD include both right and left ventricular systolic and diastolic dysfunction, elevated cardiac output, cardiomegaly and myocardial ischaemia. Progressive heart damage from iron overload occurs in patients requiring routine transfusion therapy. Pulmonary hypertension resulting from intravascular haemolysis has also been recognized as a major complication that independently correlates with survival.
In our global and enlarged society is important for internist to know and consider problems that mainly affect people coming from other country in order to not miss and delay important diagnosis.

Pegylated interferons and ribavirin therapy for the treatment of chronic hepatitis C in thalassaemia major patients: preliminary results

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Introduction: Hepatitis C virus (HCV) infection is a major cause of liver-related morbidity and mortality among thalassaemic patients. HCV is responsible for 90 % of acute hepatitis in these polytransfused patients, and up to 80 % of them develop chronic hepatitis, being at risk of cirrhosis and hepatocellular carcinoma. Currently, pegylated interferons (PegIFNs) alone or in combination with ribavirin (RBV) are approved as first line therapeutic agents for chronic HCV infection

in transfusion-dependent thalassaemia, but very few data are available in literature. Interleukin 28B (IL28B) rs 12979860 genotype has been demonstrated to predict the sustained virological response (SVR) rates among HCV patients without hemoglobin disorders.

Aim of the Study: We want to evaluate the efficacy and the safety of combination therapy with PegIFNs plus RBV, and to assess the role of IL28B in predicting SVR rates on chronic hepatitis C infection in patients affected by thalassaemia major (TM).

Materials and Methods: We considered all TM patients with chronic hepatitis C treated with combined antiviral treatment, who were referred to our Clinic from 2006 to 2011. HCV genotype, HCV viral load and IL28B polymorphism were tested in all the patients. The severity of liver disease was assessed according to percutaneous liver biopsy and/or Fibroscan, before starting antiviral treatment. PegIFN and RBV were administered at standard dose. A SVR was defined as HCV-RNA undetectable 6 months after the end of the treatment (EOT).

Results: Among 57 TM patients with HCV chronic infection, 23 patients (11 females, 12 males—2 of them with cirrhosis) with mean age 36 years (range 23–46), underwent PegIFN plus RBV treatment. In this cohort, 17 patients (74 %) were infected with genotype 1, and 6 patients (26 %) with genotype 2. The C/C genotype of IL28B was detected in 6 patients (25 %), the C/T genotype in 12 patients (52 %), and the T/T genotype in 5 patients (22 %). A SVR was achieved by 13 patients (54 %), i.e. 5/6 patients (83 %) with HCV genotype 2, and 8/17 patients (47 %) with HCV genotype 1. Among patients with genotype 1, IL28B genotype did not influence the treatment outcome. RBV dose was reduced in 6 (26 %) patients after a median period of 24 (13–46) weeks, whereas RBV withdrawn was not necessary; among patients with RBV reduction, 5 (83 %) achieved a SVR. Neutropenia was observed in 5 (22 %) patients, in which PegIFN was reduced after a median period of 5 (3–36) weeks; a SVR was achieved by 4 (80 %) of them.

Conclusions: SVR rates among TM patients with HCV chronic infection were similar to those reported in patients without haemoglobin disorders and were not influenced by IL28B genotype, probably as a consequence of the small sample size. However, the use of RBV at standard dose was safe, since our patients required only temporary modification in their transfusion regimen and iron chelation therapy. No severe side effects were observed and RBV withdrawn was not necessary from any patient.

An atypical cause of chest pain

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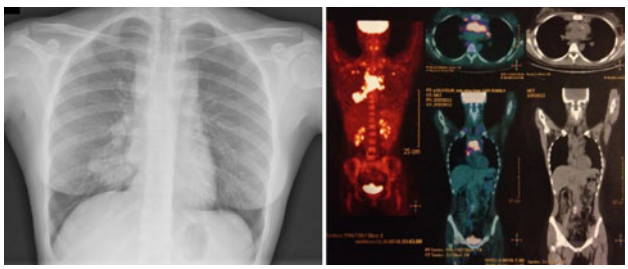
A 27-year-old woman was referred to us because of a 10-days history of chest pain. Pain was felt as a continuous anterior mid-chest pressure radiating to the right side of chest wall and to the jugulum. The physical activity did not increase the pain but was associated with mild fatigue and moderate dyspnoea. Previous clinical history was unremarkable and she had smoked 10 cigarettes/day over the past 10 years. Physical examination showed blood pressure 120/80 mmHg with pulse and respiration rates of 88 and 15 per minute, respectively. Temperature was 37 °C. In both supraclavicular spaces there were several enlarged lymph-nodes which, at ultrasound evaluation, were round-shaped, and partially conglobated (30 mm of maximum diameter). The chest X-ray showed multiple lymphadenopathy of the superior mediastinum and a poly-lobated mass in the middle lobe of the right lung (5.5 cm size). The pathological examination of a supraclavicular lymph-node was diagnostic for sclero-nodular Hodgkin's lymphoma. The diagnostic work-up included a bone marrow biopsy showing no bone marrow involvement and a PET–CT scan which showed multiple, partially conglobated lympho-adenopathies located in the anterior mediastinum (8.7 cm size), in the supraclavicular fossae, and in the right pulmonary hilum, with intraparenchymal extension. According with the diagnosis of a stage IIa Hodgkin lymphoma ABVD chemotherapy plus sequential radiotherapy were started.

Chest pain is one of the most common symptoms in Internal Medicine and, when it manifests as mid-chest pressure, a cardiac origin is usually feared. However an extra-cardiac origin should be considered and evaluated in all patients. In young female patients, that are unlikely to have cardiac ischemia, pericarditis and esophagitis are preferentially investigated, but also a simple chest X-ray may orientate the diagnosis.



Early aspects of hemophagocytic syndrome on a duplex hemopathy

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A 78 years-old man presented to our Division due to worsening fatigue, slight effort-dyspnea and palpitations. He had a three-years history of smouldering multiple myeloma (SMM) with biclonality (IgG-k and IgA-k). Seven months before, because of a severe macrocytic anemia, α-epoetin (40,000 U/week) was prescribed, without a complete resolution but rather worsening and becoming symptomatic over time. Physical examination evidenced tachycardia (102 bpm), hypotension (PA 100/70) and hepatosplenomegaly. Blood tests were: Hb 7.0 g/dL, HCT 20.7 %, MCV 102.6 fL, reticulocyte count 18.09 × 10^3/mmc, WBC count 2.9 × 10^3/mmc, PLT count 290 × 10^3/mmc, β_2-microglobulin 6.0 mg/dL, creatinine 1.44 mg/dL, uric acid 3.8 mg/dL, calcium 9.1 mg/dL, LDH 252 UI/L, ferritin 853 ng/mL. Seric vitamin B12, folate and aptoglobin were normal. The serum protein electrophoresis as well as the immunohistochemical test confirmed the biclonality of the plasma cells. Laboratory tests for bacteria, viruses and autoimmune diseases were negative. Moreover, skeletal survey didn't show any lytic lesions. Bone marrow smear examination revealed mild dysplasia of myeloid and erythroid lineages, 10 % of plasma cells, rare plasmoblasts, macrophages with aspects of hemophagocytosis. The bone marrow biopsy showed hypercellularity, 15 % of Marshalko-like plasma cells, macrophages with hemophagocytotic activity and multilinear dysplasia. All these findings were suggestive for a combined hemopathy: refractory cytopenia with multilinear dysplasia (a subtype of myelodisplastic

syndrome, MDS) and SMM with aspects of hemophagocytosis. Thus, pulse corticosteroid therapy was started (dexamethasone 20 mg/day for 4 consecutive days, repeated every 8 days). Three months later, because of several steroid-related side effects (asthenia, sarcopenia, peripheral edema, severe herpes labialis and hyponatremia), the patient was shifted to the less potent prednisone (25 mg/day for 4 days, then reduced to 12.5 mg/day), with progressive improvement and resolution of the above signs. After a 2-months of prednisone, the patient was asymptomatic and his blood tests were: Hb 14.4 g/dL, HCT 45.3 %, MCV 103.1 fL, WBC count 7.21 $\times$ 10^3/mmc, PLT count 204 $\times$ 10^3/mmc, creatinine 1.12 mg/dL, uric acid 8.2 mg/dL, calcium 9.5 mg/dL, LDH 446 UI/L. Surprisingly, biclonality disappeared both in the serum protein electrophoresis and immunohistochemical test, as well as the reduction of plasma cells (2 %) and the hemophagocytic macrophages on the bone marrow examinations was observed. On date, he is taking 6.25 mg/day of prednisone. In our patient we supposed an early manifestation of hemophagocytic syndrome (HPS) associated to a duplex hemopathy: SMM and MDS. HPS is a clinical manifestation of hyperactivity of morphologically normal, reactive macrophages, presenting as morphologic hallmark the phagocytosis of hematopoietic elements. These aspects can be found on bone marrow smears/biopsies, liver, spleen or lymph nodes. HPS can be classified according to underlying etiology into either primary (genetic) or secondary (acquired) HPS, this latter to be considered related to bacterial/viral infections, autoimmune disorders and malignancies, many of these latter hematological. The pathogenesis of HPS is still debated. It has been proposed an underlying uncontrolled stimulation of T cell and macrophages, leading to a release of large amounts of circulating pro-inflammatory agents (hypercytokinemia). Diagnosis is based on the evidence of bone marrow benign and reactive macrophages actively phagocytosing hematopoietic cells. The treatment of HPS, based on corticosteroids, cyclosporin and ethoposide, is aimed at controlling and inducing a remission of signs and symptoms by inhibiting the lymphocytic activity and suppressing the hypercytokinemia. Owing to the risk of secondary malignancies, ethoposide is not recommended in mild cases of HPS, in which steroid pulse therapy could be sufficient. Being a rare but aggressive and potentially life-threatening disorder, early diagnosis of HPS is a very important goal for a successful outcome. In our report, a rapid and complete diagnostic workup and a prompt treatment permitted to avoid the development of a frank and potentially fatal HPS. Regarding the MDS, Mailankody et al. (Blood 2011) observed an 11-fold increased risk in MM patients to develop MDS or another myeloid disorder, because of either therapy with melphalan or not yet completely known nontreatment-related factors. In our patient, these latter could have played an etiologic role in the development of MDS following SMM.

A chromosomic fever

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A 59 year-old man was proposed to our attention for a 2-months history of fever (T_c max 39° C), asthenia, lumbar pain and sore throat. He had been previously hospitalized at the Department of Infectious Diseases: he didn't take any medication previously, his remote and physiological anamnesis were negative for relevant pathologies, laboratory tests were remarkable for macrocytic anemia (GR 2.48 $\times$ 10^6/mmc, Hb 8.9 g/dl, HCT 28.9, MCV 116.3 fL, MCHC 31.0 g/dl) thrombocytosis (775 $\times$ 10^3/mmc) and increased blood levels of VES (48 mm/h). The evaluation for common causes of anemia, including assessment of serum creatinine, vitamin B12, folate, iron balance and the study of the gastrointestinal tract by esophagogastroduodenoscopy and colonoscopy were all normal, as well as immunological and infectivological screening. Antibiotic therapy with amoxicillin/clavulanic acid was administered, with regression of sore throat but residual asthenia, slight fever (mean T_c 37.3 °C) and persistence of the cellular blood count (CBC) alterations. Suspecting a hematologic disorder, we followed him as an outpatient. On physical examination his blood pressure was 127/84 mmHg, heart rate 96 beats/min; thoracic, cardiac, abdomen and neurological exams were negative. The peripheral blood smear examination evidenced mild anisocytosis/poikilocytosis and schistocytes in the erythroid lineage. We performed a bone marrow smear examination, which showed well-represented myeloid lineage with morphologic evidence of dysplasia and slight increase of blasts, erythroid lineage with partial maturative arrest and some macrocytes, mononuclear megakaryocytes. Therefore, a bone marrow biopsy was carried out, showing hypercellularity with dysplasia of both granulocyte and erythrocyte maturation, 3 % of CD34+ blasts, immature erythroblasts and occasionally clustered megakaryocytes with single/bilobal nuclei. This latter morphological appearance was suggestive for 5q- syndrome, which was subsequently confirmed by the cytogenetic analysis revealing the heterozygous deletion located at locus (5q31). Thus, therapy with lenalidomide (10 mg daily for 21 days every 4 weeks) was prescribed to the patient, which is ongoing and proving to be effective. To date, he is asymptomatic, his hemoglobin and platelet counts are normalized and he is waiting for a new, monitoring bone marrow biopsy.

The 5q- syndrome is a disorder recognized by the World Health Organization as a distinct entity of myelodysplastic syndromes (MDS), defined by a medullary blast count of less than 5 % and the deletion of the long arm of the chromosome5 (5q-), most frequently falling into 3 types: del(5)(q13q31), del(5)(q13q33) and del(5)(q22q35). This syndrome includes a severe macrocytic anemia, a normal or most frequently typical elevation of platelet count with hypolobated micromegakaryocytes, a normal or slight decrease of neutrophilic count and a low rate of progression to acute myeloid leukemia (AML) in comparison to the other types of MDS. Deletions are somatically acquired, heterozygous, and encompass many genes. Particularly, heterozygous loss of the RPS14 gene on 5q leads to activation of p53 in the erythroid lineage and to macrocytic anemia characteristic of the 5q syndrome, while megakaryocytic and platelet phenotype has been attributed to heterozygous deletion of miR145 and miR146a.

Usually, the bone marrow examination shows hypercellularity/normocellularity, erythroid hypoplasia, increase of clusters of megakaryocytes with abundant cytoplasm but unilobate/bilobate hyposegmented nuclei. Diagnosis must be supported by bone marrow and genotype examinations. Typically, <5 % marrow and <1 % peripheral blasts are observed. Lenalidomide, an immunomodulatory and antiangiogenetic agent, is the treatment of choice in the 5q-syndrome with symptomatic anemia. The rationale of its administration is based on dramatic therapeutic effects in patients with this specific disorder or other MDS however presenting a del(5q), due to high rate of response associated with sustained suppression of the del(5q) clone in the bone marrow, as well as its ability to reduce transfusion requirement and reserve cytologic and cytogenetic abnormalities. We emphasize the concept that in cases of macrocytic anemia not otherwise explained a MDS or another primitive hematologic disorder should always be suspected. In our case report macrocytic anemia and thrombocytosis were strongly suggestive for 5q- syndrome.

An aphthous stomatitis covering a myeloproliferative disease

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A 76-years old white man came to our attention due to aphthous stomatitis and musculoskeletal pain. He was under symptomatic treatment with corticosteroids from some months in the suspect of Behcet's syndrome. He was in good clinical condition with only one aphthous ulcer. Laboratory data showed a mild leukocytosis with a normal white blood cell count and macrocytosis. Two months later corticosteroids were reduced and aphthous stomatitis reappeared together with eosinophilia and renal failure in the form of nephritic syndrome and mild elevation of cholestatic signs. So we decide to perform more diagnostic investigations: autoimmunity tests were negative (ANA low-title, ENA, dsDNA antibodies, ANCA negative), HLAB51 and virological tests (HBV, HCV, HIV) were also negative. A peripheral blood smear showed vacuolated eosinophils. This data together with macrocytosis suggested a myeloproliferative disease. A bone marrow biopsy and a positive assay for FLIP/PDGFR confirmed the diagnosis of hypereosinophilic syndrome (HES).The patient started therapy with imatinib with good clinical and laboratoristic response and he continues regular follow-up. Aphthous stomatitis is a non specific sign of a large number of medical diseases. Cutaneous involvement occurs in 27–64 % of patients with HES. Only fifteen cases of HES with oral aphthous ulcerations are previously described. So an integrated internistic approach is often necessary in order to obtain a correct diagnosis. Excessive early treatment may complicate the clinical picture and it may hind the right diagnostic path.

Fever, anemia and splenomegaly: a case of non-Hodgkin's lymphoma

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A forty-five year-old woman was admitted to the hospital with complaint of severe anemia and generalized weakness.Two months before admission mild abdominal distension developed but was not accompanied by abdominal pain. She looks pale but otherwise seems well.

The temperature was 38.6 °C, the pulse 93 beats per minute and the respiratory rate 18 breaths per minute. The blood pressure was 130/75 mmHg, and the oxygen saturation was 95 percent while the patient was breathing ambient air.

On physical examination, no jaundice or scleral icterus was seen. A grade 1 systolic ejection murmur was present along the left sternal border. The abdomen was distended, and the navel protruded, a non-tender liver edge was 2 cm below the right costal margin and the splenic tip descended to the pelvic brim; no shifting dulness was found.

	Patient's value	Normal range
Red blood cell count	4.09	4–5.6 × 10^6/uL
Hemoglobin concentration	6.70	12–16.5 g/dl
Hematocrit	24.40	38–48 %
Mean corpuscular volume	66.10	82–98 fL
White blood cell count	4.09	4–10 × 10^3 μ/L
Neutrophils	61.40 %	
Lymphocytes	31.80 %	
Monocytes	6.60 %	
Reticulocytes count	2.43 %	0.5–2 %
Platelet count	225.00	150–450 × 10^3 μ/L
Total bilirubin	0.81	0.2–1 mg/dl
Indirect bilirubin	0.5	0.2–0.8 mg/dl
Lactate dehydrogenase	185.4	135–214 UI/L

Abdominal ultrasonographic studies confirm the presence of a marked spleen enlargement.

A computed tomographic (CT) study of the abdomen performed after injection of contrast material shows a marked splenomegaly (26 cm) and several retroperitoneal lymph nodes larger than 1 cm were visible.

A supportive blood transfusions was administered.

Mesenteric lymph nodes biopsy results showed non-Hodgkin's lymphoma: follicular lymphoma. According to the REAL classification the disease is graded into I-II.-CS IV B Bone Marrow Biopsy (+).

Immunophenotype:

CD 20+; CD 79 alfa+; CD 10+/−; BCL 2+; BCL 6+; Cyclin D1 neg; CD 3 neg; UCHL1 neg; CD 5 neg: CD 43 neg; CD 30 neg; CD 15 neg; Mib-1 = 35 %.

The patient was discharged with hemoglobin concentration 9.70 g/dl, hematocrit 32.70 % reticulocytes count 2.08 %, and while taking folic acid.

Twelve days later, the patient was readmitted in an another hospital because of abdominal pain, asthenia.

Laboratory tests shows:

	Patient's value	Normal range
Hemoglobin concentration	6.9	12–16.5 g/dL
White blood cell count	4.44	4–5.6 × 10^6/μL
Platelet count	199.00	150–450 × 10^3 μ/L
Lactate dehydrogenase	1,353	135–214 UI/L
Aptoglobin	<6	32–205 mg/dL
Direct Coombs' test	Positive	

The diagnosis is an iatrogenic anemia on bone marrow infiltration and hemolytic component.

A supportive blood transfusion was administered and started R-CHOP chemotherapy protocol + Rituximab.

Conclusion: Follicular lymphoma is an indolent B cell lymphoproliferative disorder, characterized by diffuse lymphoadenopathy, bone marrow involvement. In general, cytopenia can occur but

constitutional symptoms are uncommon, diagnosis is based on histology biopsy of a lymph node and immunohistochemical staining.

A bit bulky spleen

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In January 2012, G.V., a 79 years old woman, a retired farm worker, came to our observation because of poor control of long-lasting diabetes mellitus. Family history was negative for cardiovascular, autoimmune or hereditary diseases. Physiological anamnesis did not reveal any relevant data. She denied tobacco and/or alcohol abuse. Diabetes mellitus type 2 on treatment with insulin, hypertension and hepatic steatosis were reported. Home therapy consisted of FAS, colchicine, ACE-I, ASA, statin, IPP and insulin therapy. On examination: the patient was pale, there was no evidence of lymphadenopathy at the surface stations and there was no jugular venous distention. No fever. BP 130/70 mmHg. Heart rate of 90 pulses per minute, regular pulse. Nothing pathological at the chest examination. Heart: muffled tones. Abdomen: hepatomegaly, great splenomegaly of hard consistency. Patient's relatives reported that a circumferential pericardial effusion had been detected by echocardiography 12 months earlier; in August 2011, due to increasing pericardial effusion, the patient had been treated with methylprednisolone and colchicine, without any improvement. They also referred that the patient's splenomegaly had been observed 20 years earlier and controlled time by time by ultrasonography imaging. The patient did not report any symptom or abdominal discomfort that might be related to splenomegaly. ECG showed ST elevation concave upwards in leads D1 and aVL. Laboratory tests showed leukocytosis (14,420/cmm) with neutrophilia (12,500/cmm), lymphocytopenia (1,100/cmm), minor normocytic anemia (Hb: 10.8 g/dl, MCV 87 fL, MCH 28 pg), with normal reticulocyte count, platelet low count (58,000/cm) and elevated serum levels of inflammatory markers. Abnormal serum levels were detected for urea (148 mg/dl), creatinine (2.55 mg/dl), uric acid (18.5 mg/dl), LDH (730 UI/L), iron (41 mcg/dl) and ferritin (320 ng/ml).

Echocardiography showed: "…circumferential pericardial effusion, estimated in ca. 500 cc. No space for the safe execution of pericardiocentesis ", while ultrasonography of the abdomen revealed: "… increased liver volume. Increased spleen volume (about 25 cm longitudinal diameter) with finely heterogeneous echotexture." The total body CT scan confirmed previous findings.

A more accurate evaluation of splenomegaly was undertaken; the assay of beta 2-microglobulin was very high, while search for Philadelphia Chromosome was negative. The long lasting history of asymptomatic splenomegaly, the increased levels of LDH and beta-2-microglobulin, the normocytic anemia with low platelet counts, the more recent detection of chronic pericardial effusion, suggested the possible diagnosis of chronic lymphoproliferative disease and, more precisely splenic lymphoma. Therefore a ultrasonography-guided splenic biopsy was performed; histological and immuno-histochemical examination of the biopsy was compatible with the diagnosis of "Follicular non-Hodgkin's B cell splenic marginal Lymphoma". This form of splenic lymphoma has a indolent natural history with symptom-free long survival. In our patient, treatment will be required only if symptoms and severe cytopenia develop. Splenectomy or monoclonal Antibodies specific for the B cell CD20 surface molecule, as single agent therapy or in association with fludarabine or cladribine will be therapeutic options for the patient.

Anti-CD20 therapy in HIV-negative kidney transplant recipient with multicentric Castleman's disease and high levels of HHV-8 replication

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We describe the case of a 62 years old man who received a kidney transplantation in 2004 and was treated with immunosuppressive therapy (tacrolimus, mycophenolate and steroids). The patient developed cutaneous Kaposi's sarcoma one year after transplantation and was treated by surgery intervention and replacement of tacrolimus with rapamycin.

Six years thereafter he developed fever, night sweats, weakness, fatigue, anorexia, weight loss, hepatosplenomegaly, diffuse lymphadenopathy and peripheral edema, without evidence of Kaposi's sarcoma. Laboratory findings showed monoclonal gammopathy, severe anemia and thrombocytopenia, reticulocytosis, hypoalbuminemia, elevated values of C-Reactive Protein (CPR) (>200,000 mcg/L) and of beta 2 microglobulin. CT-scans revealed hepatosplenomegaly and enlarged abdominal lymph nodes. A bone marrow biopsy was within normal limits. Histological examination of a laterocervical lymph node biopsy revealed follicles with transformed germinal centers showing strong immunoreactivity for Human Herpes Virus-8 (HHV-8), especially in the immunoblastic/plasmablastic lambda restricted elements located in huge cloaks. Plasmablastic Multicentric Castleman Disease (MCD) was diagnosed. High circulating levels of HHV-8 DNA were detected in the absence of HIV infection (Fig). Kidney anti-rejection immunosuppressive therapy was decreased and ganciclovir iv was started with a evident temporary reduction of fever, weakness, CRP and HHV-8 DNA copies. For the persistence of anemia, thrombocytopenia, and given the poor clinical condition with recurrence of fever and raise in CRP, he was started on anti-CD20 antibodies (rituximab 375 mg/m^2); a quick reduction of HHV8 viral load was observed (Fig) but his clinical condition rapidly deteriorated and he died shortly.

Castleman's disease (CD) is a rare lymphoproliferative disorder characterized by angiofollicular nodular hyperplasia. Three histological patterns (hyaline vascular, plasmocellular and plasmablastic) and two different clinical presentations have been documented: localized or unicentric variant and systemic or multicentric variant (less common and more aggressive). The symptoms are heterogeneous, from asymptomatic mass seen in the unicentric form, to life-threatening systemic inflammatory state in the multicentric form.

The disease is found primarily in chronic HIV-positive patients and is strictly associated with HHV-8 coinfection, which is believed to play a key role in the pathogenesis of MCD. Recently the disease has been diagnosed in HIV-negative patients, who are usually elderly or immunosuppressed, as our patient. It has been demonstrated that lymph nodes from patients with HHV-8 related MCD harbor HHV-8 in IgM-restricted plasmoblasts localized in the mantle zone and marked by variable expression of CD20, a phosphoprotein expressed on the surface of mature B lymphocytes. IL-6, the major mediator of CD symptomatology, can be produced by activated B lymphocytes.

The ability to eradicate HHV-8–infected B lymphocytes by targeting CD20 with anti-CD20 monoclonal antibody, rituximab, has been shown in HIV-positive patients with MCD. Recently rituximab has been proposed, on the basis of phase 2 studies, to treat HIV-negative patients with MCD. In our case, a relevant reduction of HHV-8 viremia levels after rituximab administration was observed. Few cases of plasmablastic microlymphoma associated with HHV-8 infection

are described, in particular associated with prominent viral replication. It is possible that HHV-8 viremia may represent the epiphenomenon of the more aggressive form of MCD, characterized by lymphoproliferative disorder of plasma cells not responsive to the sole rituximab therapy.

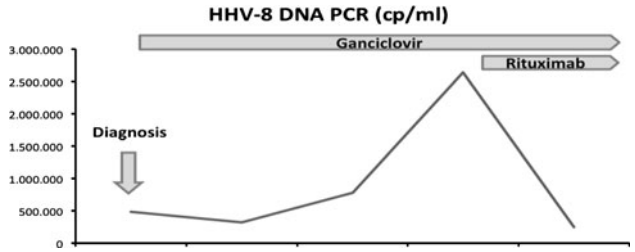

Figure Levels of HHV-8 viremia during the course of therapy

Thrombosis and Hemostasis

Cerebral vein thrombosis: long term recanalization rate and clinical outcome

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Background: Only few studies have investigated the long term recanalization of cerebral venous thrombosis (CVT) and the role of recanalization on clinical outcome of these patients is still unclear. Unfortunately, all these studies have a small sample size preventing any definitive conclusion.
Methods: Individuals from two large cohort of objectively diagnosed consecutive CVT patients were evaluated for inclusion. Only patients with a objective follow up imaging (angio-computed tomography or angio-magnetic resonance imaging) performed at 3 and 12 months after the index event were included. Patients with a CVT recurrence during follow-up were excluded. Vessel status at follow-up was categorized as complete, partial, or no recanalization. A complete or near complete recovery was defined as a score of 0 or 1 on the modified Rankin Scale (mRS). The following potential predictors of absence of recanalization and of clinical outcome were evaluated: age, gender, personal history of venous thromboembolic events, use of hormone therapy at the time of index event, unprovoked nature of the index event.
Results: 309 CVT patients (71.5 % female, mean age 40.2 years) were included; 143 patients had a follow-up imaging at 3 to 6 months and 166 patients at 7 to 12 months after the index event. Complete and partial recanalization in patients evaluated at 3 to 6 months and in patients evaluated at 7 to 12 months were not statistically different (76.9 vs. 71.8 %; $p > 0.2$). At univariate analysis only age > 45 years was associated with a higher risk of no recanalization ($p < 0.05$). This result was confirmed at multivariate analysis with a per year Odds Ratio [OR] of 1.020 (95 % confidence interval [CI] 1.003, 1.037; p 0.02). mRS at the time of follow-up imaging was available for 248 patients (80.3 %); 223 of these patients (89.9 %) had complete or near complete recovery.
Complete or partial recanalization and use of hormones was associated with a better outcome at the univariate analysis and these results were confirmed at the multivariate analysis (OR 2.63, 95 % CI 1.05, 6.61, p 0.039 and OR 3.88, 95 % CI 0.99, 15.19, p 0.05 respectively).
Conclusions: About three quarter of CVT patients had complete or partial recanalization. Age was the only independent predictor of absence of recanalization. Complete or partial recanalization and use of hormones seem to be associated with a better outcome in these patients.

ABO blood group phenotype and risk of VTE recurrence: results of a multi-centre case–control study

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Introduction: The ABO blood group phenotype has been associated with increased risk of a first venous thromboembolic event (VTE) in several studies. On the other hand, no study has evaluated its role in patients with recurrent VTE. Thus, we conducted a multi-centre case–control study to evaluate the role of ABO blood group phenotype in these patients.
Methods: In a multi-centre case–control study, the ABO blood group phenotype was evaluated in consecutive patients with objectively confirmed recurrent deep vein thrombosis (DVT) or pulmonary embolism (PE) and in age (±3 years) and sex matched controls without VTE.
The presence of known risk factors for VTE was documented. The prevalence of different blood group phenotypes was compared between VTE patients and controls. Odds Ratio (OR) and the corresponding confidence interval (CI) were calculated. Subgroup analyses including only patients with unprovoked VTE and patients with VTE secondary to known risk factors were provided.
Results: Two hundred and fifty one patients and 228 controls were enrolled. As expected age and sex were similar in the two groups (mean age 55.7 and 56.3 years; male sex 53.3 and 55.7 % respectively). One hundred and thirty seven (54.6 %) of the first episodes and 142 (56.6 %) of the second episodes of VTE were unprovoked. VTE was unprovoked in both episodes in 88 patients (35.1 %) whereas was secondary to a risk factor in both episode in 60 patients (23.9 %). Non-OO blood type was present in 192 VTE patients (76.5 %) and in 126 controls (55.3 %) for a corresponding OR of 2.63 (95 % CI 1.78–3.89; $p < 0.001$). Results of subgroup analyses including only patients with unprovoked events and only patients with events secondary to a risk factor gave similar results (data not shown).
Conclusion: Non-OO blood type seems to be associated with a clinically important increased risk of recurrent VTE. Future studies should evaluate its prevalence in comparison to patients without recurrence.

Clinical history of patients with superficial vein thrombosis: results of a multicenter Italian cohort study

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Introduction: Superficial vein thrombosis (SVT) is a common disease. Traditionally, SVT has been considered a relatively benign

disease. However, only a few studies have evaluated the long term clinical history of these patients. Thus, we performed a multicenter cohort study to evaluate their clinical history.

Methods: At each participating center, data on consecutive cases of patients with a objectively diagnosed SVT were collected. All eligible patients have been regularly followed by the local anticoagulation clinics. Furthermore, all included patients were contacted by the investigators that collected information on their clinical history. Only objectively diagnosed events were considered. Presence of potential risk factor for deep vein thrombosis (DVT) and pulmonary embolism (PE) was evaluated.

Results: Of the 473 patients initially evaluated, 76 were excluded for the presence of a concomitant DVT or PE and 39 did not have a follow-up leaving 358 (225 females; 62.8 %; mean age 55.1 years) patients for inclusion. Median follow up was 32 months and patients were followed for a total of 1,267 patient-years. More than 85 % of patients were treated with low molecular heparin or fondaparinux and in 85 patients (23.7 %) oral anticoagulant therapy was subsequently introduced. The mean treatment duration was 30 days and 29 patients were treated indefinitely. At the end of follow up, 12 patients died (3.4 %), 63 (17.6 %) had a SVT recurrence and 48 had a DVT or a PE (13.4 %) for an overall incidence of 31.2 events per 1,000 patient-years. DVT/PE patients were more frequently obese than patients without these events (45.8 vs. 24.2 %, p 0.006).

Conclusions: The long term risk of DVT and PE appears to not negligible in patients who had a previous SVT. Presence of obesity at the time of index event may be associated with a higher risk of DVT or PE.

Management of a refractory patient with thrombotic thrombocytopenic purpura (TTP)

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Thrombotic thrombocytopenic purpura (TTP) is a serious disease characterized by microangiopathic hemolytic anemia, thrombocytopenia, and a severe deficiency of the vonWillebrand factor-cleaving protease ADAMTS13. ADAMTS13 deficiency is usually severe (<10 % of normal activity) and results from autoantibodies directed to the protease (acquired TTP) or from mutations of the encoding gene. Acquired TTP occurs in association with specific diseases: connective tissue diseases, HIV infection, cancer. Daily therapeutical plasma exchange (TPE) is the basis of the management of acquired TTP. Mechanism underlying acquired TTP explain the effectiveness of immunosuppressive treatment (high-dose glucocorticoids), associated with TPE. Recently, the anti-CD20 monoclonal antibody rituximab has been used in patients with refractory disease. We report a case of a 53-years-old woman admitted for an episode of acute transient ischemic attack, occurred one day before, associated with anemia and thrombocytopenia. She maintained good health until then, except for reported recent infection by Herpes Simplex virus. The laboratory tests revealed: microangiopathic hemolytic anemia (marked increase in schistocytes at peripheral blood smear, elevated reticulocyte and lactate dehydrogenase, reduced haptoglobin) and thrombocytopenia. Antibodies against ADAMTS13 were present, ADAMTS13 activity was <3 % (with normal values between 45 and 138 %). A diagnosis of TTP was made and TPE was started, associated with glucocorticoids (1 mg/kg). The patient underwent 8 consecutive daily TPE without laboratoristic and/or clinical advantage. At day 9, she started 4 weekly intravenous doses of rituximab, (375 mg/kg/weekly) concurrently with TPE, with clinical and laboratory improvement in 2 weeks. Also antibodies against ADAMTS13 decreased in a few weeks. During hospitalization the patient reported several infectious respiratory events, because of the immunosuppressive agents, requiring invasive ventilation procedure. She also presented Cytomegalovirus activation. The patient has not presented any evidence of autoimmune diseases or cancer. Interestingly, her father experienced an episode of idiopathic acquired haemophilia A. Our experience suggest efficacy of rituximab in case of refractory TTP.

Thoracic aorta thrombosis with peripheral embolism associated with heterozygous prothrombin G20210A mutation

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Heterozygous prothrombin G20210A mutation is associated with venous thrombosis. However, arterial thromboembolic events may also occur in carriers of this genetic alteration when other risk factors are associated. We here report two cases of thoracic aorta thrombosis complicated by peripheral embolism in subjects with the G20210A prothrombin mutation.

The first patient is a 47 year-old woman admitted to our hospital with acute abdomen and critical right upper limb and lower limbs ischemia. She was a smoker, and was on oral estroprogestinics since 3 years. Whole-body CT scan and aortography showed a massive mesenteric infarction with perforation of small intestine loops and spleen infarction. An irregular floating thrombus was also seen, apparently hanged on the aortic wall, extending for 4.7 cm from the arch till thoracic aorta, occupying the arterial lumen for 2.5 cm. The right subclavian artery was occluded. The peripheral angiography showed obstruction of the popliteal arteries and right forearm vessels. She underwent emergency partial ileal resection and recanalization of the forearm and right subclavian arteries and the two femoral arteries. The next day, a new procedure was needed because of persistent obstruction of popliteal arteries. Protein C and protein S, antithrombin, lupus anticoagulant, anti-cardiolipin antibodies, homocysteine were all within the normal range. On genetic screening, she resulted heterozygous for the prothrombin G20210A mutation. She eventually needed multiple amputations of feet fingers.

The second patient is a 74 year-old woman with persistent fever and sudden critical ischemia of the right lower limb that required urgent surgery. CT scan showed a floating thrombus on the descending thoracic aorta and a mitral valve vegetation. Because of suspected infective endocarditis, she underwent blood cultures and was started on full dose amoxicillin/clavulanate and gentamycin. No anticoagulant or anti-platelet treatment was started because relatively contraindicated in left sided infective endocarditis. However, 4 days later she presented with a massive pulmonary embolism and was found to have a deep femoral vein thrombosis. On further work up, thrombocytosis was noted that was unrelated to the transient inflammatory reaction and was also present at prior exams. She therefore underwent bone marrow biopsy that revealed a JAK-2 negative myeloproliferative disorder compatible with essential thrombocytemia. Genetic thrombophilia study also showed the presence of heterozygous G20210A mutation of the prothrombin gene. The patient was put on hydroxyurea, aspirin and warfarin, and recovered completely.

These cases further confirm that the prothrombin G20210A mutation, even in the heterozygous form, may cause a significant hyper-coagulable state and concur with other risk factors in triggering not only venous thrombosis but also severe arterial thromboembolic events.

An unusual case of acute abdominal pain

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A 32-year-old man, referred to the Emergency Department because of severe, acute, abdominal meso-hypogastric pain. He underwent an abdomen ultrasonography which revealed a thrombotic portal vein obstruction. An abdomen CT-scan with contrast showed marked portal vein dilatation (3.5 cm) with characteristics of an aneurismal-like enlargement at the site of the splenic-portal vein confluence, which appeared wholly occupied by thrombotic material. A thrombus of 3 cm of diameter extended also to the mesenteric vein. A moderate splenomegaly was documented while pancreas and liver parenchymas seemed normal with no evidence of intra- and/or extra-hepatic biliar ducts dilatation. The patient was admitted to our Internal Medicine Department (IMD). The patient reported no significant family or personal history of venous thromboembolism (VTE). He was a smoker, but there were no other clear risk factors for VTE. Nevertheless, the patient reported that, due to persistent constipation and occasional hematochezia in the 2 months prior to admission, he had undergone a proctosigmoidoscopy with diagnosis of an "aspecific proctitis". At physical examination, the epigastric and mesogastric regions were mildly painful. Peristaltic movements were normally *auscultable* with negative Blumberg and Murphy signs. Laboratory tests revealed a mild microcytic hypochromic anemia associated to hyposideremia and normal ferritinemia. White-cell and platelet count, inflammatory markers were normal. Neoplastic markers were also negative. Lupus anticoagulant, antiphospholipid and anticardiolipin antibodies, coagulation protein C and S, antithrombin III, activated protein C resistance, factor V Leiden and prothrombin 20210G>A mutations were negative; the patient was heterozygous for the MTHFR677C>T polymorphism. Upon arrival at IMD, intravenous sodium heparin infusion was promptly initiated or the persistence of mild abdominal pain, a thrombolytic therapy approach was initially hypothesized. However, since the strict follow-up by radiologic imaging during the succeeding hours showed a progressive reduction of the mesenteric-portal thrombus extension with complete regression of the abdominal pain, this option was discarded and oral anticoagulation was simultaneously initiated. The recent history of hematochezia associated with changes in bowel function needed further investigation, A colonoscopy revealed a picture suggestive for ulcerative colitis in active phase, which was confirmed by histological examination of colon biopsies. Thus, the porto-mesenteric thrombosis could be attributed to a complication of inflammatory bowel disease (IBD). Therefore, oral-rectal mesalazine associated folic acid was commenced. At discharge, the patient was asymptomatic and clinically stable while continuing the IBD therapy associated to warfarin. About a year after the diagnosis, an abdominal ultrasonography confirmed a splenic-portal vein axis free from thrombotic material and the colonoscopy documented a quiescent state of IBD, so that oral anticoagulant therapy could be discontinued. VTE infrequently involves uncommon sites as the splenic-mesenteric-portal vein system. Early diagnosis is often difficult because the most recurrent symptom, i.e. moderate to severe abdominal pain in the upper quadrants, as occurred to our patient, is largely aspecific and this rare disease may be associated to severe morbidity and mortality. Imaging techniques (Doppler ultrasonography, CT-scan, MRI) greatly contribute to early diagnosis. Regarding IBD, Talbot et al. observed that VTE occurred in 1.3 % of the patients during a 11-year follow-up study. Mesenteric and portal vein thrombosis were mainly post-surgery complications, while 77 % of peripheral venous thrombosis occurred spontaneously. In most cases (73 %) the disease was in active phase as demonstrated by the finding of increased inflammatory markers. On the other hand, it has been observed that mesenteric thrombosis may develop even during clinical remission with a mean time of 24.6 ± 13.5 years since IBD diagnosis. Mortality among patients with portal-mesenteric vein thrombosis is rather high, ranging from 25 to 50 % according to different clinical settings. Because of its rare occurrence, studies on splanchnic vein thrombosis are few and there are no randomized trials of adequate size to provide convincing data on appropriate duration of oral anticoagulation therapy, long-term prognosis, morbidity and mortality, which remain mostly unknown. Treatments with catheter-directed or systemic thrombolysis have been proposed in severe cases but results are contradictory in terms of efficacy and safety. Anticoagulation with vitamin K antagonists is associated with recanalization in 45 % of the cases and protects from recurrence. Lifelong anticoagulation is therefore recommended for splanchnic vein thrombosis where the vein is not recanalized and for those patients with inherited thrombophilia such as prothrombin or factor V Leiden mutation carriership. The issue of an appropriate anticoagulant therapy use in splanchnic vein thrombosis is even more complex than for other rare venous thrombosis for several reasons. Portal vein thrombosis often leads to severe sequelae such as portal hypertension, which in turn increases the risk of bleeding because of both esophageal varices and hypersplenism-related thrombocytopenia. Indeed, the decision on the duration of oral anticoagulation should be individually tailored according to the risk/benefit ratio due to presence or absence of major risk factors for bleeding or recurrent thrombosis. If the bleeding risk is low or absent, anticoagulant therapy should be continued until vessel recanalization is documented. In the presence of esophageal varices, an endoscopic bending and medical therapy with beta-blockers is suggested, while in the presence of thrombocytopenia oral anticoagulation is to be avoided if platelet count is below 50,000/mmc. Considering the prolonged remission of IBD, as it refers to the here described case, oral anticoagulation was discontinued when portal-mesenteric vein axis was completely recanalized.

A case of misunderstood diagnosis

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On June 2011 a 53 year old woman with severe anemia, thrombocytopenia and confusion was admitted to our division, following a transfer from another hospital. Medical history reported only the presence of hypertension under pharmacological treatment with beta-blocker (nebivololo 5 mg 1 tablet/day) and previous hysterectomy for uterine fibromatosis. The patient had been previously healthy up to 5 days before, when developed fatigue and headache: so she went to her family doctor who detected jaundice, pale skin, tachycardia and hypertension. The following day, due to an episode of syncope, she went to the Emergency Department of the localo hospital where severe anemia (Hb 7.6 g/dl), thrombocytopenia (PLT 5,000/mm^3) with normal coagulation's tests and hyperbilirubinemia (total bilirubin 2.3 mg/dl) were detected. So she practiced red cells and platelets infusions and she was also treated with orally prednisolone 1 mg/kg

for suspected Evan's syndrome. Early, after the transfer to our division, the patient presented psycho-motor agitation and confusion. The physical examination showed a pèale skin and mucous membranes, jaundice, petechial lesions on the extremities, tachycardia (101 bpm), hypertension (BP 150/90 mmHg), bilateral reflexes akinesia of upper and lower limbs, bilateral depressed pupillary refles and Glasgow Scale Score of 12; the ECG was normal. Later blood sampling for routine laboratory examinations, fearing intracranial hemorrhage, the patient practiced emergency in emergency encephalic CT scan with negative results for blood extravasation; at the same time tests confirmed the presence of severe anemia and thrombocytopenia (Hb 7.7 g/dl, PLT 18,000/mm^3) with normal coagulation's tests (PT 10 s, INR 0.9, aPTT 35 s, fibrinogen 355 mg/dl), negative direct and indirect Coomb's tested and showed a disproportionate increase in the levels of LDH (7,651 UI/ml); the microscopic examination of a smear peripheral blood also indicated the presence of schistocyte.

The presence of microangiopathic anemia not associated with consumption of clotting factors, and contextual encephalopathy addressed the diagnostic suspicion toward thrombotic thrombocytopenic anemia: therefore it was alerted the transfusion center for plasmapheresis but just 2 h after arriving at our clinic the patient experienced cardiac arrest with subsequent exitus despite the implementation of resuscitation.

This case report draws attention about a disease, thrombotic thrombocytopenic purpura, infrequent but burdened by high mortality (80 % of cases if not diagnosed and treated early): in this case, the signs of diffuse cerebral damage, which is a very specific diagnostic criterion, happened late and probably only after the administration of platelet meals. This therapeutic intervention is strongly discouraged because it causes a worsening of disseminated intravascular thrombosis.

Accuracy of emergency physician-performed ultrasonography in the diagnosis of deep vein thrombosis: a systematic review and a meta-analysis

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Background: Duplex ultrasound is the first-line diagnostic test for detecting lower limb deep vein thrombosis (DVT) but it is time consuming, requires patient transport, and cannot be interpreted by most physicians. The accuracy of emergency physician-performed ultrasound (EPPU) for the diagnosis of DVT, when performed at the bedside, is unclear. We did a systematic review and meta-analysis of the literature, aiming to provide reliable data on the accuracy of EPPU in the diagnosis of DVT.

Methods: The MEDLINE and EMBASE databases (up to November 2011) were systematically searched for studies evaluating the accuracy of EPPU compared to either colour-flow duplex ultrasound performed by a radiology department or vascular laboratory, or to angiography, in the diagnosis of DVT. Weighted mean sensitivity and specificity and associated 95 % confidence intervals (CIs) were calculated using a bivariate random-effects regression approach.

Results: There were 15 studies included, with 2,152 patients. The pooled prevalence of DVT was 23.1 % (474 in 2,152 patients), ranging from 7.4 to 47.3 %. Using the bivariate approach, the weighted mean sensitivity of EPPU compared to the reference imaging test was 96.6 % (95 % CI 90.5–98.8), and with a weighted mean specificity of 96.8 % (95 % CI 94.3–98.2).

Conclusions: Our findings suggest that EPPU may be useful in the management of patients with suspected DVT. Future prospective studies are warranted to confirm these findings.

Epidemiology of portal and deep vein thrombosis in hospitalized cirrhotic

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Introduction: Gastrointestinal bleeding is a common complication in cirrhotic patients, but it is now well known that the unbalance between pro and anticoagulant factors may also lead to the development of thrombosis, frequently of the portal vein (PVT; 1–25 %) but also of the deep veins (DVT; 0.5–1.8 %).

Aims and Methods: We retrospectively assessed the incidence of portal vein thrombosis and deep vein thrombosis in cirrhotic patients requiring hospitalization in the last 20 years in our hospital. We reviewed 16, 994 clinical records of cirrhotic patients admissions to the Agostino Gemelli Hospital in Rome between January 1982 and February 2012. DVT diagnosis included: deep vein thrombosis of the lower or upper limbs, thrombosis of the cerebral veins, other unspecified deep vein thrombosis. Statistical analysis was performed using Student's *T* test and Chi square test.

Results: Among 16,994 admissions to our hospital, we identified 10,334 cirrhotics. 230 of them were also discharged with the diagnosis of PVT or DVT (218/230, 94.7 %, PVT; 12/230, 5.2 %, DVT). Thus, overall, 218/10,334 (2.1 %) patients presented with PVT and 12/10,334 (0.01 %) with DVT. PVT patients were 157 male and 61 female, mean age at the first admission of 63 $\pm$ 11 (24–89) etiology 169 virus-related, 45 alcohol-related, 4 due to primary biliary cirrhosis. DVT patients were 5 male and 7 female, mean age at the first admission of 69 $\pm$ 9 (49–82) etiology 11 virus-related, 1 alcohol-related.

Among DVT patients, 8 presented with deep vein thrombosis of the lower limbs, and 4 with thrombosis of the cerebral veins. Admission for PVt patients was due to: decompensation (97), clinical re-assessment (93), symptomatic PVT (9), fever (4), hepatocellular carcinoma (HCC) treatment (4), malignancy (4), anemia (3), intestinal infarction (1), laparocele (1), cholelitiasis (1), cardiac decompensation (1); for DVT patients: clinical re-assessment (5), decompensation (3), flebitis (2), hemiparesis (1), cardiac decompensation (1). 65 patients in the PVT group and 1 in the DVT one presented also a HCC. There was no difference between age, liver disease etiology and the presence of HCC between the two groups; however, male patients seem more prone to develop PVT than females (Chi Square 5.032, $p = 0.025$). CONCLUSION: DVT incidence in cirrhotic patients admitted to our hospital (0.01 vs. 0.5–1.8 %) is low, while PVT incidence seems to be comparable to that reported in literature. In conclusion, DVT remains probably an underdiagnosed disease in hospitalized cirrhotic patients, unless it becomes symptomatic.

Prudent clinical-anamnestic assessment, first of all!

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Introduction: Dyspnea may be the only manifestation of serious disease. The authors describe a case of difficult diagnosis, started with dyspnea.
Case Report: Annalisa, female, 30, after surgery for ovarian cancer dx, in prophylaxis with nadroparin 5,700 once/day, on the third day after surgery, complains of dyspnea on minimal effort.

- Chest X-ray and ECG within the limits;
- A/B balance: pH 7.41, pCO_2 44, pO_2 56, HCO_3^- 27.9;
- Echocardiogram: mild tricuspid regurgitation and pulmonary pressure estimated at 30 mmHg;
- D-dimers never >250 ng/ml;
- Angio-CT lung: not perfusion defects.

These tests lead to conclude the consultant cardiologist for "lack of instrumental and laboratory data giving evidence for pulmonary embolism (PE)". Therapy: methylprednisolone 20 mg twice/day.
Dyspnea persisted, prompted consulting internist who, on the basis of further *A/B balance* (pH 7.5, pCO_2 32, pO_2 56, HCO_3^- 25), contends *"clinical assessment and A/B balance compatible with PE, in the absence of laboratory and instrumental elements that can suggest alternative diagnosis"*. He therefore recommends enoxaparin 100 mg/kg twice/day, starting oral anticoagulant therapy and requires *pulmonary scintigraphy* which, after 10 days of onset of dyspnea, shows *"image suggestive of widespread micro-PE"*.
A/B balance, practiced after 20 days: pH 7.38, pCO_2 42, pO_2 97, HCO_3^- 24.8; no dyspnea.
Discussion: The evaluation of clinical/medical history (*Wells score*) showed intermediate probability of PE, making unnecessary the determination of D-dimer. A/B balance and echocardiography were suggestive but Angio-CT lung (Gold Standard) is negative. In the specific case, normal D-dimer and Angio-CT lung negativity, made difficult, nearly hazardous, the diagnosis and, therefore, therapy, that aroused particular worry with the increased risk of bleeding (recent surgery. However, the clinical conviction and the absence of alternative diagnoses have led to practice adequate necessary anticoagulant therapy immediately and to request scintigraphy, which is highly sensitive but not available in emergency.
Conclusions: PE is burdened by high mortality if not promptly recognized and treated. It's a challenge to the physician in daily practice, because often symptoms, signs and instrumental tests are nonspecific. The case highlights the daily problems, which hospital physicians face, and enormous importance of prudent clinical/anamnestic assessment, first of all!

Relationship between ABO blood group and hemorrhage: a systematic review and meta-analysis of the literature

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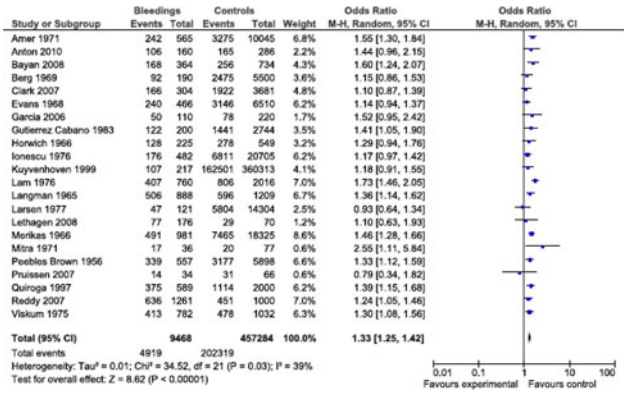
Background: Since the first description in the 1960, a number of studies have documented over many decades that ABO blood group has a profound influence on hemostasis, as it is a major determinant of plasma levels of von Willebrand factor and of factor VIII. Several studies and recent meta-analyses have suggested that patients with non-O blood group have an increased risk of venous and arterial thromboembolic events. On the other hand it is still not clear the role of ABO blood group on the risk of bleeding complications. Thus, we conducted a systematic review and meta-analysis of the literature with the aim of evaluating this potential association.
Methods: MEDLINE and EMBASE databases were searched up to March 2012. Research was supplemented by manually reviewing abstracts books from the Congress of the International Society on Thrombosis and Haemostasis (2003–2011) and the reference lists of all retrieved articles. Studies comparing the prevalence of different ABO blood groups in bleeding patients and in controls without bleeding complications were potentially includible. Two reviewers independently selected studies and extracted study characteristics, quality and outcomes. Pooled odds ratios (ORs) and 95 % confidence intervals (CIs) were calculated for each trial and pooled using a random-effects model. Statistical heterogeneity was evaluated using the I(2) statistic. Sensitivity analysis according to study quality and subgroup analysis including only patients with mucosal bleeding were performed.
Results: 22 studies for a total of 9,468 bleeding patients and more than 450,000 controls were included. The prevalence of O blood group was significantly higher in bleeding patients compared to controls with a resulting pooled OR of 1.33 (95 % CI 1.25, 1.42; $p < 0.001$), Figure 1. Sensitivity analysis including only high quality studies and subgroup analysis including only patients with mucosal bleeding gave similar results (OR 1.30, 95 % CI 1.20, 1.40 and 1.35, 95 % CI 1.26, 1.45 respectively).
Conclusion: Our results on a very large sample of bleeding patients and controls suggest that O blood group is a potentially important genetic risk factors for bleeding. High quality prospective studies are warranted to confirm our findings.



Diagnostic accuracy of lung ultrasound for pulmonary embolism: a meta-analysis

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Background: Computed tomographic pulmonary angiography (CTPA) has simplified the diagnostic approach to patients with suspected pulmonary embolism (PE). However, PE diagnosis is still

probabilistic and CTPA should be used with caution in several patients at high PE risk, such as patients with severe renal insufficiency and pregnant women. Among new alternative imaging procedures, lung ultrasound is the most promising technique. Based on available evidence, international guidelines have recently suggested it use in patients with suspected PE. The aim of our systematic review is to assess the diagnostic accuracy of lung ultrasound for PE diagnosis.

Materials and Methods: Studies evaluating the diagnostic accuracy of lung ultrasound in the diagnosis of PE were systematically searched for in the MEDLINE and EMBASE databases (up to April 2012). QUADAS-2 tool was used for the quality assessment of the primary studies. Weighted mean sensitivity and specificity with 95 % confidence intervals (CIs) were calculated.

Results: Eight studies, for a total 859 patients, were included. Six studies included CTPA has the main reference test, one magnetic resonance imaging angiography, and one multiple criteria. No study was judged of high quality. Lung ultrasound weighted mean sensitivity was 79.0 % (95 % CI 73.0–85.0) and weighted mean specificity was 89.0 % (95 % CI 84.0–93.0).

Conclusions: Our findings suggest that lung ultrasound may be a useful diagnostic tool in the management of patients with suspected PE if integrated in a diagnostic algorithm. Before implementing lung ultrasound in the routine care of PE patients, in particular in those with a contraindication for CTPA, management studies are warranted.

Venous thromboembolism in mother and daughter with homozygosity for MTHFR polymorphism C677T and without factor V (Leiden) genetic variant G1691A and factor II genetic variant G202010A

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Mrs C.R. (born in 1970) and Mrs C.A. (born in 1943) came to our attention in different occasions. C.R. (the daughter) was hospitalized because of dyspnea and left leg pain. Common laboratory exams resulted in normal values, except for D-Dimer test (1314 ng/ml; range 0.0–250.0). Negative chest X-ray. CT angiography: thin right pleural effusion. The patient was studied for MTHFR polymorphism and she was homozygous for C677T mutations, without Factor V (Leiden) genetic variant G1691A and Factor II genetic variant G20210A. Pulmonary scintigraphy showed bilateral micro-embolism (bloodstream in the right lung: 46 %; in the left lung 54 %). Afterwards her mother came to our attention. She suffered from *cholelithiasis, hypercholesterolemia, postsurgical hypothyroidism and* anxious state with cardiovascular somatization symptoms. Some time before she was treated with left saphenectomy procedure due to popliteal vein thrombosis. Our echocolordoppler showed left popliteal vein incompressibility; D-dimer test was a bit higher then maximum value. The patient was studied for MTHR polymorphism and she was homozygous for C677T mutations too, without Factor V (Leiden) genetic variant G1691A and Factor II genetic variant G20210A.

Recurrent arterial thrombosis in a patient with tuberculous lymphadenitis and connectivitis

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Background: The connection between inflammation and coagulation represents a given emerging in the literature in recent years, resulting in the process of hypercoagulability. In the literature, cases of vascular complications in the course of infection by Mycobacterium tuberculosis have also been described. In patients with active pulmonary tuberculosis there has been shown an increase in acute phase proteins of inflammation associated with hypercoagulability, causing hyperfibrinogenemia, increased fibrin degradation products (FDP), tissue plasminogen activator (t-PA) and an increase in tissue plasminogen activator inhibitor (PAI-1), with decreased levels of antithrombin, anemia and thrombocytosis. These alterations are potentially responsible for thromboembolic events. Also described was an increased prevalence of antiphospholipid antibodies in the course of tuberculosis infection. The venous thromboembolism, especially deep vein thrombosis, has been described in association with pulmonary tuberculosis infection.

Case Report: A woman of 55 years, strong smoker, undergone PTCA with stent placement on the left coronary artery for acute coronary syndrome, previous anticoagulant therapy with warfarin and dual antiplatelet therapy with ASA and clopidogrel. The patient in fact had a history of multidistrict vascular disease previous PTCA and stent placement on the right coronary, peripheral arterial disease is borne by her upper and lower limbs; an episode of TIA. On examination, she showed iposfigmia and asymmetry of peripheral pulses. Laterocervical lymphadenopathy was also seen. Blood tests showed modest leukopenia, increased ESR 87 mm/h, presence of ANA, ENA-SSA, anti ds-DNA and ACA. LAC and screening tests for hereditary thrombophilia were normal; p-ANCA and c-ANCA was negative as well as cryoglobulins. Persistently elevated d-dimer and monoclonal component (IgGk) at low concentration (4 %) were found. This result led to the exclusion of a systemic vasculitis. An angiography showed occlusive stenosis of the axillary artery at the origin with a complete occlusion of the left subclavian artery and critical stenosis of the internal mammary artery, while the circulation of the lower limbs was functioning. The biopsy of a laterocervical lymph node showed the presence of epithelioid and giant cells compatible with non-necrotizing granuloma (tubercular lymphadenitis). *M. tuberculosis* infection was confirmed by ELISPOT and was formulated by the diagnosis of undifferentiated connective disease (UCTD). A therapy with rifampicin, isoniazid and ethambutol was prescribed for 6 months with low dose corticosteroids (prednisone 15 mg/day), while the anticoagulant therapy associated with the dual antiplatelet therapy was continued together with the therapy with statin. After the first 3 months of therapy methotrexate (7.5 mg per week) was added. At the fifth month of therapy, the patient was subjected to coronary revascularization with bypass (CABG) due to evidence of trivasale coronary artery disease. Since the beginning of immunosuppressive therapy and CABG after the end of TB treatment, the patient had no

other thromboembolic events, a normalization of the indices of inflammation and of autoimmunity was also observed.
Conclusion: This case report suggests a possible association between TB disease, connective tissue and blood clots. The patient had episodes of severe and recurrent arterial thrombosis, in the absence of significant cardiovascular risk factors, except cigarette smoking, in the absence of congenital thrombophilia and during antithrombotic ceiling therapy. The inflammatory stimulus, associated with tuberculous infection, and UCTD induced a state of acquired thrombophilia also supported by the presence of ACA. In this condition the triple antithrombotic therapy was not sufficient to prevent recurrent thromboembolism. The pathogenic role of the patient's autoimmune and inflammatory disease would be supported by the absence of thromboembolic recurrence after eradication of the tuberculosis infection and after initiation of the appropriate immunosuppressive therapy. The concomitant diagnosis of UCTD and tuberculosis had suggested starting a mild immunosuppressive therapy with low doses of prednisone with MTX added later. In any case, complete remission was achieved both clinically and regarding laboratory analyses.

Atypical presentation of pulmonary embolism: a cohort study in an Emergency Department

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Introduction:
Background: The diagnosis of pulmonary embolism (PE) is not always easy because not all patients show the classic signs and symptoms of the disease and clinical presentation of PE may be lowly, atypical or masked by other conditions. On the other hand, the majority of deaths secondary to EP are due to the lack of recognition of embolic disease rather than to the therapeutic failure.
Objective: Description of a population of patients referred to the Emergency Department (ED) who were admitted because of a diagnosis of PE with an atypical presentation.
Materials and Methods:
Study Design: Retrospective cohort study.
Setting: ED in an Academic Hospital (Ancona, Italy).
Study Population: Consecutive patients who referred to the ED from January 2005 to May 2010, admitted because of a principal diagnosis of PE and presented with atypical symptoms for PE. The atypical symptoms of PE was defined by the absence of one or more of the following symptoms or signs: dyspnea, chest pain, hemoptysis or signs of deep vein thrombosis.
Study Protocol: We collected for each patient the following data: age, sex, symptoms, PE-Wells score, formerly known diagnosis of cancer, blood pressure, heart rate, shock index, D-dimers and the results of imaging tests (thoracic contrast-enhanced spiral CT or perfusion lung scan), in particular the finding of massive PE.
Results: We identified 342 patients admitted with a diagnosis of pulmonary embolism (68 patients/year). The cases with atypical presentation of PE were 86/342 (25 %): 54 % were male and the mean age was 72 years. The clinical presentation at arrival was the following: 34 (39 %) patients were asymptomatic and they were sent from Radiology Department to the ED because of the detection of PE on contrast-enhanced thoracic CT performed for other clinical reasons, 21 patients (24 %) with a syncope, 12 patients (14 %) with malaise, 10 patients (12 %) with trauma, 5 patients (6 %) with palpitations and 5 patients (6 %) with drowsiness. 60 % of patients with atypical presentation of PE had a high risk ($\geq$4) of the PE-Wells score, while only few patients had a shock index $\geq$1 or high value of D-dimer ($\geq$500 ng/ml): respectively 17 and 12 %. Overall 40 (46 %) of these patients had cancer and 72 % of this subpopulation showed no symptoms None of the asymptomatic patients with cancer had a high risk of the PE-Wells score and in 55 % of the cases, the value of D-dimers were high. On the other hand, a shock index $\geq$1 was calculated only in 38 % of patients with PE and syncope and a massive pulmonary embolism was found at the same rate.
Discussion: In our cohort, one in four patients with final diagnosis of PE occurred with atypical symptoms at arrival in ED and the most frequent presentation, apart from asymptomatic patients, was the syncope. The predictive value of the PE-Wells score, of a high value of D-dimers and a shock index $\geq$1 was low, even within the given subpopulations. These results confirm the difficulty of diagnosis of PE and suggest to maintain a high clinical suspicion for PE in those patients whose symptoms and signs are unexplained after the first diagnostic assays.

Endocrinology

Impaired GH secretion induced by physical exercise in primary hyperparathyroidism

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Background: Impaired GH secretion has been reported to occur in primary hyperparathyroidism (PHP) in various experimental conditions. In the present study we wondered whether these patients show a defective GH secretion during physical exercise.
Materials and Methods: In order to answer this question, 9 women with PHP (age 42–50 years) due to single parathyroid adenoma and 13 normal controls age-matched subjects (41–52 years) were evaluated. After fasting overnight in all subjects exercise was performed on a bicycle ergometer. The workload was gradually increased at 3 min intervals until exhaustion and lasted about 20 min in all subjects.
Results: Basal serum GH concentrations were similar in all subjects. Mean peak of GH during physical exercise was significantly lower in PHP patients than in the control group. Serum GH peak after physical exercise was unrelated to serum IGF1, PTH or inionized calcium.
Conclusion: The present results demonstrated that GH secretion induced by physical exercise is impaired in PHP suggesting that hypercalcemia has a deleterious action on GH release also during physical exercise.

Seasonal TSH variation and vitamin D status in an overweight euthyroid population

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Background: Several studies reported a circannual periodicity in TSH secretion but the determinants of this phenomenon are still undefined. As vitamin D is known to influence directly the pituitary axes, aim of this study was to investigate the role of vitamin D status,

tightly associated with seasonality, in determining circannual TSH changes in euthyroid subjects.
Methods: For this purpose, 294 euthyroid subjects (M/F: 133/161, 48.5 ± 12.4 years) among subjects referring to our Internal Medicine Unit for metabolic screening were studied. Study participants underwent clinical examination and routine biochemistry assessment. Serum 25(OH) vitamin D levels were measured by colorimetric method (LAISON) and hypovitaminosis was diagnosed for values <25 nmol/l.
Results: Significantly higher TSH levels were found in subjects who underwent blood sampling during the autumn–winter compared with individuals evaluated in spring-summer (2.3 ± 1.3 vs. 1.8 ± 1.1 μIU/ml, $p < 0.03$). Hypovitaminosis D was strongly associated with higher TSH levels ($p < 0.01$) and accounted for 45 % of TSH variability after adjusting for sex, age and sample's season. The presence of hypovitaminosis D was also associated with a higher prevalence of metabolic syndrome and its components.
Conclusions: These data demonstrate the presence of seasonal variability of serum TSH concentration in euthyroid subjects and provide evidence for the first time that an association exists between the seasonal serum 25(OH) vitamin D excursions and the circannual rhythm of TSH secretion.

A contended pituitary gland

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A 57 years-old woman presented with mild-effort dyspnea, fatigue, headache, recurrent fainting (especially after meals), evidence of high levels of blood pressure. On blood exams, evidence of microcytic hypochromic anemia (patient affected by thalassemia minor), neutrophilic leukocytosis; normal iron and ferritin levels. Hystory of hypertension, diarrhea with mucus in stoles, dysphagia (since 4 years) with diagnosis of ineffective esophageal motility, cholangiopathy with AMA-positivity; pangastritis; polyps of colon; thyroid multinodular goiter with hyperthyroidism on the first presentation, then evolved in hypothyroidism.
A heart disease was supposed: the ECG showed prolonged QT interval; the echocardiogram revealed mild mitral insufficiency; a perfusion lung-scan was negative for pulmonary embolism. The patient then performed a 24 h ABPM with diagnosis: "mild hypertension"; 24 h Holter ECG was normal. In consideration of headache, fatigue, recurrent fainting, dysphagia for liquids and paresthesias of the hands, a neurological consultation was requested; after a normal neurological exam, a brain MRI was indicated in the suspicion of a vascular or pituitary gland disease. MRI showed "increased volume of pituitary gland with homogeneous enhancement after contrast medium infusion, suspicious for pituitary adenoma". A visual field examination was performed with evidence of "incomplete homonymous hemianopia" of the left eye; at the hormonal profile: LH, FSH, cortisol, somatomedin-C levels were under normal range, ACTH was at lower limits; prolactin levels resulted normal. Therefore diagnosis of "hypopituitarism with pituitary macroadenoma" was set and a hormone replacement therapy was started.
Five months later, the patient underwent neurosurgical intervention for removal of pituitary gland. Histologic finding revealed "sarcoid granuloma".

A rare cause of syndrome of inappropriate antidiuretic hormone secretion: extrapulmonary small cell carcinoma

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Introduction: Hyponatremia occurs in about 30 % of hospitalized patients, while severe hyponatremia has been detected in 1 % of hospital inpatients. This condition has many different causes, each of which needs an accurate diagnosis in order to start the appropriate treatment. The Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) is the most common cause of severe hyponatremia. When severe (plasma sodium <120 mmol/L), there is an exponential increase in mortality. The in-hospital death rates are of 25 and 50 % in patients with plasma sodium concentration <125 and <115 mmol/L respectively.
SIADH can be secondary to a variety of problems ranging from drugs to malignancies, pulmonary disorders, central nervous system disorders, surgery, HIV infection. It may be, very rarely, idiopathic.
The Authors describe an uncommon case of SIADH that needed a relevant diagnostic effort to reach the correct diagnosis.
Case Report: A 83-years-old man came to our attention because of an accidental fall to the ground occurred at home. The patient lived alone; he remained a whole night on the floor before the admission to our Emergency Room. His previous clinical history included peripheral vascular disease treated with by-pass grafting, partial transurethral prostatectomy for benign prostatic hypertrophy, and mild progressive cognitive decline. His medical treatment included only aspirin 100 mg OD.
On admission the patient was alert, only slightly disoriented, presenting with normal vital signs. The laboratory examinations showed rhabdomyolysis (creatine phosphokinase 3862 U/L, n.v. 39–308), severe hyponatremia (114 mmol/L, n.v. 136–145), hypochloremia (80 mmol/L, n.v. 98–107). The ECG showed a first-degree atrioventricular block and a marked prolongation of QT interval (QTc 648 ms). The chest radiograph and the echocardiogram were unremarkable. The head CT revealed chronic vascular encephalopathy of mild degree. The patient was admitted to the Geriatric department.
Prompt treatment with intravenous hypertonic saline was started. Muscular enzymes progressively normalized but serum sodium remained markedly below the lower limits, despite further therapeutic measures, including water restriction, dietary salt supplementation, infusion of hypertonic saline up to 120 mmol of NaCl daily, and furosemide administration.
In the meanwhile, a diagnosis of SIADH was made: in fact, the patient was euvolemic, with decreased plasma osomolarity (255 mOsm/kg), elevated urinary sodium (168 mEq/L), a normal thyroid function, a normal pituitary-adrenal axis, a normal renin-angiotensin-aldosterone system. ADH values were inappropriately "high", resulting 3.1 pg/mL (n.v. 0–6.7) and 3.8 pg/mL on a second occasion.
In order to identify the cause of SIADH, we performed extensive clinical and laboratory investigations, including: chest and abdomen CT; head and spine MRI (for worsening of neuromotor activity). All this exams resulted not diriment.
Before starting treatment with tolvaptan, total-body PET CT was performed, that showed diffuse intense accumulation of 18-FDG at the whole skeleton (SUV max 6), suggestive of neoplastic bone marrow infiltration, and focal accumulation of 18-FDG at the right portion of the prostatic gland (SUV_{max} 7). Bone marrow biopsy revealed massive infiltration by small cell carcinoma with

neuroendocrine features. Of note, Neuron Specific Enolase (NSE) and chromogranin A were significantly elevated, i.e. 201.2 ng/mL (n.v. 0–16.3) and 374 UI/L (n.v. 0–20) respectively.
Conclusions: The case presented underlines the difficulty sometimes to reach a definite diagnosis of the cause of SIADH before concluding for an idiopathic form, and the difficulty in the treatment of SIADH-related severe hyponatremia; tolvaptan, a specific antagonist to the vasopressin-2 receptor (currently available also in Italy although expensive and not reimbursable by the National Health System), may be an useful but it needs to be used cautiously.
Although a very rare condition, the extrapulmonary small cell carcinoma should be keep in mind when approaching a patient with SIADH, especially when NSE is elevated and CT investigations are negative.

Subclinical hyperthyroidism and atrial fibrillation in elderly subjects

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Introduction: Subclinical hyperthyroidism, defined by low thyrotropin level with normal concentrations of free thyroxine (FT4) and triiodothyronine (T3), has been associated with several biological effects on cardiovascular system, such as carotid intima-media, thickness, increased heart rate, left ventricular mass, and plasma fibrinogen levels. Several observational studies have also reported an association between clinical hyperthyroidism and atrial fibrillation (AF), a common arrhythmia which may occur in paroxysmal and persistent forms. In elderly people, atrial fibrillation is common and subclinical hyperthyroidism occurs more frequently than overt hyperthyroidism. However, whether in this population patients with subclinical hyperthyroidism have an increased risk of AF is still controversial.
Aim and Methods: In the present study, we evaluated TSH levels, free thyroid hormone concentration and several cardiologic parameters in 785 consecutive elderly patients (378 men and 407 women, aged 68–82 years) with atrial fibrillation in the persistent or paroxysmal forma. All patients underwent routine laboratory exams with assessment of thyroid hormones levels, including TSH, FT3 and FT4. Standard electrocardiogram (ECG), transthoracic echocardiography and Holter ECG were performed in all patients.
Patients were excluded if they had elevated FT4 or FT3 levels. Also excluded were patients with nonthyroidal illnesses who were acutely ill when TSH was measured; patients ingesting thyroid supplements, glucocorticoids, or amiodarone. None of the patients included in the study showed the presence of other known risk factors for atrial fibrillation, including dilatative, hypertrophic or valvular cardiomyopathy, hypertension, diabetes and/or atrial dilatation. The final study group consisted of 175 elderly patients with atrial fibrillation in the persistent ($n = 84$) or paroxysmal ($n = 91$) form. The patient were divided in three groups according to the TSH levels (Group A = TSH < 0.5 μUI/ml; Group B = TSH comprised between 0.5 and 1 μUI/ml; Group C = TSH > 1 μUI/ml.
Results: Serum TSH values resulted <0.5 μUI/ml in 58 (33.1 %, Group A), comprised between 0.5 and 1 μUI/ml in 55 (31.4 %, Group B) and above 1 μUI/ml in 62 (35.4 %, Group C) patients. No significant differences were observed among the 3 groups for echocardiographic parameters (left ventricular end-diastolic, Left ventricular end-systolic, Interventricular septum thickness, Posterior wall thickness, Left atrial size, E/A ratio, Ejection fraction). Holter registration showed: Heart Rate (24 h) of 67.7 ± 10.8 b/m in the group A, 71.8 ± 8.9 b/m in the group B and 70.5 ± 18 b/m in the group C; Heart Rate (Max) of 134.6 ± 35.2 b/m in the group A, 124 ± 22.8 b/m in the group B and 119.6 ± 40.8 b/m in the group C; Heart Rate (Min) of 43.8 ± 8.3 in the group A, 43.7 ± 11 b/m in the group B and 45.8 ± 14.6 b/m in the group C; Diurnal Heart Rate of 71 ± 10 b/m in the group A, 75.3 ± 8.9 b/m in the group B and 69.7 ± 12 in the group C and Nocturnal Heart Rate of 68 ± 11 b/m in the group A, 65.6 ± 8.4 b/m in group B and 61.4 ± 9.5 b/m in the group C. Persistent AF was observed in 39/58 (67.2 %) patients in the group A, in 23/55 (41.8 %) patients in the group B and in 22/62 (35.5 %) patients in the group C. In the patients that returned to sinus rhythm, no differences in the E/A ratio was found in the 3 groups. However, both the wave A and E were significantly reduced in the Group A compared to the group B and C (wave E, Group A = 44 ± 25.7, Group B = 71.3 ± 10.2, Group C = 69 ± 17.8, $P < 0.0001$ and $P < 0.0001$, respectively; wave A, Group A = 49.4 ± 38.3, Group B = 85.6 ± 9, Group C = 80.2 ± 25.5, $P < 0.0001$ and $P < 0.0001$, respectively).
Conclusions: In summary, the 24 h, the Maximal and the Minimal Heart Rate did not significantly differ among the 3 groups; the circadian heart rate variation was lost in group A patients, while it was present in the other groups; the frequency of persistent AF was significantly increased in group with serum TSH values <0.5 μU/ml; both, the wave A and E were significantly reduced in the group with subclinical hyperthyroidism. In conclusion, these data suggest that low TSH concentrations are associated to increased chronotropism and represent a risk factor for AF in elderly subjects.

Epicardial fat thickness and left ventricular changes in subjects with adrenal incidentaloma

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Background: Whilst the majority of adrenal incidentalomas are nonfunctional adenomas, the occurrence of subclinical Cushing syndrome (SCS) has been reported. Abnormal left ventricle (LV) morphology and function have been described in patients with adrenal incidentaloma. Whether these changes are due to presence of the incidentaloma or SCS is still unclear. Epicardial fat is known to play a role in LV changes. Whether epicardial fat can be associated with the cardiac abnormalities in patients with incidentaloma is unknown.
Aim: We sought to test the hypothesis that excessive epicardial fat thickness, as measured with ultrasound, is independently related to cardiac changes in a well-studied group of subjects with adrenal incidentaloma.
Subjects and Methods: 46 consecutive patients (mean age 59 ± 9) with imaging diagnosis of adrenal incidentaloma and 30 healthy controls underwent standard transthoracic echocardiogram for epicardial fat thickness and LV mass measurement.
Results: 40 subjects presented non functional incidentaloma, whereas 6 patients were actually diagnosed with SCS. Epicardial fat thickness was significantly higher in patients with incidentaloma than controls (7.9 ± 0.8 vs. 7.4 ± 0.6 mm, $p < 0.05$) and in subjects with SCS when compared with those with incidentaloma (8 ± 0.7 vs.

7.4 ± 0.6 mm, $p < 0.01$). $LVM^{h2.7}$ was slightly higher in subjects with adrenal incidentaloma than in controls (50 ± 10 vs. 47 ± 8 g/$m^{2.7}$). Multiple regression analysis including also BMI, waist circumference and cortisoluria as independent variables showed that epicardial fat thickness was the best correlate ($R^2 = 0.36$, β 2.8, $p < 0.01$) of LV mass in patients with incidentaloma and SCS.

Conclusions: This study shows for the first time that subjects with adrenal incidentaloma present higher epicardial fat thickness that correlates with LV mass independently of the traditional markers of obesity and regardless the presence of SCS. Echocardiographic epicardial fat may serve as non invasive marker of earlier and asymptomatic cardiac abnormalities in patients with adrenal incidentaloma.

A very low vitamin D threshold, within the range of severe deficiency, identifies an increased risk of non-classical vitamin D-related outcomes in medical inpatients: a role for parathyroid hormone?

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Background: Vitamin D deficiency is a topical, worldwide health issue. Besides classical consequences on mineral and bone metabolism, low vitamin D levels have been associated with adverse outcomes, including arterial hypertension, diabetes mellitus (DM), heart failure (HF), chronic kidney disease (CKD), infections, and falls. Nevertheless, it is still unclear whether these associations are causal or, in contrast, mediated by other factors, such as secondary hyperparathyroidism.

Methods: We studied 115 consecutive inpatients (mean age 78.4 ± 12.4 years), admitted to two medical units of the major hospital in Genova, Italy (latitude 44°N), from October 2010 to April 2011. Vitamin D status was assessed by measuring serum concentrations of 25-hydroxyvitamin D (25OHD), as recommended by current guidelines. The CKD-EPI equation was used to estimate glomerular filtration rate (eGFR) and renal failure was defined as eGFR below 60 ml/min/1.73 m^2. Age, gender, season of observation, presence of a home-bound condition, hypertension, DM, HF, CKD, and infections were analyzed as possible determinants of 25OHD values in a linear regression model. Linear regression was also used to investigate the relationship between vitamin D status and parathyroid hormone (PTH) levels, with adjustment for age, gender, and eGFR. The relation of 25OHD values to: prevalent arterial hypertension, DM, HF, renal failure, and infection; risk of fall; and New York Heart Association (NYHA) class (hereafter referred to as "outcomes of interest") was studied by logistic regression.

Results: Median serum 25(OH)D concentration was 6.5 ng/ml (interquartile range 4–12.1 ng/ml). One hundred thirteen (97.8 %) patients had vitamin D deficiency (25OHD ≤30 ng/ml), being severe (25OHD ≤10 ng/ml) in 78 (67.8 %). Prevalence of severe vitamin D deficiency was even higher among elderly subjects (aged ≥65 years), reaching 70.3 % (71 out of 101 cases).

Age (β −0.35, $p < 0.01$) and DM (β −0.20, $p < 0.05$) were significant determinants of 25OHD values.

As expected, a significant inverse correlation between PTH and 25OHD levels was found, which persisted after adjusting for age, gender, and eGFR (β −0.26, $p < 0.01$).

Compared to concentrations equal to or higher than 8 ng/ml, 25OHD values below 8 ng/ml were associated with an increased risk of arterial hypertension (OR = 2.76; 95 % CI 1.07–7.22), HF (OR = 2.40; 95 % CI 1.06–5.92), symptoms of HF, as defined by NYHA classes 2 to 4 (OR = 2.84; 95 % CI 1.24–6.58), and infection (OR = 2.44; 95 % CI 1.02–5.87). In subjects with < vs. ≥ 8 ng/ml 25OHD, PTH was 88.0 ng/l (interquartile range 68.5–129.5) and 123.0 ng/l (interquartile range 92.7–208.2), respectively ($p < 0.01$). Since PTH was significantly correlated with 25OHD in the study population and may be responsible at least for some effects of vitamin D, it was considered along with 25OHD as independent variable in logistic regression for the outcomes of interest. Age and DM were also included, as they were determinants of vitamin D status in our patients. The analysis showed that PTH, but not 25OHD, was significantly associated with HF (OR 2.22; 95 % CI 1.10–4.85) and NYHA class 2–4 (OR 2.60; 95 % CI 1.13–5.96). As for prevalent infection, the association was found only in elderly, not bed-bound subjects (OR 2.75; 95 % CI 1.06–7.12).

Conclusions: Vitamin D deficiency was almost universal among medical inpatients. A small increase in concentrations of 25OHD, still within the range of severe deficiency, was associated with a significantly decreased risk of arterial hypertension, HF, and infection. Raised PTH levels may be partially involved in the mechanism underlying this association.

Resistant hypertension and heart failure

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A 54 yr old women was referred to Emergency Department for worsening dyspnea and palpitations occurring even at rest and nighttime. One year earlier she had discharged from another hospital with diagnosis of "idiopathic dilated cardiomyopathy", without arterial hypertension or diabetes mellitus. At admission blood pressure was 210/105 mmHg, heart rate was 75 beats/min; chest auscultation revealed mild expiratory wheezes and rales in both lower lobes. Electrocardiogram showed signs of left ventricular overloading and hypertrophy; blood tests showed a severe hypokalemia (1.8 mEq/L) and metabolic alkalosis (pH 7.51; pCO_2 41 mmHg; pO_2 86 mmHg; HCO3- 32.6 mmol/L; BE 10 mmol/L). Chest X-rays revealed an enlarged cardiac silhouette, congested pulmonary hilum, bilateral pleural effusion. Echocardiography showed an increase of left ventricular end diastolic diameter (LVEDD 58 mm) and of left atrial volume (LA 46 mm), normal walls thickness with values of interventricular septum (IVS 9 mm) and of posterior wall (PW 9 mm) an important decrease of global left ventricular performance (EF 30 %). The 24 h blood pressure monitoring (ABPM) revealed severe systo-diastolic hypertension without physiological nocturnal fall (no-dipper pattern). The patient was started on oxygen (4 L/min) and treated with potassium supplementation, amlodipine, carvedilol, digoxin and diuretic. Subsequent investigation showed a suppressed plasma renin activity (PRA) 0.08 ng/ml/h (normal range 0.2–2.7 ng/ml/h), high plasma aldosterone (PAC) 16.17 ng/dl (normal range 7.5–15 ng/dl) and the PAC/PRA ratio was 202.17 ng/dl: ng/ml/h (normal value <30 ng/dl: ng/ml/h). Including all these parameters (hypertension, hypokalemia, metabolic alkalosis and high PAC/PRA ratio) we suspected a PA. To confirm these data we have performed a captopril test: after 60 min by captopril 50 mg per os the PAC/PRA ratio was still elevated (529.93 ng/dl: ng/ml/h). In order to define the subtype of PA, a RMN of superior abdomen was performed and imaging of the adrenal glands demonstrated a 20 mm nodule in the left adrenal gland.

Thus, spironolactone (50 mg per os) was added to her treatment regimen and the patient underwent laparoscopy adrenalectomy. Histopathology revealed an adrenocortical adenoma. Subsequently his blood pressure has overaged 140/90 mmHg with amlodipina and ramipril and serum potassium was normalized. When last seen, 6 months after referral to this centre, her blood pressure was 110/80 mmHg, serum potassium 4.1 mEq/L, serum sodium 138 mEq/L. A new echocardiography demonstrated an important improvement of left ventricular hypertrophy and ejection fraction (EF 50 %). The patient was asymptomatic and was discharged without anti-hypertensive agents.

Primary aldosteronism (PA) is a common cause of secondary hypertension, defined as autonomous hypersecretion of aldosterone from adrenal gland, mainly due to either unilateral adrenocortical adenoma (APA) or to idiopathic bilateral hyperplasia (IHA), and it results in moderate-severe or drug resistant hypertension and increased awareness cardio-vascular remodelling, such as cardiac hypertrophy, fibrosis and vascular endothelium injury. Recently, the Primary Aldosteronism Prevalence in Italy Study (PAPY) reported a prevalence of PA of 11.2 % in newly-onset hypertensive patients. The potential comorbidity and prevention of excessive cardiovascular events and damage lead to development of accurate strategies for the timely diagnosis of PA.

The present report describes the case of a woman with PA that exhibited with heart failure due to dilated cardiomyopathy, completely reversed and cured after surgical adrenalectomy.

Cinacalcet in primary hyperparathyroidism: an alternative choice to surgery?

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Background: Primary hyperparathyroidism (PHPT) is a common endocrine disease characterized by increased serum calcium concentrations and inappropriately high serum parathormone (PTH) levels. Most of cases are due to a solitary adenoma and more rarely to multiple adenomas, hyperplasia or carcinoma of the parathyroid glands. Although parathyroidectomy remains the only curative treatment, patients affected by PHPT with contraindications to parathyroidectomy or persistent post-surgical PHPT have few non surgical options. Recently, medical therapy with the calcimimetic agent cinacalcet (Mimpara®) has been proved to be effective in reducing hypercalcemia and PTH concentrations in non-operable PHPT patients.

Aim: We report herein our experience with cinacalcet in selected PHPT patients, analysing cinacalcet therapy impact on biochemical parameters and monitoring its tolerability.

Patients and Methods: We studied 26 caucasian patients with PHPT (4 males, 22 females; mean age 66). In addition to persistent PHPT, inclusion criteria were: elevated surgical risk (7), uncertain tumour localization (8), high probability of surgical failure (1), disease recurrence after surgery (5), PHPT in the context of multiple endocrine neoplasia type 1 (4), surgery refusal (1). Biochemical data including PTH and serum calcium levels were collected before treatment with cinacalcet (time 0) and after 3–6 to 12–24 months. Mean follow-up was 13.7 months. Cinacalcet dosage was adjusted depending on the degree of calcemia reduction and drug tolerance.

Results: At time 0, 13/26 patients were symptomatic for hypercalcemia and 8/26 referred previous renal colics. Starting cinacalcet dose was 30 mg per day. After 12 months mean cinacalcet dose was 38.57 mg per day; one patient required the maximal dosage allowed (180 mg per day). At baseline mean PTH and calcium levels were 275.84 pg/mL (ULN 3.75) and 10.62 mg/dL (n.v. <10.50 mg/dL), respectively. After 6 months: PTH 197.13 pg/mL (ULN 2.60), calcium 10.11 mg/dL. After 12 months: PTH 164.87 pg/mL (ULN 2.71), calcium 9.89 mg/dL. After 24 months: PTH 151.5 pg/mL (ULN 3.00), calcium 8.86 mg/dL.

Before starting cinacalcet therapy, all patients had pathological calcium levels and after a 12 month therapy 71 % of them normalized serum calcium. As expected, most of our patients maintained abnormal PTH values during cinacalcet treatment. Cinacalcet administration was withdrawn in 8 patients for different adverse effects (face dermatitis and neck lymphoedema, asthenia, dyspepsia, nausea or vomiting, diarrhoea). In 2 patients treatment was reintroduced without disturbance. During the study one patient decided to undergo surgery previously refused.

Conclusions: Cinacalcet reduced serum calcium levels in PHPT without relevant side effects. Although further clinical studies are needed, our experience points to cinacalcet as a possible alternative treatment to surgery for several PHPT patient subgroups.

Severe hyponatremia after traumatic brain injury: a case report

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Case Presentation: A 44 years old Chinese man was admitted in Emergency Department on 15th March 2012 for polytrauma after fall of his bicycle. He showed alcoholic intoxication (serum ethanol level was 1.8 g/dl). A cranial CT scan was performed, and resulted in an extradural hematoma in right frontal region, and a composed fracture of right orbit. No sign of thoracic and abdominal injury was detected. No significant alteration of laboratory test was observed, except mild hypokalemia (Na+ 145 mEq/l, K+ 2.9 mEq/l); no anemia (Hb 13.9 g/dl), no alteration of coagulation time (PT 105 %, INR 0.99), no significant increase of cytolysis index (AST 34, ALT 46, CPK 655) were present. In his past medical history, there was only chronic HBV infection. He was then transferred to Neurosurgery unit and on 16th March evacuation of extradural hematoma was performed. Postoperative course was regular, he showed a complete neurologic recovery; only a mild hyponatremia was noticed (129 mEq/l); there was no maxilla-facial surgery indication. He was then transferred in Neurology unit on 20th March; here, he showed an increasing hyponatremia (see Table 1):

Table 1

Date	21/3	23/3	25/3	26/3	28/3	29/3	30/3
Na+ (mEq/l)	127	125	120	121	116	115	113–117

Urinary Na+ excretion was increased (522 mEq/24 h, normal values 27–287), serum osmolality was reduced (243 mOsm/kgH_2O, normal values 275–300) and urinary osmolality was 581 mOsm/kgH_2O; levels of ADH was in range of normality (6.4 pg/ml, normal value <6.7). According to laboratory findings, a diagnosis of syndrome of inappropriate antidiuretic hormone secretion (SIADH) was supposed; in particular, an increased effect of ADH action was considered. A

normal thyroid and glucocorticoid function was observed. Patient was then transferred in an Internal Medicine unit, he received treatment with supplement of NaCl (160 mEq/24 H for first 10 days), furosemide and strict water restriction. Na + levels gradually improved (see Table 2), until complete normalization observed at follow up of patient. A NRM of brain and pituitary gland was performed, and no lesions were observed. During the observation the patient did not present neurologic disorders.

Table 2

Date	31/3	1/4	2/4	3/4	4/4	5/4	7/4	8/4	9/4	12/4	13/4	16/4	10/5
Na (mEq/L)	117	121	118	121	122	118	128	127	134	136	135	141	142
	119	123	124	123									

Discussion: SIADH is present in the immediate post traumatic brain injury period (13 %), and often is completely reversible with water restriction and electrolytes supplementation. Etiology is often a damage of posterior pituitary, with a dysfunction of the gland, often in absence of radiological evidence. Correction of Na+ abnormalities must be gradual, in order to prevent possible brain hemorrhages. The outcome is often favorable.

Clinical Epidemiology

May blood donation reduce risk of illness? An observational study on a large cohort of blood donors in Ferrara, Italy

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Objectives: Empiric observations have suggested that blood donors (DBs) may represent a healthy subset of the population characterized by low mortality, but no definitive studies had been performed [1–3]. The aim of this study was to define if blood donors (BD) present an increased risk of illness or not.
Methods: We considered all subjects included in the data base of AVIS (Associazione Volontari Italiani Sangue), Province of Ferrara, but the analysis included only residents who had donated at least once. Non-residents were excluded.
For each BD from the archive master of the province of Ferrara, using a special computer program, four non-donors controls with same sex, country and data of birth (initially choosing the same year, month and as far as possible up to the same day) were selected.
For each BD from the archive master of the province of Ferrara, using a special computer program, four non-donors (NBDs) controls for sex and period of birth were selected. From the electronic databases of the Emilia Romagna Region were then extracted all hospitalizations that donors and "non-donors" had from January 2005 to December 2010.
Results: The analysis considered 37494 BDs and 149976 NBD controls. During the period considered were observed 26140 admission in BDs and 98685 in NBDs, relative to 11862 different BDs and 43138 NBDs. Hospitalized BDs subjects compared with hospitalized NBDs were characterized by: older age, lower average number of admissions, Charlson comorbidity index score, fewer hospital stays, lower rates of mortality, higher average age of death.
BDs had lower frequency of diagnosis of lung cancer, stroke, red blood cell disorders, while there was no difference for myeloproliferative disorders, heart failure and shock, or hospitalizations to perform chemotherapy. The risk of in-hospital death is lower for DBs compared to NBDs.
Average age at death was significantly higher for BDs with many years of donations and higher number of donations.
The risk of disease in relation to number of years of contributions or donations was evaluated by using the logistic regression analysis including in the model the main groups of diseases, age, sex and number of hospitalizations. BDs had an increased prevalence of obesity, osteoarticular diseases and varices.
High number and years of donations were not related with an increased risk of malignancy.
Conclusions: This study confirms that BD condition may represent advantage to reduce the risk of disease, and may be related with an increased chance of survival. If these data will be confirmed, an educational program of prevention will be needed.

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Unravelling the features of the familial Mediterranean fever (FMF) identified in Apulia and Basilicata. Our experience one year later

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Background: FMF is a rare autosomal recessive autoinflammatory disorder characterized by sporadic, paroxysmal attacks of fever and serositis with ultimate influence on gastrointestinal (GI) motility and function. FMF is typical in populations from the Mediterranean Sea (Sephardic Jews, Armenians, Turks, North Africans, Arabs, Greeks and Italians) and 100,000 people might be affected worldwide. The FMF gene (*MEFV*, cr16p) encodes a 781-amino-acid protein (pyrin or marenostrin), involved in the inflammatory cascade. To date, 222 MEFV mutations have been identified. Long-term complications of FMF include secondary (AA) amyloidosis in more than 20 % of cases. It has been also suggested that FMF patients have abnormal cardiovascular reactivity and autonomic nervous system (ANS) function, but the ultimate link with GI motility, amyloidosis, and autonomic dysfunction is poorly known.
Aim: To further characterize FMF patients in Apulia-Basilicata and relate genetic and clinical features with GI motility and ANS response.
Methods: 29 FMF patients (M:F = 13:16, age 39 ± 3SEM yrs) with MEFV mutations for compound heterozygous E148Q/R761H [57 %], R202Q/M694 V [3 %] and R202Q/I591T [3 %] or heterozygous

K695R [21 %], E148Q [11 %], R202Q [3 %], were recruited. In the asymptomatic phase, combined fasting/postprandial motility of stomach and gallbladder were assessed (functional ultrasonography), together with orocecal transit time (OCTT, H2-breath test, *Lactofan*®-Italchimici, IT) during 300 min in response to a modified 200 mL liquid test meal (*Nutridrink*®, plus lactulose 10 g). A large control group consisted of 142 age- sex- BMI-matched healthy subjects (M:F = 67:75; 38 ± 1 yrs). The study of ANS (heart rate variability, HRV and sweat spot test, SST) was performed in 14 FMF patients (M:F = 4:10) matched with 13 healthy controls (M:F = 5:8).

Results: Compared to controls, FMF patients had comparable fasting gastric antral area (FMF 3.3 ± 0.2 vs. 3.2 ± 0.1 cm^2), but significantly ($0.000001 < P < 0.001$) increased max postprandial area (FMF 14.1 ± 0.4 vs. 11.6 ± 0.2 cm^2), minimal postprandial area (FMF 4.3 ± 0.2 vs. 3.5 ± 0.1 cm^2) and delayed half emptying time (FMF 43.2 ± 1.2 vs. 26.6 ± 0.5 min). Also, FMF showed comparable gallbladder fasting vol. (FMF 19.8 ± 2.1 vs. 22.4 ± 0.5 ml), postprandial residual vol. (FMF 5.4 ± 0.4 vs. 5.5 ± 0.2 ml), and a trend to increased percent residual vol. (FMF 28.9 ± 1.6 vs. 24.8 ± 0.7 %, P = 0.059). Gallbladder emptying time was comparable (23.2 ± 1.7 FMF vs. 21.0 ± 0.5 min controls), while OCTT was longer in FMF (132.3 ± 10.5 vs. 99.5 ± 1.6 min, $P < 0.000001$). HRV was abnormal in 43 % (6/14) of FMF pts (P = 0.029 vs. control), while SST was abnormal in 71 % (10/14) of FMF pts (P = 0.0006), with decreased number of dots on the foot dorsum (FMF 478.5 ± 396.1 vs. 786.6 ± 418.8, P = 0.04) and SST score (FMF 7.1 ± 6.7 vs. 13.1 ± 7, P = 0.02). Serum amyloid protein (SAA) was increased in 33 % (8/24) of E148Q/R761H mutation patients. Motility defects persisted in spite of ANS dysfunction and SAA levels.

Conclusions: We firstly show here that FMF patients display abnormal gastric and small intestinal motility without a clear involvement of the gallbladder. Abnormalities of both HRV and SST suggest (a sublinical?) ANS dysfunction in FMF patients. In our setting, about a third of FMF patients show high level of SAA.

Clostridium difficile infection among 2008–2010 REPOSI patients

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Clostridium difficile is the main cause of hospital-acquired diarrhea in Europe and North America and *C. difficile* infection (CDI) is a cause of increasing hospital morbidity and mortality, length of hospital stay and costs of hospitalization. The increasing incidence of the disease is mainly due to the emergence of hypervirulent strains, use and misuse of antibiotics, and the increase of susceptible at-risk populations (advanced age, hospitalization, comorbidities). A recent Canadian study showed an incidences of health care–associated CDI of 28.1 cases per 10,000 patient-days. The most recent data from European studies reported a mean incidence of healthcare- associated CDI of 4.1 per 10,000 hospital patient-days; however, there was significant variability ranging between 0.0 and 36.3. Few data are available for internal medicine units and for adult population in Italy. A retrospective cross-sectional study in 4 internal medicine wards of Fondazione IRCCS Ca' Granda-Policlinico in Milan found an incidence rate of 23.3 per 10,000 patient-days. In this study, the prevalence and incidence of *C. difficile* associated diarrhea (CDAD) in patients admitted to internal medicine wards was among the highest of those so far reported. To assess the incidence of infection in Internal medicine wards on a nationwide base, we analysed data from the national REPOSI study, a collaborative study between the Italian Society of Internal Medicine and the Institute of Pharmacological Research "Mario Negri" that created a database collecting pathologies and drug therapies of elderly patients (age >65) at admission and during in-hospital staying in Internal Medicine Wards. We analysed data from 2008 to 2010, where 2713 patients were recruited to find out the incidence of CDAD. The majority of internal medicine ward patients have all risk factors for CDI (i.e. old patients with comorbidities, frequent use of wide spectrum antibiotics, prior hospitalization, use of feeding tubes and of proton-pump inhibitors). We found that 190 patients were assuming antibiotic therapy at admission and 550 received an antibiotic therapy during the in hospital staying. From this group many patients took more than one antibiotic, in particular 202 used two different antibiotics, 47 three and 14 four. Considering these data we expected an high incidence of CDI but only 20 cases were reported. So we wonder if this datum is real and we asked different questions:

Is the incidence so variable throughout the country?
Is the different incidence due to the presence of different strains?
Is the awareness about the *C. difficilis* associated disease adequate to enable the identification of all cases?

Importance of the interaction between internist and ophthalmologist in prevention of eye diseases due to systemic diseases. Epidemiological study

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Purpose: The purpose of this study, managed together between UOC A and Ophthalmology Interior Medical Service—Sapienza University of Rome—was to present in the activity area of "IAPB Italia Onlus" (International Agency for the Prevention of Blindness) the prevention of eye diseases due to systemic diseases, to have a picture of Italian population's general health, identifying the most common diseases, their treatment and the use of sanitary system for preventive purpose.

Materials and Methods: The sample considered has been extrapolated by primary and secondary prevention campaigns undertaken by "IAPB Italia Onlus" through mobile ophthalmic units from 2005 to 2011 across the whole country.

Results: 136,160 people were examined in the mobile ophthalmic units. The average age of the sample was 26, 14 years old. 12 % of the patients presented systemic diseases and more precisely a 6 % of them reported arterial hypertension. Regarding the gender, 66,036 (48 %) subjects were female and 70,124 (52 %) male.

Systemic diseases were reported by 16,784 people (12.3 % over the total sample), and in particular:

3,618 diabetes (2.6 %);
8,421 arterial hypertension (6.2 %);
905 rheumatic diseases (0.6 %);
3,804 allergies (2.8 %).

Focusing only on subjects older than 40, arterial hypertension hit about 19 % (8,225 subjects, nearly 97.6 % of the high-blood pressure sufferers) and diabetes hit 8.3 % (3,499 subjects, nearly 96.7 % of all diabetics). For the over 60′s, the percentages found were respectively 23 and 11.4 %.

Such diseases already had an impact on the eye: the fundus oculi examination, carried out on 7,248 subjects (5.32 %), showed pathological changes: 2,335 suffered from hypertensive retinopathy (1.71 %) and 892 from diabetic retinopathy (0.65 %).
One more diagnostic in-depth examination by ophthalmologist was suggested to 14,523 (10.66 %) people.
Conclusions: Considering the characteristic of the population sample with an average age of around thirty years, must be evaluated the prevalence of systemic diseases. Every eight people, one of them referred the presence. In 3,227 subjects (2.37 %), hypertension and diabetes had already resulted in irreversible changes of the fundus. The study showed that in these cases the use of a system of primary and secondary prevention is absolutely necessary. Finally, a close working relationship and daily collaboration between ophthalmologist and internist is essential for both primary and secondary prevention.

Different components of the metabolic syndrome in a large cohort of southern Italian subjects

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Introduction: The metabolic syndrome (MetS) is a common clinical condition characterized by a clustering of metabolic and atherosclerotic risk factors including visceral adiposity, dyslipidemia, hypertension, and hyperglycemia. The metabolic syndrome is associated with increased risk for both type 2 diabetes and cardiovascular disease (CVD). Several studies have shown that elevated blood pressure (HT) is the main component in subjects with MetS, but it is not clear which combination of criteria of MetS is more frequent.
Aim: Aim of this study was to evaluate the prevalence of both the different component and the different combinations of diagnostic criteria of MetS in a large cohort of Southern Italian subjects.
Methods: The study group consisted of 3614 Caucasian subjects (1894 men and 1720 women), aged between 18–70 years, participating to the CATAnzaro Metabolic RIsk factors Study (CATAMERIS), a metabolic disease prevention campaign for cardiometabolic risk factors. Subjects were excluded if they had history of cardiovascular disease including peripheral atherosclerosis, chronic gastrointestinal diseases associated with malabsorption, chronic pancreatitis, history of any malignant disease, history of alcohol or drug abuse, liver or kidney failure, and treatments able to modify glucose metabolism including lipid-lowering and antihypertensive therapy. On the first day, after 12-h fasting, subjects underwent anthropometrical evaluation, including body mass index (BMI), and waist circumference, and a venous blood sample was drawn for laboratory determinations. On the second day, after a 12-h fasting, a 75 g OGTT was performed with sampling for plasma glucose and insulin. Clinic blood pressure (BP) were obtained in the left arm of the supine patients, after 5 min of quiet rest, with a mercury sphygmomanometer. The MetS was diagnosed according the National Cholesterol Education Program-Adult Treatment Panel III (NCEP ATP III) criteria.
Results: In our study the prevalence of MetS was 57.2 % (2,068 subjects, 1,039 men and 1,029 women). 938 subjects (45.3 %) had only 3 of 5 components of MetS, 701 (33.8 %) had 4 and 428 (20.6 %) had all the components.
Even in our population, elevated blood pressure was the factor that more contributed to the MetS (96 % of cases). Analyzing subjects with only 3 factors of the MetS (n = 938, 469 men and 469 women), we observed that the combination more frequent, present in 32.7 % of cases, was represented by: elevated blood pressure, impaired glucose metabolism (IGM) and increased waist circumference (WC); 21 % of subjects had elevated blood pressure, increased waist circumference and low levels of HDL cholesterol (HDL-C); 14 % had the combination of elevated blood pressure, hypertriglyceridemia (Tg) and HDL-C and 12 % elevated blood pressure, increased waist circumference and hypertriglyceridemia. The remaining 20.3 % of subjects showed the combination of the remaining criteria. In our population the combinations: elevated blood pressure, impaired glucose metabolism, increased waist circumference and elevated blood pressure, hypertriglyceridemia and low levels of HDL cholesterol were more frequent in men while the combination elevated blood pressure, increased waist circumference and low levels of HDL cholesterol was more frequent in women. There were no differences between men and women in the other combinations.
Conclusion: In conclusion, our study shows that: (1) as a single risk factor, elevated blood pressure is the component that more contributes to the MetS; (2) the combination more frequent in the subjects with MetS is represented by the association: elevated blood pressure, impaired glucose metabolism and increased waist circumference; (3) the combinations of diagnostic criteria of MetS are different in men and in women.

Clinical Pharmacology

Prescriptive appropriateness and polypharmacotherapy in elderly patients admitted to two Internal Medicine Units

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Introduction: The lack of prescriptive appropriateness and polypharmacotherapy are two independent risk factors for an early interruption of potentially effective treatments as well as adverse drug reaction (ADR) incidence and severity.
Methods: In this study, we retrospectively sampled data related to the pharmacological therapy at admission and discharge of 250 elderly patients (M: 39.6 %, F: 60.4 %; mean age: 83.15 ± 6.73), consecutively admitted to two internal medicine Units of the St. Orsola-Malpighi University hospital. Analyses of data concerning prescriptive appropriateness on admission and discharge have been carried out using appropriate and validated international Scores (Beers 2008; Laroche 2007).
Results: At admission the 70 % of patients had polypharmacotherapy (defined as >5 molecules/day; mean drug number: 6.22 ± 3.21), the mean score of prescriptive inappropriateness was 24.4–28.8 %. A consistent proportion of patients (81.6 %) was discharged with polypharmacotherapy (mean drug number: 6.86 ± 2.89), while the inappropriateness scores were non statistically different from that at admission. Gender analysis confirmed the previously reported results. The only inappropriateness score predictors at discharge were the inappropriateness score at admission.
Conclusion: In an internal medicine setting, our preliminary data showed that elderly patients with numerous comorbidities do not receive adequate support aimed to improve prescriptive appropriateness as well as reduced excessive and potentially dangerous polypharmacotherapy.

Proton pump inhibitors and risk of 1-year mortality and rehospitalization in older patients discharged from acute care hospital

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Background: The use of proton pump inhibitors (PPIs) has rapidly increased in general population. Recent studies suggest an inappropriate use of PPI in a large percentage of patients (from 50 to 80 %) admitted in geriatric and internal medicine acute wards. There is recent evidence about potential risks associated with chronic PPI use (fractures, pneumonia) especially in older population. However, the relationship between use of PPIs and the risk of death and hospitalization in older subjects has never been fully investigated.
Methods: We used the data of the 506 patients (mean age 80.1 ± 5.9 years) from PharmacosurVeillance in the elderly Care—PVC discharged from 11 acute care medical wards throughout Italy. The study outcomes were survival or combined end-point death or re-hospitalization during 1-year follow-up.
Patients were categorized as non PPIs users and PPI users. We used the Cox regression analysis and propensity matched scores adjusted for age, gender and all the confounders known to increase the risk of adverse outcomes in older populations, hypoalbuminemia, cognitive impairment, number of lost ADLs at discharge, CIRS comorbidity score, number of drugs prescribed at discharge, antithrombotics at discharge, and NSAIDs at discharge. Finally, multivariable Cox regression models and propensity matched score were used to investigate the relationship between type, dosage, and duration of exposure to PPIs with study outcomes.
Results: Baseline characteristics were completely balanced in the propensity score matched populations. PPI users had greater incidence rates for either mortality or combined end-point when compared to non users. Overall, 10.4 % of non-users (10.9 % in the propensity score matched group of non-users) and 18.4 % of users of PPIs died during 1-year follow-up. Similar findings were obtained when considering combined end-point: 18.6 % of non-users (21.8 % in the propensity score matched group of non-users) and 30.5 % of users of PPIs died or were re-hospitalized during the follow-up period. Incidence rates for mortality were 12.0/100 (95 % CI 5.2–18.8) in non-users, and 21.5/100 person-year (95 % CI 11.8–31.2) in PPI users ($p = 0.009$). Incidence rates for combined mortality and hospitalization were 22.9 (95 % CI 13.5–32.3) and 39.8 (95 % CI 27.4–52.2) ($p = 0.003$) in PPI non users and users, respectively. Use of PPIs was significantly associated with mortality (HR. 1.51; 95 % CI 1.03–2.77) and combined end-point (HR. 1.49; 95 % CI 0.98–2.17) independent of well- known predictors of adverse outcomes in older populations. These findings were confirmed after propensity score matching. A trend for increased risk was observed across dosage and exposure time groups.
Conclusion: In a unselected population of older patients discharged from acute care hospitals, chronic use of PPIs is associated with increased risk of 1-year all-cause death and re-hospitalization.
The association depends upon dose, and at least for death, time of exposure.
The time-dependent analysis and propensity score matched analysis increases the robustness of the findings. These data suggest the need of balancing the risks versus benefits of PPI prescription and monitoring PPI use in older frail people.

Usual suspects

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A 74 years old man was admitted to our inpatient clinic for high fever (40 °C) associated with diarrhea, mental confusion and spreaded maculopapular pruritic rash. The man was an heavy drinker.
One month previously, he was hospitalized in an internal medicine department for withdrawal alcohol syndrome complicated by episode of generalized seizure in a picture of chronic vascular-degenerative encephalopathy. Since then he has followed prophylaxis with phenobarbital. During the same recovery, he presented a pneumonitis of the lower left lobe which was treated with ceftriaxone and levofloxacin, and a *Clostridium difficile* gut infection which was treated with metronidazole. At the same time, he developed a deep vein thrombosis of the lower limb which was treated with delta-heparin. After few days, a diffuse cutaneous erythema appeared, so that antibiotic therapy was discontinued. The following clear amelioration of the skin lesions induced to refer them to metronidazole.
At the entrance to the ward the patient appeared confused and dehydrated. A pruritic diffuse erythema associated with severe scratching lesions and mild edema of the lower limbs were observed. The chest X-ray showed pneumonitis of lower right lobe and of the middle left lobe. Blood tests showed neutrophilic leukocytosis and slight increase in serum creatinine.
A broad-spectrum antimicrobial (Meropenem and Teicoplanin), antihistaminic and supportive therapy was set but the patient went on presenting fever and erythema. Electroencephalography and brain MRI didn't show any acute pathologic findings. Cardiac ultrasound excluded the presence of valvular vegetations. Cultural tests of blood and urine were negative. A CT scan of the chest with contrast media (performed with steroidal premedication) showed resolution of the pneumonitis with presence of chronic peribronchial inflammation.
We substituted the heparin therapy with fondaparinux in the suspect of a drug reaction and set a new broad-spectrum antibiotic therapy (azithromycin and Piperacillin-Tazobactam).
As a result there was a significant improvement in the clinical picture, including the maculopapular rash, and a good recovery of neurological status. Blood tests showed a resolution of leukocytosis and a reduction of serum creatinine.
After few days, the patient showed new high fever episode with abundant diarrhea of greenery stools. The test for *Clostridium difficile* toxin and antigen resulted positive so the antimicrobial treatment in course was stopped and oral vancomycin was introduced. A fast and complete recovery of diarrhea was obtained, however we noted the persistence of fever and the worsening of maculopapular erythema. The blood tests showed eosinophilic leukocytosis and rise in serum creatinine again as well.
After 7 days of therapy the stool test for *Clostridium difficile* was negative. In the suspect of drug reaction due to vancomycin the therapy was discontinued. Despite that, high fever, eosinophilic leukocytosis, the increasing of serum creatinine and of lactate dehydrogenase persisted. A framework of global severe erythroderma associated with exfoliative dermatitis, edema of the lower limbs and inguinal lymphadenopathy was appeared. The analysis of lymphocytic profile, performed in order to exclude lymphoma, showed a depression of the lymphocytic B line.
At this point we did a revaluation of the patient medical history and we pointed out a time correlation between the onset of the erythema

and the beginning of therapy with Phenobarbital. We replaced phenobarbtal with levetiracetam as prophylaxis therapy for seizures and we began a treatment with intravenous corticosteroids. A rapid and progressive resolution of the symptoms occurred. In particular, we observed disappearance of fever, significant improvement of erythroderma and lower limbs edema. Blood tests showed a significant reduction in eosinophilic leukocytosis, in creatininemia and in LDH levels. The results persisted even several days after the discontinuation of steroids.

The DRESS syndrome (drug rash with eosinophilia and systemic symptoms) is characterized by the presence of at least three of following findings: fever, exanthema, eosinophilia, atypical circulating lymphocytes, lymphadenopathy, and hepatitis. The use of Naranjo adverse drug reaction probability scale indicated a probable correlation (score 7 of 10) between the development of DRESS syndrome and treatment with Phenobarbital in this patient.

The correct diagnosis was delayed by several confounding factors: the allergic reaction was first ascribed to the various antimicrobial drugs and then to heparin, which were considered the most likely culprits (usual suspects). The steroids administered as premedication for the contrast media, hided for some days the symptoms. The presence of different comorbidities (liver disease, deep vein thrombosis, pneumonitis, bronchitis, gut infection) diverted our attention from the main cause of the clinical picture.

Infliximab and TNF alfa measurement in intestinal mucosa: a new tool for the clinic?

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Infliximab (IFX) is a chimeric monoclonal antibody for patients with active Inflammatory Bowel Disease (IBD). Besides its efficacy, few information exist on its pharmacodynamic, particularly drug availability on intestinal mucosa, which could contribute to the lack/loss of response overall found in at least 30 % of IBD patients.

Aim: To investigate whether IFX levels could be measured in intestinal mucosa by ELISA technique on biopsy supernatants taken from IBD patients treated with Infliximab.

Materials and Methods: Twenty consecutive IBD patients in stable maintenance dose of IFX (10 female and 10 male, 10 Crohn's Disease and 10 Ulcerative Colitis) undergone to endoscopy were enrolled into the study. Mean age of patients enrolled was 42.2 (± 15) years with an Harvey Bradshaw index of 5.5.

Biopsies were taken from affected area, washes, weightened and cultured for 48 h in a regular culture medium added with antibiotics and fungizone. At the same time serum from patients was also collected. Patients enrolled received IFX ev from 3 days to 87 days before the colonoscopy was performed (37 ± 25 days).

A commercially available anti-Remicade levels ELISA kit (ImmuneDiagnostik, Germany) was used. Levels of TNF-a were also measured, using a commercially available ELISA kits (R&D).

IFX or TNF-a levels from biopsies were expressed as pg/ml per microgram of biopsy. Values above the lower limit were considered 1 pg per ml (or 1 pg/ml per ug of tissue), higher than the limit suggested by manufacturer.

Results: IFX levels above the limit were found in 82 % of colonic biopsies supernatants compared to the 70 % of serum IFX levels. TNF-a intestinal mucosal levels were above the limit in 100 % of patients compared to 75 % of serum levels. Mean values of IFX were 12.5 pg/ml (±4.7) in the serum and 139.7 (±54.3) pg/ml/ug of biopsy for the intestinal mucosa. Mean values of TNF-a were 11.6 (±2.8) and 9.0 (±5.9) respectively.

Conclusions: Detectable levels of IFX as well as TNF-a can be easily found in intestinal mucosal levels, suggesting that IFX distribution affect both blood stream and intestinal mucosa.

Further studies are necessary to evaluate prognostic value of IFX and TNF-a mucosal levels in response to IFX therapy of IBD patients.

Safety conversion to once daily tacrolimus in kidney transplant patients in multidrug treatment: IL-2 monitoring and subclinical rejection

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Introduction: Kidney transplantation is the treatment of choice for patients with end-stage renal disease.

Progressive renal dysfunction after kidney transplantation due to chronic rejection is a major cause of long-term graft loss (50–80 %) and recognizes subclinical rejection (SR) as leading cause. Subclinical rejection is characterized by minimal histological evidence of acute rejection in the absence of changes in serum creatinine (sCr) in patients with stable renal function.

Inflammatory cytokines, in particular interleukin-2 (IL-2), are involved in the immune reaction activating after kidney transplant. IL-2 represents the specific target of immunosuppressive therapy, and elevated plasma levels may indicate systemic activation of the immunological response associated with acute or subclinical episodes of rejection.

Immunosuppressive drugs in kidney transplantation control the silent immune reaction associated with the development of SR.

Despite advances in immunosuppressive therapy, a major weakness is the patient's behavior. Noncompliance, also referred to as nonadherence, is a major problem in chronic health care due to multidrug therapy. The majority of noncompliant patients lose their grafts because of rejection, as a manifestation of permanent alloreactivity.

Moreover, the absorption of immunosuppressive drugs can be influenced by various factors. A fatty meal reduces drugs oral bioavailability. Furthermore, the adherence rate seems to be significantly lower after meals rather than fasting in the morning.

The recently released formulation of tacrolimus (Tac), administered once daily (Tac-M) instead of twice (Tac-B), improves patient compliance because of the multidrug therapy of transplanted patients, while maintaining effective immunosuppression. Conversion from twice (Tac-B) to once daily (Tac-M) tacrolimus (Tac) formulation is considered safe on the basis of graft function, although a reduction of trough levels of 20–30 % after conversion of unclear meaning is reported.

Aim of our study is to evaluate the effect of conversion from Tac-B to Tac-M on Tac trough levels, allograft function and serum levels of IL-2.

Materials and Methods: We enrolled 46 patients 3 to 5 years post-transplant, with stable kidney function, receiving a multidrug therapy (tacrolimus, mycophenolate mofetil, corticosteroids, antihypertensive double therapy, gastroprotective therapy, statins and hypoglycaemic agents), converted from Tac-B to the same dosage of Tac-M (1 mg:1 mg). Trough levels were maintained inside therapeutic range (4–10 ng/dl). Monthly evaluation of Tac trough levels, sCr and glomerular filtration rate (GFR) were performed 1 year before and after conversion. Each patient served as his own control. IL-2 and CRP were assessed at baseline, 3, 6 and 12 months after conversion.
Results and Conclusions: We observed a slight but significant decrease of Tac trough level during the first month after conversion ($p < 0.03$). Renal function remained stable during follow-up. Alterations of CRP and cytokine profiles, IL-2 in particular, have been demonstrated to be a reliable inflammatory marker suggestive of subclinical rejection. In our study we didn't observe any episode of acute rejection. Subclinical rejection could be excluded on the basis of stability in renal function, IL-2 and CRP levels on long-time follow-up. The recently Tac-M formulation may improve compliance and life quality of transplanted patient in multidrug therapy maintaining effective immunosuppression.

Emergency Medicine

Prehospital management in polytrauma

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Introduction: Polytrauma usually results from high energy impact, therefore it is not surprising that road traffic crashes predominate as the causal mechanism for deaths and severe injuries in Italy. The best management strategy of polytrauma is still under discussion: "scoop and run" or "stay and play"?
Case Report: Advanced Trauma Life Support team arrived on scene 3 min after an hard car crash. Two injured men were standing outside the vehicle, 1 woman was extricable and a 22-years-old injured woman was trapped. Primary survey identified different conditions of life-threatening (no belts fastened and air bag not included): especially head and facial trauma with cervical spine instability, respiratory failure (bleeding from the mouth, subcutaneous emphysema, sat. O_2: 90 %), hemodynamic instability (small and frequent arterial pulse, B.P. 80/50 mmHg), possible intracranial hypertension (GCS: 11). Revised Trauma Score: 10. Duration of extrication 15 min.
The immediate application, before extrication, of the cervical collar, the finding of a 14 G venous access, the aspiration of blood in the mouth, the administration of oxygen with the reservoir allowed to obtain a saturation of O_2 of 98 % (with murmur vesicular lower but present on the left pulmonary side). After extrication we immobilized spine and we found a second venous access 14 G to start filling with 30 ml/kg of crystalloid obtaining B.P. 90/60 mmHg. Total time from call to hospital 30 min.
Discussion: We initially chose a strategy of treatment "stay and play", being the injured woman trapped in the car. Achieved a good pre-hospital stabilization in view of suspected rupture of the spleen and of the distance from the hospital (about 5 km), the patient was transferred to the nearest Emergency Department ("scoop and run"). Patients with an Injury Severity Score (I.S.S.) of 16 or more in fact have a significantly increased risk of mortality, and it is this group of patients that benefit most from rapid evacuation to definitive care. All objectives of prehospital stabilization were speedy obtained.
CT scan confirmed: SKULL (Fig. 1): Fracture of the horizontal ramus of the mandible and the mandibular left corner. Cervical spine: no fracture lines. CHEST (Fig. 2): multiple rib fractures in left hemithorax with pneumothorax and subcutaneous emphysema. Left humerus fracture. ABDOMEN (Fig. 3): rupture of the spleen. Lack of opacification of the left kidney. Multiple intraparenchymal hematoma of the liver. Abundant fluid collection in Douglas. Left transverse apophysis of L_1 and L_2 rupture. LEGS (Fig. 4): Multifragmentary displaced fracture of the left femur. I.S.S.: 75/108. GCS: 10. SpO_2: 98 %. Hb: 7.5 mg/dl, RBC: 2,503,000; WBC: 12,100 PTL: 169,000.

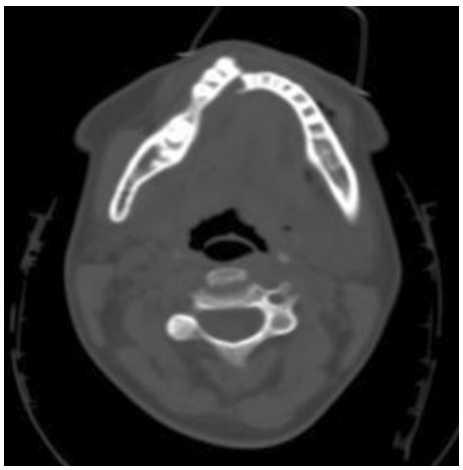

Fig. 1 Mandibular fracture

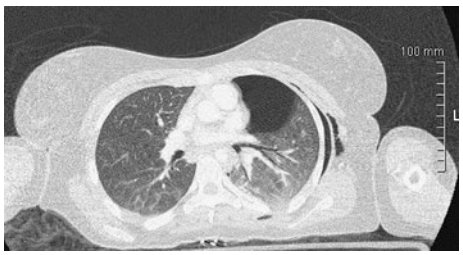

Fig. 2 Pneumothorax, subcutaneous emphysema

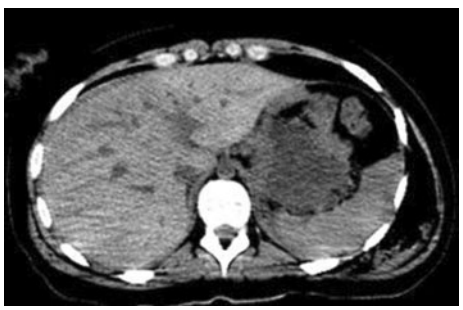

Fig. 3 Rupture of the spleen

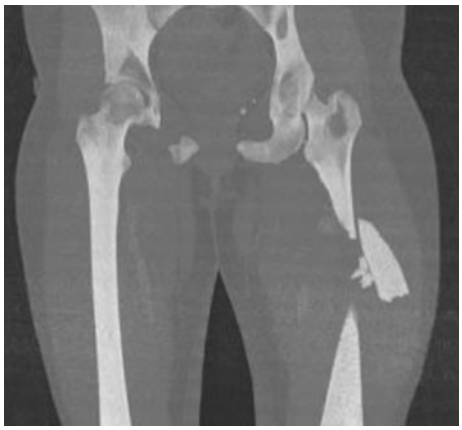

Fig. 4 Fracture of the left femur

Conclusions: The management strategy in this case was influenced by extrication and by severity of injuries (RTS:10). ATLS Team A.R.E.S. 118 REGIONE LAZIO is crucial to immediately treat on site potentially fatal conditions by proceedings that cannot be delayed (immobilization of the spine, ensuring airway patency, to decompress a tension pneumothorax or cardiac tamponade, to stop massive hemorrhage) and stabilize the patient during transport keeping a peripheral O_2 saturation >94 % and a systolic BP of 90 mmHg. In fact only the speed and quality of prehospital stabilization procedures may reduce secondary mortality rate in severe trauma. Management of priority in severe trauma could be so integrated in a "scoop and play" strategy to reach the SUITABLE hospital within the "golden hour".

Persistent difficulties in the diagnosis of acute pulmonary embolism. Data from our hospital in the last 3 months

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Introduction: Important Guidelines and Reviews on the diagnosis and management of acute pulmonary embolism have been published in the last years; however data are lacking regarding their effects in real-life clinical practice.
Aim: In order to analyze the performance of the diagnostic process on this relatively common cardiovascular emergency, that may still represent the most frequent missed or delayed diagnosis, we collected the characteristics of patients undergone CT pulmonary angiograms to confirm or exclude acute pulmonary embolism at our Hospital in the last 3 months.
Results: During the months of February, March, and April 2012, for the clinical suspicion of acute pulmonary embolism, 25 CT pulmonary angiograms have been performed, of which 13 in the Emergency Room, and 12 during stay in medical wards. All patients admitted to the medical wards have passed from the Emergency Room with a presumptive diagnosis different from acute pulmonary embolism. The CT pulmonary angiograms resulted positive in 3 (23 %) and negative in 10 (77 %) of patients evaluated in the Emergency Room, while positive in 6 (50 %) and negative in 6 (50 %) of patients evaluated in the medical wards. Only one patient with acute pulmonary embolism did not perform CT pulmonary angiogram in the Emergency Room because of shock, and died. The six missed cases in the Emergency Room were admitted to the wards with the diagnosis, respectively, of: COPD exacerbation, pneumonia, atrial fibrillation, syncope, dyspnea of undetermined origin, suspected deep venous thrombosis of the lower limb. The ten patients with negative CT pulmonary angiograms in the Emergency Room were given, before the admission in the wards, the following diagnosis, respectively: intestinal sub-occlusion, chest pain, acute respiratory failure with pleural effusion (2 cases), acute respiratory failure (3 cases), inhalation of vapors from household cleaners, COPD exacerbation, syncope. The six patients with negative CT pulmonary angiograms in the wards were then given the following diagnosis, respectively: infective endocarditis, COPD exacerbation (2 cases), heart failure in pneumonia, dehydration with slight troponin elevation.
Considerations: Our preliminary data confirm the constant attention toward acute pulmonary embolism and the diagnostic difficulty around this clinical condition.
The rate of negative CT pulmonary angiograms in the setting of Emergency Room (77 %) in our opinion might be only partially justified by the knowledge that an early diagnosis of this life-threatening condition is fundamental since immediate treatment is highly effective. On the other hand, despite the concern of the clinicians to miss a diagnosis in the Emergency Room, six patients affected by acute pulmonary embolism were given a different (preliminary) diagnosis of admission to the ward even if Wells and Geneva Scores gave a clinical high probability of acute pulmonary embolism. Fortunately, notwithstanding a delayed correct diagnosis and management in some of our cases, it did not result in unfavorable outcome.
We think that in the Emergency Room setting, the difficulty sometimes in the collection of an exhaustive history from the patient, in performing the necessary diagnostic flow-chart (due to overcrowding and/or unavailability) could have had a role in the results presented.
Finally, we think that our data, although preliminary, indicate the need to ameliorate our clinical practice regarding acute pulmonary embolism, that remains a great challenge and, according to some studies, the most commonly missed or delayed diagnosis along with drug reaction and overdose.

Characteristics, hospitalization and mortality of patients with GI bleeding admitted to all emergency departments of the Italian Lazio region

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Background and Aim: While GI bleeding often represents a true emergency, there are no data concerning the number of patients admitted for GI bleeding to the Italian Emergency Departments (ED). We therefore conducted a retrospective study, based on data contained in the GIPSE-SIES system, which collects data from all the regional ED.
Materials and Methods: This analysis for the year 2009 was promoted by regional gastroenterology societies AIGO, SIED and SIGE; admitting hospital, area of residence, age, sex, final diagnosis, final decision and final destination of the pts were analyzed. Data were

then compared with those of the general population admitted to the ED for all other causes.

Results: Overall, 1719 pts (962 males, mean age 60 ± 22 years) were admitted to an ED for GI bleeding; prevalence increased significantly with age with a highest value between 70 and 80 years ($p < 0.001$). Total number of admitting hospital was 53, with only 16 admitting at least 40 pts ($p < 0.0001$). 1294 pts showed a lower GI bleeding while 425 an upper GI bleeding ($p < 0.0001$). Concerning lower GI bleeding, rectal and anal bleeding was the most common final diagnosis (1,158 pts) followed by diverticulitis with GI bleeding (136 pts) ($p < 0.0001$). Among upper GI bleeding, acute hemorrhagic gastritis was the most common cause (162 pts), followed by peptic ulcer (92 pts), esophageal bleeding (76 pts) duodenitis (22 pts) and others ($p = ns$). 845 pts were admitted to the hospital wards ($p < 0.001$ vs general population) and 16 pts died in the ED ($p < 0.001$ vs general population and $p < 0.001$ vs mortality for GI bleeding described in the general literature). Final destination was general surgery (425 of 1719), internal medicine (140 of 1719), ED observation unit (101 of 1719), gastroenterology (63 of 1719), resuscitation unit (9 of 1719) and others (42 of 1719) (general surgery vs internal medicine and gastroenterology: $p < 0.05$).

Conclusions: The majority of pts admitted to the ED in the Lazio region shows a lower GI bleeding. General surgery and not internal medicine or gastroenterology is the most common final destination of the patients. Mortality for GI bleeding in the ED is higher compared to that observed in the population admitted to the ED for any other cause but is lower compared to that described in the general literature.

Predictive value of triage system code for elderly patients in the emergency department (ED)

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Older patients represent an ever-increasing population in emergency medicine. Such patients often present with atypical signs and symptoms and multiple co-morbidities that complicate diagnosis and treatment. We evaluated all patients admitted into the ED of the Fatebenefratelli Hospital in Milan during year 2010. Patients had been classified according to the current Italian Health Ministry priority emergency code of red, yellow, green and white, in descending order of priority. Discharge (out), death (dead), and admission to hospital (in) were the outcomes used for stratification purposes. We evaluated 50,564 patients (group 1: aged 18–74; n° 43,365 and group 2: ≥75 years old; n° 7,199) and from this group we excluded patients classified under the white code, ophthalmic and pediatric cases. Thus, 45,766 patients (38,965 of group 1 and 6,801 of group 2) could be evaluated. Statistical significance was achieved in the red/dead (−26.63; −34, −19), yellow/out (37.93; 35–41) and yellow/in (−36.59; −41, −32) strata as well as in the green/out (22; 20–24) and green/in strata (−21, 98; −23, −21) (Fig. 1). We interpret these results as indicative that patients over 74 years classified under the red code had an increased probability of death compared to patients <74 years. In the green code subgroup, admission of patients over 74 years was also statistically significant. In conclusion, we suggest that the current Italian triage method can assume a proxy predictive value for elderly patients admitted into emergency department. This is particularly true for patients over 74 years who have an increased risk of death if classified under the red code or of geriatric ward admission if classified under the green or yellow code. We suggest these data argue in favor of the introduction of a "silver code" into the Italian triage coding system to screen specifically for the population herein sampled.

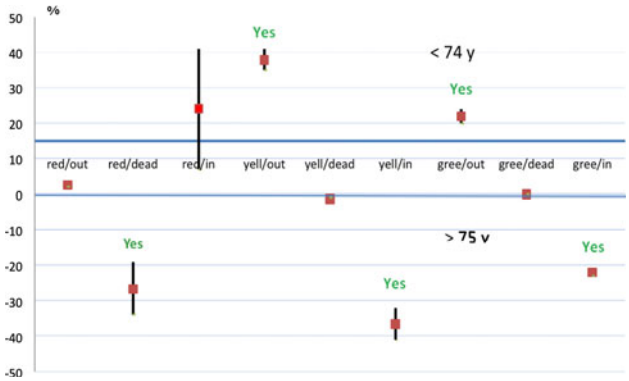

Fig. 1

Copeptin and chest pain: a new biomarker in early diagnosis of myocardial infarction

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Chest pain is a common reason for access to the Emergency Department (ED): the main cause is acute coronary syndrome (ACS), whose identification is crucial for the selection of patients at risk and to ensure a timely start of treatment. The diagnostic procedure involves the presentation (Chest Pain Score-CPS), ECG evaluation and determination of specific markers of myocytolysis. These could be able not to become positive before 3 h after the acute event: for this reason, studies are underway for new biomarkers that can identify a cardiac ischemic event in the early stage. Among these, the antidiuretic hormone arginine-vasopressin (AVP) secreted in response to stress for the endogenous regulation of homeostasis cardiovascular: its short half-life and biological instability, however, restricting the use. It 'was, therefore, identified the copeptin, C-terminal portion dell'AVP, proved more in the laboratory as an indicator of stress endogenous vascular. Its levels were elevated in acute ischemic event (up to 6 h before troponin) and then decreases in the 10 h. The initial levels of copeptin normal in combination with an initial negative troponin exclude the diagnosis of ACS (sensitivity 99 %), facilitating the differential diagnosis of chest pain on arrival in the ED.To test the validity of copeptin, between February 2012 and April 2012, 82 patients (58 M, 24F, mean age 57 ± 16) with suspected ACS were consecutively enrolled in this study. Inclusion criteria are: typical chest pain arising from <6 to 8 h; ECG negative for ACS, STEMI and NSTEMI patients; aged between 16 and 70 years. In triage (time 0) were recorded vital signs, a 12-lead ECG, routine laboratory parameters (myocytolysis conventional and copeptin). At 6 and 12 h of the onset of symptoms conventional markers myocytolysis were measured only. We then evaluated, once the diagnosis, the actual correlation between the values of copeptin obtained and the diagnosis of cardiac ischemia or less. At the first evaluation of our results showed that patients, whose value of copeptin was detected at time 0 high (24/82), with initial values of troponin negative, an indication has been given to the hospitalization for further study clinical-instrumental, confirming then the diagnosis of initial suspicion of ACS in 17 of 24 patients. Instead, in patients whose initial value of copeptin appeared negative (58/82), the subsequent clinical investigation, required hospitalization and confirmed the diagnosis of ACS in 7

patients only. The dosage of copeptin in patients with chest pain arising from <4 h facilitates the early diagnosis of ischemic heart disease: values of copeptin and normal baseline troponin seem to rule out cardiac origin of symptoms, allowing an early differential diagnosis and possible early discharge. In addition, elevated copeptin in patients with ECG "silent" and the first determination of the negative troponin identify patients at high risk for cardiovascular disease presenting acute directing the emergency doctor to a rapid hospitalization and perform further diagnostic tests.

An observational study about intracranial hemorrhages in Emergency Departments: effect of therapy on the outcome

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Background and Aim: Intracranial haemorrhage (ICH) is a life-threatening adverse event of antithrombotic drugs. Guidelines for the management of patients with ICH on vitamin K antagonists (VKA) are widely available. However, a prompt diagnosis and treatment of the iatrogenic haemostatic defect are often lacking in clinical practice. Our aim was to assess the prevalence of antithrombotic drugs use in patients with ICH and the number of correctly treated patients.
Materials and Methods: We conducted a 2 years retrospective cohort study in the emergency department (ED) of the IRCCS Policlinico of Milano.
Results: From January 2010 to December 2011, 316 consecutive adult patients with ICH were admitted to our ED (32 subarachnoid, 35 subdural, 249 intraparenchymal haemorrhages). 119 patients (37.7 %) were on antithrombotic treatment, 51.3 % males, 53.5 % >75 years. Five of these 119 patients (4.2 %) were in combined antithrombotic treatment (2 VKA plus ASA, 1 clopidogrel plus ASA, 1 clopidogrel plus heparin, 1 ASA plus heparin). Seventy-eight of the 119 patients (65.5 %) were on antiaggregating treatment (74.4 % ASA, 15.4 % ticlopidine, 6.4 % clopidogrel, 3.8 % others), 36 patients (30.3 %) on anticoagulant therapy, 10 patients (8.4 %) on heparin. Overall, 13 of the 316 patients with ICH (4.1 %) died during their stay in the ED (< 24 h): 9 (69.2 %) were on antithrombotic treatment (6 AVK, 1 AVK plus ASA, 1 heparin, and 1 ASA). Only 21 of the 36 patients on VKA (58.3 %), and only 2 of the 7 on VKA who died, received prothrombin complex concentrates.
Conclusions: We found a high prevalence of antithrombotic drug treatment among patients admitted to ED and dead for ICH: more than 1/3 of patients admitted, and more than 2/3 of patients dead were on antithrombotic treatment (the latter group mainly with VKA). Our data suggest the need to improve the diagnosis and the correction in ED of the frequent iatrogenic haemostatic defect in patients with ICH.

	Number of patients	Number of deaths
No treatment	197	4
Antiaggregant	78	1
Anticoagulant	36	7
Combined therapy	5	1
Total	316	13

A strange weakness

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Background: Sometimes the execution of a simple and inexpensive diagnostic test can help to diagnose and quickly resolve very insidious diseases.
Case Report: SA, female, age 72, non smoker, non drinker, is hospitalized for protracted and recurrent vomiting.
Because of rapidly progressive weakness, just days before she practiced:

- Consultation with a Neurologist: "pain in the lower back, difficulty in walking and tetra-hyposthenia; we recommend further evaluation with imaging techniques and subsequent evaluation by a neurosurgeon"
- Cranium CT: within normal limits
- MRI brain: within normal limits

Medical History: hypertension, carotid atherosclerosis, previous bladder cancer (surgery 20 years earlier)
Abnormal Laboratory Tests: WBC: 14,000; Hb: 9.2, K 2.7; Cl: 130, Ca: 7.2; *ECG* within limits; *CXR*: Signs of vascular congestion; *A/B balance*: pH 7.16, pCO_2: 23; pO_2: 91, HCO_3^-: 8.2.
Subjected to appropriate reintegration of bicarbonate and potassium, as well as rehydration, the patient also undergoes:
EGD: duodeno-gastric reflux; hyperemic antral gastritis.
Echocardiogram: hypertensive heart disease.
She's discharged after six days of hospitalization, after complete regression of symptoms, normalization of blood tests; *A/B balance*: pH 7.44, pCO_2: 34; pO_2: 74; HCO_3^-: 23.2.
Diagnosis: *Severe hyperchloremic metabolic acidosis, probably secondary to loss of bicarbonate in patient with ureter-sigmoido-stomy (previous bladder cancer). Hypertensive heart disease. Hyperemic gastritis. Carotid atherosclerosis*
Discussion: The patient had undergone to ablation of her bladder and uterus, and to ureter-sigmoido-stomy, 20 years earlier. Hyperchloremic metabolic acidosis is a relatively frequent complication of ureter-sigmoido-stomy because of the exchange Cl^-/HCO_3^- at the intestinal level and should always be considered in the evaluation of patients operated on for bladder cancer. The protracted and recurrent vomiting can be viewed in the context of a compensatory mechanism (elimination of HCl).
Conclusions: This case emphasizes the importance of a simple and inexpensive diagnostic test, such as A/B balance, not only, as frequently happens, in case of dyspnea, but whenever we can hypothesize a possible alteration of the delicate acid–base, fluid and electrolyte equilibrium, on the basis of a prudent clinical-anamnestic global assessment of the patient, avoiding often considerable expenditure of time and economic resources.

Differential diagnosis of pulmonary embolism in outpatients with non-specific cardiopulmonary symptoms and the expert system Bayes Pulmonary embolism Assisted Diagnosis (BayPAD) II

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Background: Most cardiopulmonary diseases share at least one symptom with pulmonary embolism (PE). Primary aim of this study was to identify the most common acute causes of dyspnea, chest pain, fainting and/or palpitations, which diagnostic procedures have been performed and used appropriately. Secondary aim was to implement Bayes Pulmonary embolism Assisted Diagnosis (BayPAD) II, a probabilistic expert system developed to overcome pitfalls of available algorithms for PE diagnosis.
Materials and Methods: Eight hundreds hospitalised patients were selected through a block random sampling procedure from 17,497 Emergency Department admission records in six Italian hospitals in a 6-months time frame. Case-mix of enrolled patients was assessed in terms of cardiopulmonary symptoms and prevalence of acute disorders. Actual performance of procedures was compared with a measure of their accuracy as expected in the most common clinical presentations.
Results: PE occurred in less than 4 % of patients with cardiopulmonary symptoms. Pulmonary edema was common in patients with isolated dyspnea (12 %), while acute myocardial infarction occurred in about 10 % of patients with chest pain. Atrial fibrillation is the reason for palpitation in almost half of the patients. Echocardiography was commonly used in patients with chest pain (41 %). B-type natriuretic peptide (BNP) was rarely performed but in patients with dyspnea and palpitations (19 %). Among diagnostic procedures for PE, D-dimer was mainly requested in patients with isolated syncope (36 %), isolated palpitations (24 %) and chest pain, with or without dyspnea (46 and 30 %, respectively). Echocardiography, computed tomographic pulmonary angiography, perfusion lung scan, D-dimer and B-type natriuretic peptide were performed less than expected from their accuracy.
Conclusions: Diagnostic strategies should be mainly based on exam's accuracy in discriminating among several competing hypotheses rather than in only testing PE presence. The availability of an expert system, such as BayPAD II, is probably of great help for clinicians.

A sense of impending doom

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A 48 years-old female patient presented to the Emergency Department for the recent onset of intense chest pain with scapular irradiation, palpitations and a "sense of impending doom", followed by syncope associated with respiratory stridor. The patient was a physical education teacher, mother of one healthy child with no cardiovascular risk factors. Her medical history was unremarkable, except for menometrorrhagia that needed the application of a progesterone medicated intrauterine device and an history of migraine treated with ergot derivatives. She denied any use of vasoconstrictor or recreational drugs. There was no clinical evidence of marfanoid habitus or connective tissue disease. At the admission to our Division, vital signs were normal (BP 120/80 mmHg in both arms, HR 72 bpm, RR 18 breaths/min, T 36.4 °C) and the physical exam was negative (h. 175 cm, w. 53 kg). Chest X-ray, electroencephalogram and brain-CT were negative. Troponin I and CK-MB increased from 0.112 ng/mL and 1.8 ng/mL on admission, to 5.223 ng/mL and 7.7 ng/mL after 6 h, respectively, without ECG changes. An echocardiogram showed a normal sized aorta (3.7 cm) with normal left ventricular kinetic, EF 70 %, mild mitral, pulmonary and tricuspid valves abnormalities. An Holter-ECG revealed constant sinus rhythm, average HR 70 bpm, rare supraventricular extrasystoles.

Laboratory investigations were performed, in order to assess the inflammatory (C-reactive protein) and infective risk (Coxackie A and B virus, Echovirus, Flu and Paraflu virus, CMV, EBV, HZV) as well as coagulation (lupus anticoagulant, platelet count, partial thromboplastin time, international normalized ratio, C and S proteins, AT III, factor V Leiden, factor II and MTHFR mutations, homocysteine) and autoimmune disorders (antinuclear antibodies, antimitochondrial antibodies, immunocomplexes, anticardiolipin antibodies, complement), with no pathologic findings. A treatment with beta-blocker, anti-platelets and protonic pump inhibitors was started. During hospitalization daily electrocardiographic and laboratoristic monitoring was planned, showing a progressive normalization of cardiac markers. Conversely, T wave inversion appeared in anterolateral precordial leads on day 3. Therefore, coronary angiography examination was performed and revealed the anterior interventricular artery with aspect of "corkscrew" and a spontaneous dissection in its distal section until the apex, with a downstream discrete flow. The circumflex coronary also showed a "corkscrew" appearance. Three days after, patient experienced severe precordialgia with subsequent syncope and cardiopulmonary arrest. The ECG showed a ventricular fibrillation and the patient died despite of repeated electrical cardioversion and cardiopulmonary resuscitation.

Spontaneous coronary acute dissection (SCAD) is a rare cause of acute coronary syndrome and of sudden cardiac death. It consists in a spontaneous dissecting hematoma formation in a coronary vessel. It can be distinguished into either primary and secondary form, the latter due to connective tissue and inflammatory diseases, immunosuppressive and progestin therapy, post-partum, heavy exercise, drugs consumption and inherited conditions. SCAD should be suspected in young women without risk factors, mainly during peri/post-partum period or progestin treatment ongoing. Therapeutic approach represents the real obstacle to its management because of the lack of agreement among medical and/or surgical options. The described evidence of the perfusion downstream the dissection led us to keep a "watch and wait" approach; unfortunately, being the SCAD an unpredictable disease because of a high risk of recurrence, every our initiative resulted unproductive.

Safety and efficacy of dronedarone in the treatment of atrial fibrillation

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Aims: Atrial fibrillation is a growing epidemic with an estimated prevalence of 0.1 % of the population over 50 years of age and 9 % over 80 years. Arrhythmia not only carries prognostic implications, but also represents a significant economic burden. Dronedarone is one of these new compounds developed for treatment of atrial fibrillation The drug is a benzofuran derivative structurally related to amiodarone but free of iodine and with a sulfonamide group placed on the benzofuran ring. The electrophysiologic properties of dronedarone are very similar to those of amiodarone, which is presently the most effective drug to maintain sinus rhythm in patients with atrial fibrillation.
Methods: This is a prospective study and is effected in 6 month (January 2011 to July 2011) Patients of either sex, aged 21–85 years were eligible with paroxysmal. Atrial fibrillation patients with one or more of the following criteria were excluded from the study: unstable angina pectoris or recent myocardial infarction; QT interval >500 ms, or history of torsades de pointes; severe bradycardia; advanced atrioventricular block; treatment with other antiarrhythmic drugs; congestive heart failure NYHA class III or IV; left ventricular ejection fraction of less than 35 %; Wolff–Parkinson–White syndrome; implanted cardioverter defibrillator. All study patients underwent a baseline evaluation that included a medical history, symptom review, cardiovascular examination, assessment of vital signs, 12-lead electrocardiography, chest radiography, and laboratory tests, including a complete blood count and tests of serum electrolytes, urea, creatinine, and thyroid and liver, left atrial size and left ventricular ejection fraction were determined by echocardiography We scheduled follow-up visits that included a review of symptoms, assessment of vital signs, and performance of electrocardiography on days 7 and at 1, 3 and 6 months. The above mentioned blood tests were repeated.
Results: 23 eligible patients with a history of paroxysmal are atrial fibrillation treated with dronedarone, 400 mg bid, after DC shock, or after rhythm control because patients cannot use amiodarone for allergy, for toxicity, for thyroid disease or other, The patients are 60.8 % males and 39.13 % females. The mean age of the population was 69 years in the 56.2 % there is also hypertension, in the 34.6 % heart disease, in the 17.39 % chronic bronchitis, in the 82.6 % thyroid disease. 47.8 % is in NYHA class II, 34,8 in NYHA class I, in 17.4 % NYHA class II/III. After 1 month in follow up there were 69.56 % of patients, the 17.39 % had a new atrial fibrillation, one patients had a increase in serum creatinine, one patient had dizziness. After 6 months the patients were in sinus rhythm 60.86 %, in 21.7 % patients there was another atrial fibrillation, 17.39 % drop out There was PR interval >0.20 ms. in 13 %, and QT interval >500 ms. in 4.3 %, there was bradycardia in 8.6 % of patients.
Conclusion: The study assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular hospitalization in patients with atrial fibrillation Dronedarone is indicated to reduce hospitalization for AF in patients in sinus rhythm with a history of paroxysmal., this treatment significantly reduced the risk of hospitalization. Therefore, allowing the use of dronedarone in atrial fibrillation patients with NYHA class I or II heart failure seems prudent, but it do not currently recommend.

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Gastroenterology and Hepatology

Acoustic structure quantification (ASQ) B-mode: a new software for ultrasound (US) study of liver fibrosis?

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Purpose: To evaluate normal and steato-fibrotic liver by means of the ASQ and to assess any differences of ASQ values in healthy subjects, NAFLD and cirrhosis.
Materials and Methods: A total of 22 Pts were evaluated, including three Groups: Group 1 = 19 healthy subjects (5M/4F, mean age 35 years, range 18–45); Group 2 = 6 NAFLD Pts (5M/1F, mean age: 47 years, range: 41–52); Group 3 = 7 patients with cirrhosis Child A (4M/3F, mean age 62 years, range 47–71, Group 3). ASQ measurements were performed by means of ASQ-B mode (Toshiba Aplio XG V5), a software application of clinical US recently proposed for the study of liver fibrosis. It analyzes the hepatic echotexture by statistical test (chi-square) measuring the amplitude of echo signals from the liver parenchyma and the results are expressed as: parametric imaging, graphs and Range Average $C_m^2 \pm$ SD (RASD), the latter obtained from ROI curves. In each Patient were performed intercostal high and low US scans, for the right lobe, and subcostal epigastric US scans, for the left lobe. According to the guide of the parametric imaging, at least three ROI curves were positioned in each portion of the liver lobes, visualized by the US scans. As a final data, the RASD values obtained by the three measurements of ROI curves was considered. The results were expressed as RASD. Due to the small sample size, statistical analysis was not possible.
Results: Similar ASQ mean values in all portions of the liver lobes were found both in healthy subjects (Group 1) and NAFLD Pts (Group 2): RASD = 109/129 ± 13/10 and RASD = 98/118 ± 10/0 respectively. As concerns liver cirrhosis (Group 3) different mean values between right and left hepatic lobes were observed: RASD = 114/144 17/21 for the right lobe and RASD = 109/132 ± 13/19 for the left lobe.
Conclusions: Our data show that ASQ B-Mode may identify different values of RASD distribution among healthy subjects, NAFLD and cirrhosis. ASQ values (either Range Average and SD) of fatty liver are lower with respect to healthy subjects and cirrhotics. Moreover ASQ may detect areas with different severity of fibrosis in cirrhosis. This latter finding is concordant with histological studies which have already demonstrated various grades of fibrosis in different areas of cirrhotic liver.

Liver fibrosis measured by ultrasound (US) and histological comparison on surgical specimens: preliminary report

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Purpose: To evaluate normal hepatic tissue and steato-fibrotic areas of liver tumors by means of the acoustic structure quantification (ASQ) b-mode ultrasonography and to compare them to pathological evaluation on surgical specimens.
Materials and Methods: We studied a total of 7 Patients (3 males and 4 females, mean age 74 years, range 62–81), affected by liver tumors and candidates for surgical resection (metastases 4 Pts, hepatocellular

carcinoma 2 Pts, and cholangiocarcinoma 1 Pt). The median tumor nodule diameter was 5 cm (range 1.5–7.0). Acoustic structure quantification measurements were performed by means of ASQ-B mode (Toshiba Aplio XG V5), a software application of clinical US recently proposed for the study of liver fibrosis. It analyzes the hepatic echotexture by statistical test (chi-square), measuring the amplitude of echo signals from the liver parenchyma and the results are expressed as: parametric imaging, graphs and Range Average $C_m^2 \pm$ SD (RASD), the latter obtained from ROI curves. ASQ measurements were performed inside the nodule (a), on the margins of the nodule (b) and in the surrounding liver tissue, within 3 cm from the nodule capsule (c). According to the guide of the parametric imaging, at least three ROI curves were positioned in each area (a, b and c), visualized by the US scans. As a final result in each area (a, b and c), the RASD mean value obtained by the three measurements of ROI curves was considered. The results are expressed as RASD. Due to the small sample size, statistical analysis was not possible.

Results: The mean values of all 7 lesions concerning the (a) areas were RASD = 109–120 ± 14–10 and RASD = 112–130 ± 7–9. As concerns the (b) areas the results were RASD = 110–130 ± 13–18 and RASD = 131–150 ± 15–25 (Figs. 1–2), in the (c) areas we obtained RASD = 111–134 ± 18–19 and RASD = 110–143 ± 14–12 in cirrhotic livers and RASD = 109–118 ± 15–19 and RASD = 110–121 ± 11–13 in non-cirrhotics.

Conclusions: Our data show that ASQ B-Mode may identify different values of RASD distribution among different areas of fibrosis in liver tumors and between normal and cirrhotic livers as histologically confirmed on surgical specimens. The 3 tumor cases with higher values of ASQ correspond on histology to a larger component of fibro-sclerotic tissue. In the surrounding parenchyma the highest values of ASQ B-Mode correspond to the highest grade of fibrosis (F4).

Hepatitis B virus reactivation in HBsAg-negative patients after chemotherapy: HBV-DNA monitoring and tenofovir prophylaxis

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Background: Reactivation of hepatitis B virus (HBV) has been recognized as one of the most serious complications in patients receiving chemotherapy.

Aims: Recently, the reactivation of HBV has been often reported in Hepatitis B surface antigen (HBsAg) negative patients with fulminant hepatic failure.

Methods: From April 2010 to April 2011, chemotherapy was administered to 30 patients. HBsAg, antibody to hepatitis B surface antigen (anti-HBs), and antibody to hepatitis B core antigen (anti-HBc) tests were performed in all patients. In patients who were positive for anti-HBs or anti-HBc, serum HBV-DNA was measured monthly.

Results: Of the 30 patients, 2 (6.6 %) patients with positive HBsAg received preemptive tenofovir (TDF), and none of them developed HBV reactivation, and 7 (23.3 %) patients were positive for anti-HBs or anti-HBc or both. Of the 7 patients, four patients were negative for HBsAg but positive for HBV-DNA. These four patients also received preemptive ETV. For the rest 3 patients, HBV-DNA was monitored monthly during the chemotherapy and until 1 year after completion of the chemotherapy. During this period, HBV reactivation was observed in 1 (%) patient. Hepatitis was prevented in 2 patients by the administration of TDF at the time HBV-DNA turns positive. Another patient developed de novo hepatitis B due to failure of monitoring.

Conclusions: All patients for chemotherapy should be screened for HBsAg, anti-HBs, and anti-HBc prior to initiation. Pre-emptive TDF therapy for HBsAg positive and/or HBV-DNA positive patients is able to prevent HBV reactivation and hepatitis. HBsAg negative patients with anti-HBs and/or anti-HBc who receive chemotherapy should be followed by HBV-DNA testing monthly during therapy and for 12 months after cessation of therapy, and should be treated with TDF upon confirmation of HBV-DNA reactivation. All this will be very useful for patients undergoing chemotherapy if our results are confirmed in a large number of subjects.

Complication and hospitalisation after percutaneous liver biopsy: a cohort study of 12 years

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Background: Percutaneous liver biopsy (LB) remains the gold standard to assess grading, staging of liver disease and liver fibrosis. Bedossa et al. (2003) concluded that the length of a liver biopsy should be ≥25 mm for accurate assessment of fibrosis with METAVIR. Percutaneous LB is one of the most important and widely used methods for diagnosing chronic liver diseases; however, controversies related to the potential risk of complications and patient discomfort still exist.

Aim: The rationale of this study was to determine the percentage of complications in patients undergoing liver biopsy. Furthermore, we analysed the association between complications and risk factors.

Methods: We evaluated all percutaneous liver biopsies consecutively performed between May 2000 and May 2012 in our hepatology unit to identify the number and type of complications. Males predominated (62 %), mean age was 46 years. In each case LB was US-assisted. An 16-gauge 11 cm Menghini-type needle was used in all cases. The length of the specimen ranged between 2.5 and 5 cm in 279 (99.5 %) cases. Complications were classified as (1) mild: hospitalization <2 days, no intervention or no blood transfusion; (2) Moderate/severe: hospitalization >3 days, intervention or blood transfusion. Type of complications: pain, fever, vasovagal syncope, bleeding, oder (haemobilia, pneumothorax, haemothorax).

Results: During the study period (12 years) 3795 patients underwent ultrasound-assisted percutaneous liver biopsy performed by experienced hepatologists. The total complications proportion was 50 (1.31 %)—mild complications: 50/3795 (1.3 %); moderate/severe: 0/3795 (0 %). Type of complications—pain: 45 (1.18 %) fever: 0, vasovagal reactions: 5 (0.13 %), bleeding: 0, oder (haemobilia, pneumothorax, haemothorax): 0. Less operator experience was significantly associated with a higher rate of procedure failure (P = 0.002). Statistical significance of the relationship between individual operator efficiency and complication rate (P = 0.000) and that between individual operator efficiency and biopsy failure rate (P = 0.002) was observed.

Conclusions: Percutaneous LB is a safe invasive procedure for diagnosing chronic liver diseases and to assess liver fibrosis. The total complications proportion after liver biopsy was low. Percutaneous LB is a safe and effective invasive procedure, despite the fact that noninvasive fibrosis assessment methods are currently widely available and used instead of histological evaluation. Complications risk and failure rate are low if indications and contraindications are considered carefully and the biopsy is performed by a skilled and experienced operator.

Inflammatory and angiogenic factors serum levels in patients with non-alcoholic fatty liver disease

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Background: Non-alcoholic fatty liver disease (NAFLD) is present in 20–35 % of obese individuals and can range from simple steatosis to the more severe non-alcoholic steatohepatitis (NASH). The onset of a chronic inflammatory reaction marks the progression from steatosis to NASH and the expansion of adipose tissue is strongly associated with angiogenesis. Therefore, we determined the expression of inflammatory tumor necrosis factor alpha (TNFa) and interleukin 6 (IL6) and angiogenic (vascular endothelial growth factor (VEGF), soluble VEGF receptor 1 (sVEGFR1) and sVEGFR1) cytokines in the serum of an obese patient population with simple steatosis and NASH compared to healthy controls.
Aim: The rationale of this study was to reveal the expression pattern of TNFa, IL6, VEGF, sVEGFR1 and sVEGFR2 in a population of control subjects and biopsy proven steatosis and NASH patients.
Methods: The expression of these cytokines was determined in the serum by commercial available ELISA kits (R&D systems, UK). The population consisted out of 250 obese patients, which were diagnosed with simple steatosis and 108 patients with NASH and compared to 90 age-and-sex matched healthy controls.
Results: Mean serum TNFa levels were elevated in the serum of steatosis and NASH patients compared to healthy controls, reaching significance in NASH patients ($p < 0.05$). IL-6 was significantly increased in steatosis and NASH patients compared to the healthy controls ($p < 0.001$). VEGF levels were significantly elevated in patients with steatosis ($p < 0.05$) and borderline significantly elevated in NASH patients compared to the serum levels of healthy control subjects ($p = 0.070$). The expression of sVEGFR1 was significantly increased in steatosis and NASH patients compared to controls ($p < 0.001$). sVEGFR2 expression was not significantly different in the three groups ($p > 0.05$).
Conclusion: The study indicates the involvement of not only inflammatory (TNFα and IL6) cytokines but also of angiogenic (VEGF, sVEGFR1 and sVEGFR2) cytokines in the pathophysiology of NAFLD.

On-treatment HBsAg decline is associated with subsequent HBsAg reduction in HBeAg negative chronic hepatitis B

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Background: Early decline of serum HBsAg level at month 6 is associated with improved sustained response to peginterferon treatment in hepatitis B patients, and it is believed to reflect a better immune clearance of intrahepatic hepatitis B virus (HBV).
Aims: We aimed to investigate the kinetics of serum HBsAg level among HBeAg-negative patients who have early decline in serum HBsAg on oral antiviral therapy.
Methods: Hepatitis B e antigen (HBeAg)-negative chronic hepatitis B patients on antiviral therapy with follow-up for 4 years were studied. All patients had compensated liver disease with serum alanine aminotransferase (ALT) <10 times upper limit of normal. Serum HBsAg level was measured by Abbott Architect® HBsAg assay at baseline and 6 month intervals.
Results: Overall, 34 patients were studied. 17 (50 %) and 17 patients were on entecavir and telbivudine, respectively. Overall, the baseline HBsAg level was 3.7 ± 0.42 log IU/ml, and the change of HBsAg level from baseline to month 24 was -0.15 ± -0.25 log IU/ml. Only 2 (5.9 %) patients had early decline in serum HBsAg, i.e. ≥0.5 log reduction, at month 6. At baseline, patients with early HBsAg decline had higher serum ALT (165 ± 110 vs. 85 ± 62 IU/l; $p = 0.003$), HBV DNA (7.2 ± 0.9 vs. 5.0 ± 1.0 log IU/ml; $p < 0.001$) and HBsAg (3.8 ± 0.5 vs. 2.4 ± 0.4 log IU/ml; $p < 0.001$) than those without. Otherwise, there was no difference in age, gender and antiviral drug used between the 2 groups. There was a modest correlation between the magnitude of HBsAg reduction in the first 6 months and the HBsAg reduction from month 6–24 ($r = 0.33$, $p < 0.001$). Numerically, patients who have early HBsAg decline had lower HBsAg level at month 24 (2.40 ± 0.70 log IU/ml) than those without early decline (2.70 ± 0.65 log IU/ml) ($p = 0.11$). Similarly, patients who have early decline tend of have a more dramatic reduction in HBsAg from week 6–24 as compared to those without early decline (-0.34 ± -0.50 vs. -0.11 ± -0.17 log IU/ml; $p = 0.24$).
Conclusions: Early HBsAg decline during antiviral treatment is uncommon among HBeAg-negative patients, but it probably reflects an improved immune clearance of HBV.

Efficacy of combination therapy with pegylated-interferon and ribavirin in HCV-related type II mixed cryoglobulinemia

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Background: Mixed Cryoglobulinemia (MC) is the most frequent extrahepatic disease in patients affected by chronic hepatitis C virus (HCV) infection. It has been supposed that the association of pegylated-interferon (peg-IFN) alpha-2A and ribavirin (RBV) could represent a rational and effective therapy for HCV-related MC with detectable HCV RNA, not only in patients with hepatic disease [Chronic Hepatitis (CH), Child-Pugh Class A Hepatic Cirrhosis (HC)] but also without clinical, biochemical and histological signs of hepatic involvement.
Aim: To evaluate safety and efficacy of peg-IFN alpha-2A in combination with RBV for treatment of HCV-related MC with detectable HCV RNA, in patients with and without hepatic disease.
Methods: 235 patients affected by chronic HCV infection: 175 with CH, 38 with Child-Pugh Class A HC and 22 without hepatic disease. 24/235 patients affected by HCV-related type II MC: 16 with chronic liver disease (14 with CH, 2 with Child-Pugh Class A HC) and 8 without hepatic disease. All 24 patients affected by HCV-related type II MC, previously untreated, underwent treatment with standard dose of peg-IFN alpha-2A 180 mcg once weekly and weight based RBV (WBV) 1000–1200 mg/day.
Results: At 12 weeks, 4/16 (25 %) patients with hepatic disease (2 with CH and 2 with Child-Pugh Class A HC) were non-responders to therapy and stopped it. Twenty remaining patients (12 with CH and 8 without hepatic disease) early virological responders (EVR) continued therapy until to 48 weeks. At the end of therapy, we observed a strict association between the eradication of HCV and a complete clinical response (disappearance of cutaneous manifestations of cryoglobulinemic vasculitis) with a complete virological and clinical response in

12/16 (75 %) and 8/8 (100 %) patients with and without hepatic disease, respectively. Some patients (4 with hepatic disease and 1 without hepatic disease) relapsed both virologically and clinically a few weeks after the end of therapy. At the end of follow-up (72 weeks), in the first group 8/16 (50 %) patients achieved a complete clinical response and sustained virological response (SVR), 4/16 (25 %) non-responders and 4/16 (25 %) relapsers, while in the second group 7/8 (87.5 %) patients achieved a complete clinical response and SVR and 1/8 (12.5 %) relapsers. Therefore, we observed a higher rate of complete clinical response and SVR (87.5 vs. 50 %) in patients without hepatic disease compared with patients with hepatic disease ($p < 0.01$).

Conclusions: Our data suggest that the therapy with standard dose of peg-IFN alpha-2A in combination with oral WBV seems safe and useful in patients affected by genotype 1b HCV-related type II MC. Moreover, it seems that the antiviral therapy is more efficacy in patients without hepatic involvement than in those with hepatic disease, although more data are necessary to confirm these results. However, an higher response rates could be obtained with different treatment schedules, such as higher drug dosages or longer treatment periods. New drugs, such as anti-CD20 monoclonal antibody or new immunosuppressive agents, should be considered for the future, hoping these new approaches will offer a better understanding of this disease and significant advantages for its therapy.

Effectiveness of telbivudine in field practice: a real-life observational study

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Background: Due to a high proportion of an Asian patient population in the GLOBE-study, effectiveness data for Caucasian patients treated with Telbivudine (LDT) for CHB in a real life setting are limited.

Aims: The aim of this study is to present data from patients at 48 weeks of treatment with telbivudine.

Methods: Prospective ongoing non-interventional observational study. Patients were treated for Chronic Hepatitis-B (CHB) with 600 mg LDT daily. Study documentation consisted of baseline demographics, virological data, medical history, as well as follow-up visits for hepatology, safety and treatment success at month 3, 6, 9, 12, and optional at month 24.

Results: 15 CHB patients were enrolled into the study at date of interim analysis, 100 % were HBeAg negative, 100 % male, median age 56 years, 55 % were treatment naive. 14 patients completed the 36 months survey and 1 completed 48 months up to end of December 2011. Average viral load at baseline was 1×107 log copies. After 36 weeks of treatment the mean reduction in viral load was 6×104 log copies in HBeAg negative CHB patients; after 48 weeks the viral load of a (1) patient was 2.0 log. With this reduction, 93 % of all patients became HBV DNA undetectable (<300 copies/ml). Patients who became HBV DNA undetectable at week 24 remained negative in 100 % of cases at week 48. ALT levels decreased from 80 ± 10 to 30 ± 2 U/l ($p < 0.001$).

Conclusion: Telbivudine suppressed HBV replication to undetectable levels in most patients in field practice and showed relative high HBeAg loss rates. It appears that European patients with lower viremia and in majority HBeAg negative CHB demonstrate a favourable outcome during Telbivudine therapy.

The proconsul score: prognosticating coeliac patients survival

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Background: Coeliac disease (CD) is a very frequent chronic enteropathy characterized by an increased mortality caused by its complications, i.e. refractory CD and small bowel lymphoma. It was shown that age at diagnosis of CD, diagnostic delay for CD, pattern of clinical presentation and HLA typing correlate with mortality rates of coeliac patients.

Aims: To create a tool that individuates those coeliac patients at higher risk of developing complications. To set up the follow up of coeliac patients according to the specific risk of complications.

Patients and Methods: Thanks to Fondazione Associazione Italiana Celiachia and Coeliac Common Interest Group, clinical data from 106 patients (68 F, mean age 53 ± 14 years at enrolment) affected by complicated CD (i.e. cases) were collected. To set up a multicenter matched case–control study, 171 controls (110 F, mean age 55 ± 13 years at enrolment) were selected among coeliac patients without complications. For each case, two (or at least one) controls, matched to cases according to the year of assessment, gender and age, were selected. Diagnostic delay, pattern of clinical presentation, HLA typing and age at diagnosis of CD were used as predictors.

Results: Differences between cases and controls were shown for diagnostic delay (median 9 months, IQR 3–27, vs. 19 months, IQR 6–84, $p = 0.025$), classical presentation (75/105 vs. 71/171, Chi square $p < 0.001$), and HLA DQ2 positivity (96 vs. 85 %, $p = 0.025$). Age at diagnosis did not differ between cases and controls. Conditional logistic models based on these statistically different predictors allowed the development of a score system. Tertiles analysis showed a relationship between score and risk of being a case (Chi square, $p < 0.001$).

Conclusions: A score that shows the risk of a newly diagnosed coeliac patient to develop complications was developed for the first time. This will allow to set up the follow up of CD patients with great benefits for not only their health but also management of economic resources.

Micro-RNA expression profiling identifies miR-29b as a relevant pro-fibrogenic factor in Crohn's disease intestinal strictures

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Background and Aims: Intestinal fibrosis is a frequent complication in Crohn's disease (CD), with subsequent stricture development that may require surgical intervention. MicroRNAs (miRNAs) are a novel class of post-transcriptional gene regulators implicated in cardiac, hepatic and pulmonary fibrosis. MiRNAs play a key role as modulators of the potent profibrotic cytokine transforming growth factor (TGF)-β, which is up-regulated in CD intestinal strictures. Here, we aimed to identify and investigate the functional characteristics of miRNAs with differential expression between strictured and non strictured CD.
Methods: Intestinal surgical specimens were collected from 17 patients with fibrostenosing CD, and total RNA was extracted from uninflamed ileal mucosa. MiRNA expression profiling was performed using Illumina v2.0 microRNA array comparing matched strictured to non-strictured areas from the same patient within each experimental group. Subsequent validation of differentially expressed miRNAs was performed using qRT-PCR. Primary mucosal myofibroblast cultures were derived from strictured CD and healthy control tissue. Overexpression of miRNAs was induced in myofibroblasts by transfection and changes in mRNA expression were detected by RT-qPCR.
Results: We detected 11 miRNAs significantly up-regulated and 10 miRNAs significantly down-regulated (all $p < 0.02$) between the strictured and non strictured ileum. Validation experiments confirmed the changes in miRNA expression detected by the microarray. Among differentially expressed miRNAs, we selected miR-34a (up-regulated in CD strictures) and miR-29b (down-regulated in CD strictures) and we studied their functional consequences on collagen expression by mucosal myofibroblasts. Induced expression of miR-29b resulted in a decrease of both *COL1A2* and *COL3A1* mRNA levels, whereas miR-34a overexpression did not induce any significant changes.
Conclusions: This study confirms that differences in miRNA expression profiles between CD strictured and non-strictured areas can be detected. Down-regulation of collagen mRNA shows that miR-29b may play a functional role in modulating fibrosis in CD, however further studies to investigate the impact of increased collagen protein are required. Manipulation of miRNA profiles may be a novel therapeutic strategy against fibrosis in CD.

Cluster of enteropathies negative for coeliac disease genetics but carring HLA DQ6

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Background and Aims: Genetic susceptibility to coeliac disease (CD) is strongly associated with HLA DQA1*05-DQB1*02 (DQ2) and HLA DQA1*03-DQB1*0302 (DQ8) and a gene-dosage effect of DQB1*02 was shown. Nevertheless, rare cases of patients negative for both patterns were described. Our aim was to look for patients with a flat duodenal biopsy but negative DQ2/DQ8.
Methods: Among all the patients attending our Clinic from Jan 1999 to March 2012, we selected those with a villous atrophy and negative to HLA DQB1*02/*0302. Clinical features, coeliac antibodies and response to gluten-free diet (GFD) were also collected.
Results: Among 243 patients with villous atrophy and available HLA-type, there were 10 patients (4.12 %) who did not carry either HLA DQB1*02/*0302. They had received the following diagnoses: 3 non-complicated CD, 1 enteropathy-associated T cell lymphoma, 3 enteropathy in common variable immunodeficiency (1 sustained by Giardia), 3 undefined sprue.
Four of them have a very similar HLA pattern (A*03; B*35; DRB1*11; DQA1*0102,*0505; DQB1*0301,*06). They all presented with chronic diarrhoea, weight loss, electrolyte malabsorption and hypoproteinemia. They were all negative for coeliac-specific and enterocyte antibodies, immunoglobulin deficiency, HIV serology, stool parasite infestation, familial history of gastroenterologic diseases, personal history of autoimmune diseases. Mucosal monomorphic lymphocyte infiltrate was excluded in all the intestinal biopsies. However, in case 4 a monoclonal rearrangement of T cell receptor gene was shown. Case 1 (F, 29) presented a complete clinical and histological response after 12 months on a GFD and was considered coeliac. Case 2 (M, 33) after 91 months of strict GFD, still demonstrated subtotal villous atrophy, but stable clinical conditions in the last 4 years. He was considered to be affected by undefined sprue and started budesonide therapy, without any improvement of villous atrophy after 6 months. Case 3 (M, 56) started a GFD; after 1 month without any clinical improvement he was started on steroids. He had a clinical improvement and he will be re-evaluated in the next months. Case 4 (F, 60) started a GFD; after 5 months without any clinical improvement she was also started on steroids and will be re-evaluated in the next months.
Conclusions: We described 4 cases of uncommon enteropathy negative for both coeliac serology and genetics, who share HLA-type. They have a similar clinical presentation but only one of them responded to GFD. However the two of the other three patients who have a persistent villous atrophy show an unexpected favourable clinical evolution.

Coeliac disease in chronic autoimmune thyroiditis: an incidence study

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Introduction: Prevalence of coeliac disease (CD) among Hashimoto thyroiditis and Graves' disease is known to be between greater than 5 % [1]. However, no "active" studies about the incidence of CD in these at-risk-populations are available so far. To understand whether it is necessary to follow up chronic autoimmune thyroiditis (CAT) patients already found to be negative to endomysial antibody (EMA), we investigate whether EMA negative CAT patients can subsequently become EMA positive.
Patients: In the last 3 years, EMA were tested in 130 adult CAT patients (115 females, mean age 49.9 ± 15.1 years, 122 Hashimoto's and 8 Graves' disease, mean thyroid disease duration 7.2 ± 6.7 years). After at least 1 year, we contacted the CAT patients found to be EMA-negative

for a second EMA testing: 31 of them accepted (29 females, mean duration of follow up 35.9 ± 19.7 months).
Results: At the first EMA testing none of the CAT patients were positive. At the second testing, none out of 31 EMA-negative CAT patients became positive. None Duodenal biopsy showed a variable degree of villous atrophy in all of them.
Conclusions: Prevalence of coeliac disease among asymptomatic adult chronic autoimmune thyroiditis patients was lower to that found in the literature, also after a long duration of the disease. Moreover, incidence of coeliac disease among adult chronic autoimmune thyroiditis patients previously shown to be EMA negative seems to be very low (0 % in 3 years).

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The prevalence of small bacterial overgrowth and gas production in patients with spina bifida

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Introduction: The term spina bifida (SB) is referred to a group of congenital neural tube defect with a variety of clinical manifestations, resulting from the lack of vertebral arches in the median line during the 3th and the 4th week of gestational age. The injury in the lumbosacral spine compromises the sensory and motor functions of the perianal region, leading to a delayed colonic motility and anorectal dysfunction, which result in functional obstruction and severe constipation. Impaired intestinal motility is often associated with small-bowel bacterial overgrowth (SIBO) with high level of gas production.
Aims and Methods: The aim of the study is to assess the prevalence of SIBO in children affected by SB.18 (M 6-F 12, 16.4 ± 7.6 mean age) consecutive children affected by SB were enrolled at the Spina Bifida Center, Pediatric Department of Gemelli Hospital, Rome. All subjects underwent H_2/CH_4 lactulose breath test to assess SIBO and oro-caecal transit time (OCTT). All patients performed a visual analogical scale (VAS) investigating abdominal pain/discomfort, constipation, diarrhoea, bloating and flatulence, a diary of the frequency and consistency of the stool (Bristol Stool Scale) during the previous 7 days. A nephro-urological clinical evaluation of the number of urinary tract infection (UTI) was also performed.
Results: 38.8 % (7/18) patients showed a SIBO and 61 % (11/18) present a delayed OCTT. Moreover 44.4 % (8/18) produced high level of CH_4. Interestingly SB children with a delayed OCCT produced high level of CH_4 and showed a higher incidence of UTI, with a lower frequency of evacuation, compared to those with a normal or accelerated OCTT. SIBO pts showed a significant higher incidence of abdominal pain and flatulence compared to those without SIBO.
Conclusion: Recent studies have demonstrated that CH_4 gas as produced by gut bacteria was able to slow small intestinal transit. The association between CH_4 and constipation suggests that CH_4 has an active role in the development of constipation. While CH_4 appears to be associated with, and perhaps contributing, to constipation, what is more important is that it potentially identifies a subgroup of patients that respond to antibiotic therapy directed at eliminating or reducing the production of this gas.

The prevalence of "H2 non producers" in IBS population

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Introduction: Hydrogen breath test has become popular in clinical practice as it is useful for diagnosing small intestinal bacterial overgrowth (SIBO) and carbohydrate intolerance. Hydrogen (H_2) and methane (CH_4) gas are produced in the body from intestinal bacteria. The H_2-containing blood travels to the lungs where the H_2 is released and exhaled in the breath where it can be measured. 15 % of population have gut flora that contain *Methanobrevibacter smithii*, which converts 4 atoms of H_2 into 1 molecule of CH_4. These subjects may not exhale H_2.
Aim: We performed a retrospective study to evaluate the real prevalence of H_2 non producers in our geographic area.
Methods: From November 2010 to November 2011, 197 pts [F 142/M 55] performed H_2/CH_4 lactose and lactulose breath test in our gastroenterology unit for IBS. The breath sample were analyzed with Quintron Breathtracker Digital Microlyzer. Patients without H_2 production neither in lactose or lactulose breath test were defined as "H_2 non producers". We performed twice the tests to confirm this data.
Results: 15/197 pts (7.6 %) do not produce H_2 during lactose neither lactulose breath test. The second breath tests confirmed the previous diagnosis. In this patients the CH_4 production was found in 5/15 (33.3 %), so they are considered false negative.
Discussion: The majority, but not all population, produces H_2 gas. Our study revealed a prevalence of 7.6 % of H_2 non producers. Moreover, around 30 %, were false negative in fact they were CH_4 producers. In this kind of patients is very important the use of a CH_4/H_2 machine to avoid achieving false negative, as they have symptoms compatible with SIBO and/or lactose malabsorption. We can hypothesize that another 70 % of H_2 ad CH_4 non producers, may exhale other gases, more study are necessary to better understand the characteristics of these gases.

S.boulardii efficacy in the treatment of IBS: a pilot prospective study

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Introduction: Gut microflora is involved in pathophysiology and treatment of irritable bowel syndrome (IBS). S. boulardii is an yeast able to improve the antibiotic-associated diarrhea and the quality of life of IBS patients.
Aims: evaluate the efficacy of S.boulardii on IBS symptoms.
Methods: we enrolled 10 IBS Rome III criteria pts that underwent lactulose breath test (LBT) to exclude the presence of small intestinal bacterial overgrowth (SIBO). Then they were treated with S.boulardii (250 mg bid) for 1 week. The gastrointestinal symptoms were collected with a VAS questionnaire at the moment of breath test and at the end of the treatment.
Results: 4 pts were constipation (IBS-C), 4 diarrhea-predominant (IBS-D), and 2 were mixed (IBS-M). All pts completed the study without reporting adverse events. S.boulardii significantly reduced the overall symptoms score (5.0 vs. 2.8, $p < 0.05$, ANOVA); 8/10 pts

showed a overall symptoms improvement (100 % IBS-D, 50 % IBS-C, 50 % IBS-M). In IBS-D, diarrhea significantly changed over baseline (4.9 vs. 2.6, $p < 0.05$, ANOVA); in IBS-C, constipation was significantly improved (5.0 vs. 2.6, $p < 0.05$, ANOVA); in IBS-M, bloating and abdominal pain/discomfort were significantly improved (5.0 vs. 2.7, $p < 0.05$, ANOVA). S.boulardii administration did not change the colonic hydrogen production during LBT, evaluated as area under curve (AUC), before and after the treatment: 882.8 ± 170 vs. 705.4 ± 185 ppm/min ($p = NS$, ANOVA); however post hoc analysis showed that S.boulardii was able to change the LBT AUC according to IBS pattern: in the IBS-D group, showing a normal transit time, AUC was significantly decreased (899 ± 120 vs. 567 ± 143 ppm/min, $p < 0.05$, ANOVA); in the IBS-C and M group, showing a slowed transit time, when AUC was evaluated in the last hour (180–240 min) of the LBT, was significantly reduced (845.1 ± 111 vs. 625.5 ± 134 ppm/min, $p < 0.05$, ANOVA).
Conclusions: S.boulardii seems to be effective in IBS symptoms treatment with different symptoms' profile response according to the prevalent alvus. Its efficacy seems to significantly correlated to the colonic sugar fermentation as assessed with LBT. Further placebo-controlled studies are needed to confirm these preliminary results.

Hyperadiponectinemia in patients with chronic hepatitis C virus infection

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Background and Aims: Hepatitis C virus (HCV) chronic infection (CHC) is associated with alterations in the metabolism of glucose and lipids, with development of insulin resistance (IR), which negatively affects disease progression. Based on the association of increased serum levels of adiponectin, an insulin sensitizing adipokine, with IR in CHC patients, adiponectin resistance has been hypothesized to play a role in the pathogenesis of metabolic abnormalities and liver damage in these patients. However, data from the previous studies are limited by the small sample sizes and the lack of control for genetic background and the severity of hepatic fibrosis. Therefore, the aim of this study was to compare adiponectin levels between CHC patients and accurately matched controls.
Patients and Methods: To this end, we matched (1:1) 184 CHC patients for age, gender, body mass, and adiponectin (ADIPOQ) genotype with healthy controls. To control for the severity of liver disease, a second control group consisting of 51 patients with histologically proven nonalcoholic fatty liver disease (NAFLD) further matched (1:1) for fibrosis and the previous variables was employed. ADIPOQ genotypes were evaluated by Taqman assays, serum adiponectin by ELISA.
Results: Serum adiponectin levels were higher in 184 patients with chronic HCV hepatitis than in matched healthy controls (8.96 ± 5.04 vs. 7.35 ± 4.04 μg/ml; $p = 0.001$). The difference was more marked in males ($p = 0.001$), whereas was less evident in females, who are known to have higher adiponectin levels. At multivariate analysis adiponectin levels were associated with CHC independently of age, gender, ADIPOQ genotype, ALT levels, BMI class, and the presence of diabetes ($p = 0.001$; OR 1.8, 95 % confidence interval (CI) 1.74–2.86). Adiponectin levels were also higher in 51 CHC patients than in with 51 patients with NAFLD, matched for age, gender, BMI, ADIPOQ genotype, and the severity of fibrosis (8.44 ± 4.65 vs. 4.87 ± 3.17 μg/ml; $p < 0.001$). This association was confirmed at multivariate analysis adjusted for the matching variables ($p < 0.001$; OR 3.51, 95 % CI 1.96–5.06). In CHC patients, adiponectin levels were not influenced by HCV genotype and viral load.
Conclusions: CHC is associated with increased levels of serum adiponectin independently of age, gender, body mass, ADIPOQ genotype, and the severity of liver fibrosis. Resistance to adiponectin action is likely involved in the metabolic disturbances associated with CHC.

Sustained ventricular tachycardias induced by hypokalemia due to lipomatosis of the ileocecal valve

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Introduction: Lipomatosis of the ileocecal valve is a condition known since many decades. It is characterized by diffuse circumferential deposition of fatty tissue mainly in the submucous layer. The condition is often asymptomatic, or the symptoms may be so insignificant that they are overlooked. On the other hand, some patients have long-standing gastrointestinal symptoms, such as recurrent or chronic flatulence, constipation, abdominal pain, nausea, vomiting, intestinal obstruction, bleeding, diarrhea. Surgical treatment may result in complete resolution of symptoms.
Here we describe the case of lipomatosis of the ileocecal valve in which chronic diarrhea had led to recurrent hypokalemia, that triggered many episodes of life-threatening ventricular arrhythmias. Despite the advanced antiarrhythmic treatments performed, the diagnosis of lipomatosis of ileocecal valve was overlooked, and surgery was considered too late.
Case Report: A 62 years old man was referred to our attention from the Cardiology ward of another hospital for the diagnostic assessment of chronic diarrhea. His past medical history included acute myocardial infarction 15 years ago that required coronary artery by-pass grafting; recurrence of STEMI treated 5 years ago with PCI and stenting of three coronary vessels; redo of PCI 3 years ago for intrastent restenosis.
Considering the evolution in dilated cardiomyopathy a Cardiac Resynchronization Therapy-Defibrillator was implanted. Three years ago the patient was admitted to the Surgery ward because of intestinal sub-occlusion, with spontaneous resolution. Four days after the hospital discharge the patient was admitted to the Cardiology ward because of frequent episodes of ventricular tachycardia during hypokalemia. One month later a further hospital admission occurred because of abdominal pain. Among the clinical investigations performed, a CT of the abdomen showed lipomatosis of the ileocecal valve with stretching of the last ileal loop; however, no specific treatment was considered. Then the patient presented chronic diarrhea with recurrent ventricular tachyarrhythmias and arrhythmic storms triggered by hypokalemia, inducing acute heart failure episodes. Because of persisting ventricular tachycardias despite various antiarrhythmic regimens, in the following months the patient underwent to four transcatheter radiofrequency ablations; in one occasion the procedure was complicated by ischemic stroke.

Surprisingly, the diagnostic work-up for the hypokalemia induced by chronic diarrhea was never reconsidered until the admission to our Unit. During the hospital stay in our Unit, infective, inflammatory, and neoplastic causes of diarrhea were excluded, while an abdominal CT confirmed the lipomatosis of the ileocecal valve.
Conclusions: In the case presented the simple assessment of diarrhea and hypokalemia was overlooked, favoring sophisticated diagnostic and therapeutic procedures. This emphasizes once again the need to remind us the golden rules of the clinical evaluation and management that must be comprehensive. It has to be also remembered that the lipomatosis of the ileocecal valve, when symptomatic, should be surgically treated.

Ultrasonographic score for the evaluation of activity in Crohn's disease: comparison between ultrasound and endoscopy

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Background and Aims: The use of ultrasound (US) with color-power-Doppler has been proposed for monitoring the activity index in Crohn's disease (CD), although endoscopy is still considered the gold standard in the follow-up of this disease. The aim of our retrospective study was to develop diagnostic US criteria for the evaluation of disease activity in CD, comparing our results with those obtained from endoscopy.
Patients and Methods: We retrospectively examined 23 patients affected from CD, histologically confirmed, by using bowel US followed by pancolonoscopy with retrograde ileoscopy within 7 days. US images were obtained by an experienced sonographer, using an ATL model HDI 3500 with a 3.5 MHz convex probe and a 7.5 MHz linear probe. We developed an echographic score of disease activity (Crohn's Disease Ultrasonographic Score—CDUS) by assigning a grade to the following pathological parameters: (1) intestinal loop transversal caliber (>25 mm), (2) bowel wall thickness (>3 mm for small bowel, >4 mm for colon), (3) loss of bowel wall stratification and submucosa hypertrophy, (4) increased wall vascularisation, (5) mesenteric hypertrophy, (6) intra mesenteric lymph nodes, (7) effusion between bowel loops and (8) local complications as abscesses and fistulae. CDUS included 4 grades of disease: quiescent (0–1.5), low (1.5–3.5), moderate (3.5–5), severe (>5). Endoscopy established the level of disease activity by using the Simple Endoscopic Score for Crohn's Disease (SES-CD). Histological classification included the same 4 groups of CDUS. Statistical analysis was done by using the Spearman rank test.
Results: Of the 23 examined patients, 17 were male and 6 were female, with a mean age of 37.9 years. We found a significant correlation between results from CDUS and SES-CD ($p = 0.0302$/$r = 0.4523$/C.I. 0.03–0.73). Correlation between CDUS and histological classification was not statistically significant ($p = 0.067$), probably caused by the small number of our patients.
Discussion: It is known that US gives different informations form endoscopy about bowel loops alterations. However, our results show that US is as sensitive as endoscopy and quite specific. Therefore, we think that our echographic score, based on a non-invasive method, is useful in the follow-up of patients with CD. Prospective studies on larger reference populations are needed for its validation.

The proteiform clinical profile of celiac disease (CD) in a tertiary referral center of Internal Medicine in Southern Italy

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Background: CD is a small bowel immune disorder characterized by mucosal inflammation, villous atrophy, and crypt hyperplasia, which occur upon exposure to dietary gluten and which demonstrate improvement after withdrawal of gluten from the diet. CD occurs in genetically predisposed individuals carrying a close association with HLA-DQ2 and DQ8 gene loci. It can occur after exposure to the protein fractions of wheat, rye and barley. Currently, the prevalence of CD is estimated to be approximately 1:150 in western countries. CD may become evident at any age with either gastrointestinal clinical-subclinical manifestation, and a number of non gastrointestinal manifestations.
Aims: To profile a population of CD patients observed in a tertiary referral center of Internal Medicine in southern Italy.
Methods: 45 CD patients (M:F = 9:36, 34 ± 14 years, range 5–63) entered a workup including: history, physical exams, routine lab tests, autoantibodies and HLA DQ2/DQ8, EGDS with histology (Marsh-Oberhuber and Corazza-Villanacci score). H_2 breath test for lactose intolerance was performed (25 g lactose Bedfont-Lactofan®, Italchimici, Italy) according to established italian guidelines (Aliment Pharmacol Ther 2009;29 Suppl 1:1–49).
Results: Intestinal symptoms (mainly bloating, dyspepsia, abdominal pain, aphtosis, diarrhea) occurred in 16 (35.5 %) patients. Extraintestinal symptoms (mainly neurological, endocrinological, hematological symptoms and hypertransaminasemia) occurred in 27 (60 %) patients. In 2 (4.5 %) patients CD was discovered during screening in 1st degree relatives. In the group with extraintestinal symptoms, 34 % of patients displayed neurological symptoms (e.g. demyelination, anxiety, headache, depression), 22 % had endocrinological symptoms (GH deficiency, thyroid disease, gynaecological disease), 22 % had hematological symptoms (iron-deficient anemia, lymphadenopathy), 11 % had hypertransaminasemia, 7 % had arthritis, osteoporosis, osteopenia, and 4 % skin manifestations (dermatitis). Lactose intolerance was diagnosed in 55 % of cases.
Conclusions: In a large referral center of Internal Medicine in Southern Italy, CD occurs mainly with proteiform symptoms mimicking other frequent disorders in clinical practice. This possibility requires a subtle differential diagnosis to start therapy as soon as possible, and prevent complications of malabsorption. Lactose intolerance emerges as an early feature of CD in otherwise clinically silent patients.

Bone mineral content changes in the first year after liver transplantation does not predict the increased risk of vertebral fractures

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Background and Aims: Subjects that underwent liver transplantation (OLT) regain a quasi-normal look, liver and kidney function and oral

feeding but unfortunately fractures occur frequently, mostly in the first 6 months, for a multifactorial etiology.
Our aim was to investigate the relationship between body composition (BC)/drug therapy and bone parameters in adults after OLT.
Methods: 29 patients (16 M and 13 F; ageing 52.8 [SD 10] years), were prospectively enrolled in the study after OLT. All patients received tacrolimus and steroids. BC analysis was performed by a new dual-energy X-ray absorptiometry (Lunar iDXA, GE Healthcare) after 1, 3, 6, 9 and 12 months. Fat mass (FM), non-bone lean mass (LM), bone mineral content (BMC) and bone mineral density (BMD) were assessed in whole-body and regional model.
Results: Total BMC slightly decreased without significant difference between 12-month and baseline values (BMC, 1-month: 2357 [549] g, 12-months: 2283 [775], $\chi^2 = 1.032$; $p = 0.905$). Lumbar spine (LS), femur and total body BMD showed the same behaviour (LS-BMD, 1-month: 0.943 [0.151] g/cm^2, 12-months: 0.929 [0.203], $\chi^2 = 0.498$; $p = 0.974$; femur-BMD, 1-month: 1.143 [0.182], 12-months: 1.077 [0.254], $\chi^2 = 1.003$; $p = 0.909$; Total BMD, 1-month: 1.039 [0.128], 12-months: 1.001 [0.190], $\chi^2 = 0.620$; $p = 0.961$).
LS-, femur- and total body BMD was associated with body mass index (BMI) ($Rs = 0.617$; $p < 0.001$, 0.515; $p < 0.001$ and 0.512; $p < 0.001$, respectively) and with android/gynoid index of fat distribution [android FM/gynoid FM ratio] ($Rs = 0.622$; $p < 0.001$, 0.603; $p < 0.001$ and 0.568; $p < 0.001$, respectively). Steroid dosage did not significantly affect any BMC and BMD.
Conclusions: DXA body composition assessment, although highly specific for evaluation of bone mineral reduction, is not sufficient to predict the risk of fractures. Continuous bone turnover due to immunosuppressive drugs possibly produces a less resistant tissue before the absolute reduction of mineral content. The direct relation between BMD parameters and variables measuring FM and LM makes mandatory a valid feeding after OLT.

Advanced liver disease burden: epidemiology, clinical features and economic analysis

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Introduction: Chronically evolving liver diseases represent a remarkable cause of morbidity and mortality, with both social and sanitary implications. Liver disease is often asymptomatic and cirrhosis complications are still a frequent cause of hospital admission at the first diagnosis.
Aim: To explore the epidemiologic and clinical profile of hospital admissions of cirrhotic patients and to determine their economic burden.
Materials and Methods: Epidemiological and clinical overview of liver disease burden has been achieved by the examination of discharging cards (2006–2008) of patients with cirrhosis of the Veneto Region using ICD9-CM-1997 codification. To define detailed cost analysis, 100 consecutive medical records have been carefully evaluated. The results have been compared to those of patients admitted for major chronic diseases, including heart failure and chronic obstructive pulmonary disease (COPD) and data were related to DRG reimbursements.
Results: Mean hospital admissions for cirrhosis and its complications in the Veneto Region was 14.354 per year with a mortality of about 12 %. The majority of the patients were males younger than 65 years. Rate of yearly recurrent hospital admittance for cirrhosis was 43.4 %, mainly due to encephalopathy and ascites, while it was 18.5 % for heart failure. Gastrointestinal tract bleeding has emerged as the most represented cause of hospitalization, followed by hepatic encephalopathy, ascites and hepatocellular carcinoma. Co-morbidities such as diabetes and/or bacterial infections were detected in about 20 % of cases. The median cost of each hospitalization was higher for cirrhosis than for heart failure and for COPD, with a corresponding RDG reimbursement of 66, 106 and 88 %, respectively.
Conclusions: Advanced liver disease has a relevant socio-economic impact, with higher sanitary and social costs and lower RDG reimbursement than other major chronic diseases.
The identification of the major causes of repeated hospital admission represents the target to address secondary prevention strategies, sharing therapeutic patient education and management programs at territorial level.

Treatment of portal vein tumor thrombosis (PVTT) can impact survival of patients with advanced HCC?

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Introduction: HCC with PVTT is often associated with poor prognosis. Many efforts have been made to improve prognosis in this setting, but nowadays there is not a treatment of choice for HCC related PVTT.
Aims and Methods: We retrospectively assessed epidemiologic data, tumor and underlying liver disease features, overall survival and treatment-related survival of 60 patients affected by advanced HCC complicated by PVTT. Moreover we evaluated variables associated to PVTT development and severity, and the impact of tumor thrombosis treatment on survival of patients with advanced HCC. We included both main portal vein and segmentary branches thrombosis. Diagnosis was made according to typical dynamic contrast pattern on radiological main techniques. We calculated overall survival by the time of both PVTT diagnosis and tumor onset. In addition we evaluated a possible role of performed treatment on conditioning prognosis. A Kaplan–Meier analysis was performed.
Results: From May 2008 to April 2012 60 patients (51 male, 9 female; mean age 66 ± 5.6) were recruited for retrospective evaluation. 33/60 (55 %) patients underwent systemic antiangiogenetic therapy; 6/60 (10 %) were referred to external beam radiation therapy on thrombus; 21/60 (35 %) not receive any active therapy. All patients received the best treatment on HCC concomitant nodules. A multivariate analysis showed that time between the onset of thrombosis and the diagnosis of HCC is significantly correlated to viral aetiology and BCLC stage at the diagnosis of HCC, while thrombosis extension is significantly correlated to the presence of portal hypertension. At the end of observation (47 months), survival for each group was 18, 50 and 23 %, respectively. The overall survival from the diagnosis of HCC was 753 ± 88 days and it is significantly correlated to younger age at diagnosis, BCLC A and treatment performed on HCC nodule, but not according to PVTT treatment. The overall survival from the diagnosis of PVTT was 397 ± 77 days. According to each group, mean survival was 408 ± 86 days for the first group (antiangiogenetic therapy), 855 ± 273 days for the second group (radiation therapy), 140 ± 29 days for patients who had not received any therapy ($p < 0.001$), regardless of age or severity of underlying liver disease.

Conclusion: PVTT treatment seems to improve survival of patients with advanced HCC, regardless of age. In particular radiation therapy seems to be the best treatment option for this kind of patients. Nevertheless PVTT treatment seems not to affect overall survival from time of diagnosis of HCC. Further studies are necessary to evaluate the impact of patients and tumor characteristics on treatment efficacy.

Immunohistochemistry study of the expression of the receptor for the advanced glycation end products (RAGE) in Crohn's disease

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Background: Crohn's disease (CD) is a chronic inflammatory bowel disease due to dysregulation of the immune tolerance towards components of the intestinal microbiota in genetically susceptible individuals. The consequent unbalancing between pro- and anti-inflammatory molecules leads to tissue damage. RAGE is a transmembrane receptor that belongs to the immunoglobulin superfamily that is expressed at low levels in multiple adult tissues. Upon its activation by several classes of ligands, RAGE triggers intracellular signals, mainly through nuclear factor-kB, which ultimately lead to a sustained inflammation. Up to date, an increased RAGE expression has been found in several chronic inflammatory and degenerative diseases, such as rheumatoid arthritis, diabetes mellitus, atherosclerosis, cancer and neurodegenerative conditions. Recently, the inhibition of RAGE-ligand interaction has been shown to cause a dramatic amelioration of clinical conditions and gut lesions, and reduction of nuclear factor-kB and tumour necrosis factor-α levels in an experimental model of colitis.
Aim: We investigated the expression of RAGE on the intestine of CD patients by immunohistochemistry using surgical specimens obtained from both macroscopically involved and uninvolved areas, in comparison to the level found in normal tissue.
Patients and Methods: Surgical specimens from ileum and/or colon of 20 CD patients (M/F: 12/8; mean age: 43.1 ± 10.2) and 9 sex/age matched controls (HC) who underwent colectomy for neoplasms were used. Formalin-fixed, paraffin-embedded tissue sections were taken from both inflamed and non-inflamed areas in CD patients, and from normal tissue at more than 10 cm from the lesion in HC. After pre-treatment with 3 cycles of microwave and incubation with CAS-Block solution (Invitrogen; UK), the sections were incubated with the polyclonal anti-human RAGE antibody (R&D System; USA) at 1:1000 dilution, and then stained with the biotine-avidin complex, and counterstained with Harris' hematoxylin. As positive controls, colonic tubular adenoma and normal lung tissue were used, while as negative control, a seriate section was incubated without the primary antibody. RAGE expression was evaluated by a blinded pathologist and the immunoreactivity was assessed at both epithelial and lamina propria level. Specifically, on epithelial cells a score including both the percentage of positive cells and the intensity of cellular staining was used. We thus obtained a scale with 3 different levels: grade I: <10 % of cells positive with a weak immunoreactivity; grade II: 10–50 % of cells positive with a moderate immunoreactivity, and grade III: >50 % of cells positive with a strong immunoreactivity. In the lamina propria, the quantization was performed by differential counts of positive cells on 10 fields at high-power microscopy (×40), and the results displayed as the mean number. Moreover, the intensity of the staining was calculated with an ordinal scale (0–3), where 3 = strongly positive staining, 2 = moderately positive staining, 1 = weakly positive staining, and 0 = absence of staining. Finally, we also considered the pattern of the staining that was reported as cytosolic, membranous or luminal, according to the cellular distribution. Statistical analysis was performed by the Mann–Whitney U test for nonparametric data and a level of $p < 0.05$ was considered statistically significant.
Results: The percentage of RAGE positive epithelial cells was higher in inflamed areas of CD patients than in HC ($p = 0.03$), whilst no difference was found between normal mucosa of both groups. The number of positive lamina propria cells resulted significantly higher in both inflamed and normal areas of CD patients than in HC ($p = 0.03$ and $p = 0.04$, respectively). Remarkably, we also found a higher number of positive cells in inflamed tissue and in the proximity of ulcerative lesions in comparison to health tissue ($p = 0.008$) within the CD group, although without difference in the intensity staining ($p = 0.479$). In all samples, the pattern of RAGE expression appeared apical membranous and cytosolic.
Conclusions: Our results are consistent with an increased expression of RAGE in CD in comparison with controls. Specifically, RAGE is overexpressed at both epithelial and lamina propria levels, especially in the inflamed areas. These findings suggest a possible role of RAGE in sustaining chronic inflammation in CD.

Hematopoietic stem cell transplantation restores gluten tolerance in Celiac disease

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Background: Hematopoietic stem cell transplantation (HSCT) has emerged as an effective treatment for patients with autoimmune diseases refractory to conventional therapies. Although the mechanisms by which HSCT reverts tissue damage are still poorly understood, elimination of self- or dys-reactive lymphocytes by the immune-ablative conditioning regimen and de novo development of T- and B cell repertoire from donor-derived hematopoietic progenitor cells are thought to be involved in the re-induction of immune tolerance, despite the persistence of the target antigen(s). Celiac disease (CD) is an autoimmune enteropathy caused by the breakdown of peripheral tolerance towards wheat gluten proteins and related prolamins, whose only treatment consists of long-life gluten-free diet.
Aim: We carried out a full immunological study over time on two cases of celiac patients who underwent allogeneic HSCT for *β-thalassemia major* in comparison with both celiac and non-celiac patients with the aim of providing insights into the development of gluten tolerance.
Patients and Methods: Both cases underwent search for anti-endomysium auto-antibodies and perendoscopic duodenal biopsy at time of the diagnosis of CD, and after HSCT during gluten-free regimen and after 1 and 2 years from the re-introduction of gluten in the diet. Subsequently, monitoring of serological markers was scheduled every

6 months. As control groups, 11 active celiac patients, 8 of which even after a course of gluten-free diet, and 9 dyspeptic patients were recruited. The analysis of dendritic cell and lymphocyte populations, with particular regard to regulatory FoxP3$^+$T cells, was carried out by flow cytometry on peripheral blood samples collected at each visit, while the number of mucosal FoxP3$^+$ T cells were evaluated at immunohistochemistry by using a specific monoclonal antibody (Clone 236A/E7, Bioscience) and displayed as percentage of lamina propria mononuclear cells. Moreover, the cytokine profile of mucosal samples which included the quantization of the relative transcript levels of interleukin (IL)-2, IL-4, IL-6, IL-10, interferon (IFN)-γ, and transforming growth factor (TGF)-β, was detected by means of real time RT-PCR. Finally, the proliferative response to gliadin was investigated by using mucosal T cell lines, and expressed as stimulation index.

Results: After HSCT, in both cases the introduction of a gluten-containing diet did not cause the re-appearance of clinical, serological and histological markers of celiac disease in up to four-years of follow-up. The analysis of circulating dendritic cells showed a recovery of the absolute number of both plasmacytoid and monocytoid subsets after HSCT during both gluten-free and gluten-containing diet in comparison with the values found pre-HSCT at the time of diagnosis of active CD. Similarly, a depletion of circulating dendritic cells, mainly the plasmacytoid subset, was found in both untreated and treated celiac control patients in comparison to the values found in dyspeptic patients. As far as regulatory T cells are concerned, a higher percentage of circulating FoxP3$^+$ T cells was observed in both cases before HSCT and celiac control patients in comparison with the values found after HSCT during both diet regimens and in dyspeptic patients. The same results were found at mucosal level. When analyzing the mucosal cytokine profile, a full overlap of the transcript levels of all the cytokines investigated was found between the two cases after HSCT and dyspeptic controls, with the exception of TGF-β which was higher in the two cases. Also the data obtained from treated CD controls were similar to those of dyspeptic controls. Conversely, the cytokine profile found in duodenal mucosa before HSCT was comparable with that of untreated CD control patients. Finally, the lack of proliferative response upon gliadin stimulation was found when using T cells isolated from duodenal mucosa of both cases after HSCT, either during gluten-free (mean stimulation index 1.5 ± 0.6), or gluten-containing (mean stimulation index 1.2 ± 0.5) diet regimens. By contrary, a positive response was found when using T cells obtained from mucosal samples of both active (mean stimulation index 4.1 ± 1.5) and treated CD (mean stimulation index 3.8 ± 1.6) controls.

Conclusions: These data suggest that HSCT may lead to induction of gluten tolerance in CD by restoring the tolerogenic immune response to gliadin.

The other side of the coin in refractory inflammatory bowel disease: the role of herpesviridae

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Background: Refractory inflammatory bowel disease (IBD) may be defined as the persistence of acute symptomatic disease despite adequate steroid/immunosuppressive and/or biological therapy, or as chronically active disease requiring continuous treatment for symptoms relief. The reasons for the lack or loss of response to conventional therapy is still unknown. In parallel, there is a growing and early use of immunosuppressive and biological agents which, in turn, predispose the patients to opportunistic infections. Several studies have shown the role of Herpesviridae, mainly the Cytomegalovirus (CMV) and Epstein Barr virus (EBV), in the development of acute colitis in patients under immunosuppressive therapy for bone marrow or solid organ transplantation. Only scanty information is available on the risk of IBD patients to develop a reactivation of these viral opportunistic infections and their role in the progression of the disease. Quantitative polymerase chain reaction (PCR) has emerged as the most sensitive method for the diagnosis of CMV and EBV infection. An important advantage of applying this technique relies in the possibility to use all kind of biological samples with the only drawback of a high costs. This is why immunohistochemistry (IHC) has been preferred for detection of viral infections at intestinal level.

Aim: We aimed to investigate the prevalence of reactivation of CMV and EBV infections in IBD patients and its role in refractoriness to conventional therapies. In parallel, we also compared the diagnostic accuracy of both PCR and IHC.

Patients and Methods: We enrolled 38 IBD patients (23 males, mean age 44 ± 15 years), 21 suffering from ulcerative colitis (UC), 13 from Crohn's disease (CD) and 4 from indeterminate colitis (IC), undergoing colonoscopy as part of the diagnostic workup for disease relapse or follow-up. Among them, 17 patients (12 UC, 3 CD, 2 IC) were considered refractory because of the persistence of clinical, serological and endoscopic indexes of disease activity despite an adequate treatment. As controls (HC), 16 sex/age matched subjects undergoing lower endoscopy for irritable bowel disease or screening for polyps were recruited. For each patient and control, the viral load was assessed by quantitative PCR on both whole blood samples and multiple perendoscopic biopsies taken from each colonic segment. Results were normalized to 10^5 cells. IHC study on formalin-fixed, paraffin embedded mucosal specimens was performed by using monoclonal antibodies against pp65 and LMP1 for CMV and EBV detection, respectively.

Results: All refractory IBD patients showed a mucosal viral load $>10^3$copies/10^5 cells indicative of viral reactivation (2 cases had CMV, 9 had EBV, and 6 cases both viruses; mean EBV load: 34252, mean CMV load: 36820). By contrary, a low viral load was found in 13 out of 21 non-refractory IBD patients (4 cases had CMV, and 9 had EBV; mean CMV load: 122, mean EBV load: 259), and in 6 out of 16 HC (1 case had CMV, 5 had EBV; mean CMV load: 40, mean EBV load: 14). The viral load was significantly higher in refractory patients than in non-refractory IBD ($p < 0.01$ for both viruses) and HC ($p < 0.001$), while no statistically significant difference was found between non-refractory IBD patients and HC. Moreover, mucosal viral load in refractory patients showed a significantly higher value in macroscopically inflamed mucosa (mean CMV load: 41102, mean EBV load: 45379) than in apparently normal mucosa (mean CMV load: 1, mean EBV load: 152; $p = 0.011$ and 0.0001, respectively) and no statistically significant difference was found when the viral load in not-inflamed mucosa of refractory patients was compared to viral loads in HC. Remarkably, the analysis of viral load on blood samples showed a low sensibility (23 % for CMV, 45.7 % for CMV) with a high specificity (100 % for both). Finally, when comparing the results obtained by PCR assay with those obtained with IHC, we found a very low sensibility of the latter for CMV and EBV detection (33.3 % for both), as well as the lack of specificity for EBV (0 %), despite a high specificity for CMV (90.9 %).

Conclusions: Our data clearly show the close association of a high mucosal EBV and CMV viral load with refractory IBD. Moreover, the

strong link between a high viral load and inflamed areas suggests a possible role of these viruses in inducing tissue injury, thus explaining the lack of response to current therapies. Unfortunately, the analysis carried out on blood samples showed a very low sensibility, thus not allowing its use for both diagnosis and follow-up purposes. PCR assay on mucosal samples represents the most accurate tool for the diagnosis of reactivation of CMV and EBV opportunistic infections, since IHC did not show suitable accuracy. These infections should, therefore, be actively searched in refractory patients in order to optimize their therapeutic management. The non-refractory IBD patients who show a low mucosal viral load should undergo a more strict follow up whether under immunosuppressive or biological therapy.

Neuroendocrine cells are increased in the duodenal mucosa of patients with pre-malignant and malignant complications of coeliac disease

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Background and Aim: Within the diffuse endocrine system in the gut, serotonin-producing enterochromaffin (EC) cells and somatostatin-producing D cells are the prevalent neuroendocrine cell types. EC cell hyperplasia is associated with a number of immune-mediated gastrointestinal disorders, including active coeliac disease (CD). Here we studied neuroendocrine cells in complicated CD, by assessing through immunohistochemistry the expression of serotonin, somatostatin and chromogranin A (CgA) in the duodenal mucosa of CD patients affected by refractory CD (RCD), ulcerative jejunoileitis (UJI) and enteropathy-associated T cell lymphoma (EATL).
Materials and Methods: We enrolled 14 complicated CD patients (6 with RCD, 6 with UJI and 2 with EATL), 7 uncomplicated CD patients, before and after at least 12 months of gluten-free diet (GFD), and 10 control subjects. Perendoscopic duodenal biopsies embedded in paraffin were cut perpendicular to the mucosal surface. The expression of serotonin, somatostatin and CgA was assessed by immunohistochemistry and neuroendocrine cells were quantified as percentage of positive cells per 100 crypt cells.
Results: The median percentage of both serotonin-positive cells and CgA-positive cells in the duodenal mucosa of complicated CD patients (9.4 %, range 6.6–12.8; 13.6 %, range 9.3–20.0, respectively) was significantly ($p < 0.002$) increased in comparison to uncomplicated CD patients before GFD (7.0 %, range 6.2–7.8; 10.3 %, range 9.1–11.4, respectively) and after GFD (5.0 %, range 3.6–5.4; 7.3 %, range 6.4–10.0, respectively), and control subjects (4.8 %, range 3.5–6.7; 6.4 %, range 5.5–7.6, respectively). In uncomplicated CD patients, the number of duodenal serotonin-positive cells and CgA-positive cells before GFD was significantly ($p < 0.01$) higher than control subjects, and decreased significantly ($p < 0.01$) after GFD. No significant difference in the number of serotonin-positive cells and CgA-positive cells was found between uncomplicated CD patients after GFD and control subjects. Somatostatin expression was not significantly different among any of the groups studied.
Conclusions: We observed a significant increase of serotonin-positive cells and CgA-positive cells in the duodenal mucosa of complicated CD patients. Additional studies are needed to clarify the pathophysiological mechanisms underlying this finding.

Clinical characterization of patients with suspected non-coeliac gluten sensitivity

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Background and Aims: Recent studies support the existence of a new condition, named non-celiac gluten sensitivity (NCGS), manifesting with intestinal and/or extraintestinal symptoms that improve or disappear after gluten withdrawal, in subjects in whom coeliac disease (CD) has been ruled out on the basis of the negativity of serum anti-transglutaminase antibodies (TTG) or anti-endomysial antibodies (EMA) and/or demonstration of normal small bowel mucosa. Although the clinical value of NCGS is under debate, its prevalence in the general population is supposed to be many times higher than that of CD. However, no systematic research has been carried out so far, probably because of the difficulty of demonstrating NCGS in an objective way. We here prospectively evaluated a series of suspected NCGS patients.
Patients and Methods: Among the 890 patients referring to our gastroenterology outpatient in the last 12 months, we identified 53 suspected NCGS subjects (5.9 %; mean age 37 years, range 18–67) in whom CD was ruled out on the basis of negativity for serum IgA EMA and tTG (all the patients had normal serum total IgA levels) under gluten-containing diet. Suspected NCGS patients were asked to undergo further laboratory examination, including serum IgA and IgG antigliadin antibodies (AGA), serum total IgE, faecal calprotectin, lactose hydrogen breath test.
Results: All the 53 patients complained of at least one of the following symptoms: abdominal pain/discomfort ($n = 39$; 73 %), diarrhoea ($n = 30$; 57 %) and bloating ($n = 29$; 55 %). Thirty (57 %) experienced gluten/wheat-dependent symptoms for more than 1 year. Forty-six (87 %) were female, 16 (30 %) were lactose intolerant, 43 (26 %) had a history of atophy, 6 (11 %) showed raised serum IgE levels, 4 (8 %) had increased faecal calprotectin levels, and 5 (9 %) showed positivity for serum IgG AGA. Moreover, 18 (34 %) had undergone upper endoscopy, showing a histologically normal small bowel mucosa, and 8 (15 %) lower endoscopy, showing no endoscopic and histologic sign of inflammation.
Conclusions: The prevalence of suspected NCGS among the patients referring to our gastroenterology outpatient is about 6 %. Since only in a small number of patients with putative food-sensitivity is this confirmed by means of oral food challenge tests, we are now conducting a double-blind, placebo-controlled crossover gluten challenge trial with capsules containing gluten or placebo in order to identify those patients affected by true NCGS.

Esophageal motor disorders and gastroesophageal reflux disease are highly prevalent in lung transplanted patients

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Background and Aims: In lung transplanted patients a high prevalence of gastroesophageal reflux disease (GERD) was shown

(D'Ovidio F 2005). This condition is considered the main non-alloimmune cause of chronic reject, due to bronchiolitis obliterans syndrome (Castor 2010). On the contrary, few data are available on esophageal motility. The aim of this study was therefore to evaluate the prevalence of esophageal motility disorders, besides gastroesophageal reflux in a cohort of lung transplanted (LTx) patients.

Patients and Method: We enrolled twenty-nine consecutive LTx patients and 19 NERD patients with typical symptoms on PPI as a control group. All patients underwent symptom severity evaluation by VAL, stationary esophageal manometry (Polygram, MedTronic) and 24-h impedance-ph monitoring (Sleuth ZepHr, Sundhill Sc.) on therapy.

Results: As expected, twenty-four out of 29 patients were symptomatic for typical and/or atypical GERD symptoms. Compared to NERD patients, LTx patients showed a higher acid exposure of distal esophagus: upright 1.7 ± 3.2 versus 5 ± 8 % and supine 0.96 ± 3.2 vs. 4.8 ± 7.3 %, $P < 0.05$. The number of acid refluxes was significantly higher in LTx than in NERD (16.5 ± 12.7 vs. 10 ± 9.6); no significant difference was observed in the number of weakly acid refluxes (29.3 ± 34.4 vs. 46.6 ± 28.4, P = NS). Weakly acid refluxes showed a proximal extent more frequently in NERD patients than in LTx ones.

In LTx patients peristalsis was normal in 6 (22 %) patients, 7 (25 %) showed aspecific abnormalities, in 3 (6 %) ineffective esophageal motility was present; nutcracker esophagus was evident in 7 (25 %); diffuse esophageal spasm in 6 (22 %). Hypotonic LES (<10 mmHg) was evident in 7 % of subjects, hypertonic LES in 34 %. No significant difference in LES tone was found between the two groups.

Conclusion: In lung transplanted patients, GERD is highly prevalent and PPI treatment shows a low efficacy in the control of esophageal acid exposure. Both esophageal body peristalsis and LES tone alterations are frequent. Further studies are needed to analyze whether regional alterations of esophageal motility may be responsible for the intraluminal persistence of refluxate that could facilitate aspiration.

Dyspeptic symptoms are frequently erroneously related to lactose intolerance by patients

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Background and Aims: The relationship between ingestion of food and symptom onset is frequently incorrect on an anamnestic basis (1): it was previously shown that a patient's judgement of a causative role of lactose on actual symptoms is not accurate. It is common experience to find patients who believe many foods to be responsible for their symptoms, clearly on a pathophysiological grounds unrelated to intolerance.

The aim of this study was to evaluate the symptoms that lead patients to undergo a lactose breath test in order to verify which symptoms they believe to be caused by this condition.

Patients and Methods: A group of 268 consecutive patients (M/F = 64/204, mean age 36.16 ± 10.21, range) undergoing lactose breath test was enrolled. In all the patients, symptoms they considered secondary to lactose intake were recorded and graded by VAS. A hydrogen breath test was then performed as previously described (2). Lactose oral load was 20 g as 400 ml of semi-skimmed milk. The test was considered positive if the sum of breath hydrogen values at the fifth, sixth and seventh hour was higher than 15 ppm (2.3). Zung scale for anxiety and depression was administered to the patients before the test to a group of 124 patients (80 positive and 44 negative).

Results: In 172 (64 %) patients the lactose breath test was positive and in 96 (36 %) it was negative. In the group of negative patients, a significantly higher prevalence of dyspeptic symptoms was evident, such as satiety (49 vs. 30 %, $p < 0.001$), fullness (48 vs. 29 %, $p < 0.001$), nausea (60 vs. 20 % $p < 0.0001$), and reflux-related symptoms, such as heartburn (34 vs. 18 %, $p < 0.001$), regurgitation (36 vs. 18 %, $p < 0.001$); headache was also significantly more prevalent in negative than in positive patients (23 vs. 12 %, $p < 0.02$). In patients with anxiety and/or depression the severity of unrelated symptoms was higher than in patients without anxiety and/or depression (fullness 6.76 ± 1.62 vs. 0.45 ± 1.32 $p < 0.002$; regurgitation 7.35 ± 2.65 vs. 0.60 ± 1.48 $p < 0.0022$, heartburn 6.09 ± 2.19 vs. 0.46 ± 0.96 $p < 0.0041$, headache 6.57 ± 2.4 vs. 1.59 ± 1.75 $p < 0.0072$).

Conclusions: Patients erroneously consider dyspeptic and reflux-related symptoms secondary to lactose intolerance. Anxiety and/or depression increase the reported severity of symptoms. More information should be obtained in order to clarify the true pattern of clinical presentation of lactose intolerance.

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In coeliac disease the persistence of bone derangement after long-term gluten-free diet is associated with higher circulating osteoprotegerin level

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Background and Aims: Bone mass and mineral metabolism alterations are very frequent in coeliac disease (CD). These alterations improve after gluten-free diet (GFD), but rarely normalize. The mechanisms responsible for the persistence of these alterations, after the recovery of intestinal villi architecture, are still not completely clear.

It was recently shown that mucosal immunity activation causes the production of circulating factors which in turn stimulate osteoclastogenesis, through the RANKL/RANK/osteoprotegerin (OPG) pathway (Taranta A et al., J Bone Min Res 2004).

Therefore, the aim of this study was to evaluate the putative role of inflammatory, hormonal and lifestyle factors in the pathogenesis of the persisting bone derangement in a subgroup of CD patient on long-term GFD.

Patients and Methods: Fourteen asymptomatic CD female patients (mean age 35.7 ± 5.1 years, range 27–43) with a long history of GFD (mean 16.1 ± 7.3 years) were enrolled. Diagnosis was made in adult life and perimenopausal period was excluded. Lumbar and femoral BMD was measured by DEXXA. The presence of osteopenia and osteoporosis were classified according to WHO classification. BMI was calculated for all patients. Circulating serum calcium, phosphate, PTH, osteoprotegerin, RANKL, 1.25 OH vitamin D, 25 OH vitamin D, Il-1, IL-6, and TNF-alfa level were evaluated. Validated questionnaires evaluating sunlight exposure and physical exercise were administered.

Results: Six out of 14 patients showed a pathological reduction in bone density. In comparison with the subgroup of patients with normal BMD, patients with low bone mass showed a lower BMI

(19.9 ± 1.14 vs. 22.8 ± 2.95 kg/m^2, P < 0.05); no difference in age, age at diagnosis, duration of GFD, serum levels of the above mentioned cytokines and hormonal factors was found. On the contrary, a strong inverse correlation was found, considering the whole group, between OPG level and both T score and Z score at femoral level (r = −0.73 and r = −0.69 respectively). Finally, no difference was evident in physical activity and sunlight exposure score.

Conclusions: High levels of OPG indicate the subgroup of CD patients with a persistent reduction in bone mass, despite strict adherence to GFD and architectural villi reconstitution and could, therefore, be used as a biomarker for femoral BMD reduction after long term GFD. In these patients, the persistence of low BMD after long term GFD could be associated with peripheral signs of persistent inflammatory activity.

An unexplained and sudden watery diarrhea

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A 72 years old man was admitted at the Dept. of Internal Medicine with a history of 1 week watery diarrhea and abdominal pain, resistant to antibiotic therapy, and without fever. Physical findings were abdominal tenderness at the deep palpation of lower quadrants and reduced peristalsis. Vital parameters were: BP 110/80 mmHg, HR 91 bpm (arrhythmic). The blood tests showed: normal WBC (4300/μl), severe hypoalbuminemia (1.5 g/dl, normal range 3.4–5.0 g/dl) and 21 mm/h VES. Abdomen ultrasonography showed a high relaxation of the bowel loops and a low quantity of ascites. The previous antibiotic therapy (Sulfamethoxazole plus Trimethoprim) was stopped and therapeutic agents included albumin, rehydration, customized parental nutrition and absolute fast. Due to a suspicion of intestinal infectious disease, the following investigations were performed: viral sierology, Vidal-Wright test, coprocolture, parassitological examination of stool, E. Coli verotoxin stool search, C. difficile antigen search, Campylobacter jejuni search, fecal occult blood, fecal calprotectin, bloodcolture and urinecolture. Fecal occult blood and calprotectin were positive. However, the CT scan showed a "diffuse bowel wall thickening". Thereafter, patient underwent colonoscopy, brought up only to the sigma. This endoscopic exam depicted a "proctosigmoidite with severe ulcerative activity". The therapeutic choice was absolute fast, Methylprednisolone (80 mg/day), Mesalazine (800 mg × 4 times/day), Ciprofloxacin (250 mg twice/day), Metronidazole (500 × twice/day) and medicated enemas. Despite the therapy, the diarrhea persisted (4 bowel movements/day, Bristol 7) without abdominal pain. Blood samples were performed, with normal VES value, and lower value of emoglobin (from 11 to 8.9 g/d). In according to the score "Truelove and Witts" the clinical activity was mild-moderate. The patient underwent another CT scan showing a "meteoric distension of the transverse colon and sigmoid". For this reason, patient was transferred to the Surgical Dept., where he underwent total colectomy.

The histology showed "enlargement of the large intestine, with thinned wall, disappearance of the mucosal folds, and polypoid protrusions". The microscopic findings were a neutrophil, eosinophil and lymphocyte infiltration in the bowel wall. There were also erosive lesions, cryptic abscesses and glandular distortion. The histology confirmed the diagnosis of ulcerative pancolitis with intense activity phase, complicated by inflammatory polyps.

This case revealed a discrepancy between clinical findings and instrumental evidence. In fact, the radiological and histological finding confirmed the presence of extensive and severe disease and led to the choice towards surgery. This case, therefore, suggests the predominant role of endoscopic and radiological evaluation in the management of inflammatory bowel disease.

Effect of an extra-virgin olive oil enriched with probiotics or antioxidants on functional dyspepsia

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Background: While antioxidants and probiotics have been proposed for the treatment of functional dyspepsia, current data are still heterogeneous and studies are poorly designed. Interestingly, extra-virgin olive oil, a common ingredient of Mediterranean diet, has antioxidant properties.

Aim: of this study is to evaluate the effect of extra-virgin olive oil enriched with antioxidants or probiotics on functional dyspepsia.

Methods: This study has been designed as a "proof of concept". Extra-virgin olive oil enriched with antioxidants (Oo/Ao) or probiotics (Oo/Pr) was blindly added to the common diet of 8 subjects with functional dyspepsia as follows: Oo/Ao for 7 days, no oil for 7-days, Oo/Pr for 7 days, no oil for 7 days and finally extra virgin olive without any enrichment (Oo) for 7 days. Dyspeptic symptoms (nausea, vomiting, postprandial fullness, halitosis, belching, early satiety, postprandial gastric distension, pain/upper abdominal discomfort quadrants) were then evaluated in all patients with a validated questionnaire based on a visual analogue scale (VAS).

Results: A significant amelioration of nausea was observed in subjects receiving Oo/Pr compared to Oo (P < 0.05) or Oo/Ao (P 0.04). Moreover, adding Oo/Pr to the common diet resulted in a significant amelioration of the symptom "pain/discomfort in abdominal upper quadrants" compared to Oo (P < 0.01). Interestingly, Oo/Pr was more effective than Oo (P < 0.05) and Oo/Ao (P < 0.05) in relieving belching and also showed greater efficacy in alleviating "postprandial gastric distension" and "postprandial fullness" as compared to Oo (P < 0.001 for both symptoms) and Oo/Ao (P < 0.001 for gastric distension and P < 0.06 for fullness). For both symptoms no significant differences were observed between Oo/Ao and Oo. No significant differences in halitosis and vomiting were observed between baseline and post-treatment among different groups.

Discussion: A significant improvement of dyspeptic symptoms was observed in subjects receiving the antioxidant or probiotic enriched oil diet, with a greater effect observed for the latter. Larger studies are now needed to confirm these data.

Alpha-fetoprotein and liver disease: a gastric cancer!

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Clinical Presentation: On January 2011, a 57-year-old Italian man was admitted to the Clinical Medicine and Hepatology Unit of our Hospital for the finding of severe elevation of alpha-fetoprotein (AFP) during blood tests performed for monitoring of chronic HBV-related disease.

Chronic HBV-related hepatitis had been diagnosed in 1992 and the patient was following periodic outpatient visits at another Hospital without any specific medical treatment. In the blood tests performed in the last months, a progressive rise of AFP (until 1156 ng/ml), in the absence of parallel increase in liver enzymes and of focal liver lesions by ultrasound, had been noticed.

At the admission to our hospital, laboratory tests showed only mild thrombocytopenia without anemia (hemoglobin 15.4 g/dL, platelets 120.000/μL) and normal hepatic function tests with only a mild elevation of alanine aminotransferase (ALT 49 U/L-upper normal limit 35 U/L-), while other parameters were within the normal range. Ultrasonography and magnetic resonance of the upper abdomen with hepatospecific contrast medium were performed. Liver morphology was suspect for advanced fibrosis (irregular liver edges, enlargement of caudate and left lobes), with mild splenomegaly, while only a small nodule (7 mm) was detected, not characterizable due to the restricted dimensions. Testicular ultrasonography was negative.

Diagnostic Hypotesis: Chronic HBV-related hepatopathy in suspect cirrhotic-evolution. AFP elevation of uncertain etiology, deserving further investigations and/or strict follow-up.

Diagnostic deepening, diagnosis and decision-making: To complete the evaluation of chronic liver disease in suspect cirrhotic evolution, an upper intestinal endoscopy was performed. No signs of portal hypertension were found but the exam revealed an ulcerated lesion at the gastric angulus, whose histology was diagnostic for gastric hepatoid adenocarcinoma, AFP-positive by immunohistochemistry. Total-body CT scan was negative for other organ involvement.

The patient underwent a subtotal gastrectomy with Roux-en Y reconstruction and, during surgery, he received liver biopsy, which disclosed advanced fibrosis (F1 fibrosis according to Ishak's staging). Only two lymphonodal metastases were found. After surgery, prophylactic therapy with entecavir was started and, at the moment, the patient is on adjuvant chemotherapy. After 1 month, AFP reached normal level.

Beyond hepatocellular carcinoma, gastric cancer is one of the most common among cancers potentially associated with increased AFP-levels, which can be observed in 1.3–15 % of all cases. The present case highlights the confounding clinical picture of AFP-producing gastric cancer, further complicated by the background of HBV-related liver disease. The message that can be derived is that the stomach is one of the organ which should be investigated when facing elevated AFP levels of unknown etiology, even in patients with chronic liver disease.

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Stauffer's syndrome: a case report

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Introduction: Neoplasia often causes cholestasis and hepatic disfunction due to widespread hepatic metastatic infiltration or mechanical bile duct obstruction. Occasionally, cholestasis may be the expression of a paraneoplastic syndrome, which may represents the first manifestation of the underlying disease.

Case Report: A 52 year-old Italian man was admitted to the Department of Internal Medicine with a 2-weeks history of jaundice, urine hyperpigmentation and fatigue. Before this period, the patient reported an episode of fever (39 °C) and diarrhea. Nothing significant referred in past medical history. He denied alcohol, tobacco or drug abuse while he reported the assumption of antioxidants (alpha-tocopherol) since a month.

At the admission the patient was no febrile. The clinical examination revealed mild hepatomegaly in absence of ascites without other pathological findings. The patient received a detoxifying treatment with glutathione and 0.9 % saline. Laboratory data at the admission revealed biochemical liver abnormalities including serum bilirubin, aminotransferases, alkaline phosphatise, γ-glutamyltransferase. Serological tests for major (HAV, HBV HCV, HEV) and minor (CMV, EBV, HSV) viral hepatitis were negative. Also the immunological assays (ANA, ENA profile, ASMA, AMA, p-ANCA, c-ANCA) were negative. Immunoglobulin concentration and thyroid function were normal. Upper abdominal ultrasound revealed a mild hepatomegaly without evidence of focal lesions or intrahepatic or extrahepatic dilatation of the biliary tree; furthermore it showed an exophytic mass arising from the superior pole of the left kidney. Therefore, it became necessary additional investigations to define the etiology of the liver disease and the renal mass. So, we performed an abdominal Computed Tomographic scan which revealed a nodular and patchy mass located on the left kidney containing calcifications and areas of enhancement after administration of intravenous contrast.

The liver biopsy showed a clear cell renal cell carcinoma. The patient's clinical condition was stable, his laboratory values decreased gradually, even without *restitution ad integrum,* and he was discharged home waiting to perform nephrectomy.

Conclusions: Renal cell carcinoma is labeled as "internist's tumour" because of the variety of clinical manifestation. Less than 10 % of patients occur with the "classic triad" characterized by hematuria, abdominal pain and a palpable mass while in more than 20 % of patient it occurs with a paraneoplastic syndrome that may delay the diagnosis. In 1961, Stauffer first describes a syndrome characterized by non metastatic intrahepatic cholestasis associated with renal cell carcinoma whose pathogenesis is not well known. Probably it's attributed to the production of interleukin-6.

Telmisartan/hydrochlorothiazide-induced hepatotoxicity: a case report

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Drug-induced liver injury (DILI) is a relatively unfrequent form of adverse drug reaction, its incidence being between 1:1000 and

1:100000; however, it accounts for approximately 10 % of all cases of acute hepatitis, is the leading cause of acute liver failure, mainly due to acetaminophen overdose, and is the main reason of approved drug withdrawal from the market. It is rarely predictable, in the majority of cases resulting from an idiosyncratic reaction, and some risk factors have been recognized (alcohol, diabetes, advanced age and female sex). Herein we describe a patient who developed DILI while taking telmisartan-hydrochlorotiazide.

A 72-year-old woman was referred to our department with a seven-day history of weakness, anorexia, nausea, progressive jaundice, dark-coloured urine and pruritus. The patient had a past medical history of arterial hypertension, and had been taking zanedipine for about 5 years; 4 weeks before admission she was prescribed telmisartan/hydrochlorothiazide because of uncontrolled blood pressure values. She denied blood transfusion, recent surgery, alcohol abuse and relevant family history. Physical examination showed a 2 cm hepatomegaly, other than jaundice. Laboratory testing on admission showed total serum bilirubin to be 15.6 mg/dl (range 0–1), direct bilirubin 14.8 mg/dl, aspartate and alanine (ALT) transaminases 33 IU/L and 87 IU/L, respectively (range 0–32), alkaline phosphatase (AP) 183 IU/L (range 35–105), gamma-glutamyl transpeptidase 552 IU/L (range 5–36); complete blood count, serum albumin level and coagulation profile, serum iron and ferritin, amylase, copper and ceruloplasmine were normal. Anti-nuclear, anti-smooth muscle, anti-mitochondrial and anti-liver/kidney microsome antibodies as well as viral serologic markers (anti-HAV IgM, HBsAg, anti-HBc IgM, anti-HCV and HCV-RNA, anti-CMV and anti-EBV IgM and IgG) were all negative. An upper abdominal ultrasound and computerized tomography revealed a scleroathrophic gallbladder with normal liver structure and intrahepatic bile ducts. A percutaneous liver biopsy was performed 8 days after admission; liver histopathology showed a mild mononuclear inflammatory infiltrates in portal tracts without hepatocyte necrosis. DILI was suspected and telmisartan/hydrochlorothiazide was stopped 7 days after admission. Serum bilirubin remained substantially unchanged for the first 10 days after discontinuation, thereafter gradually began to decrease. Direct bilirubin at discharge (20 days after admission) was 10.3 mg/dl and returned to normal levels within the next 15 days.

This patient was diagnosed with DILI on the basis of 1990 Consensus Meeting criteria (Benichou 1990): the time to onset of jaundice from the beginning of drugs (25 days) was suggestive, the patient was female and more than 55 years old, alternative causes have been ruled out and the course of the reaction was highly suggestive (although rechallenge has not been performed). Acute DILI can have different pattern of expression: hepatocellular, which mainly affects parenchymal cells; cholestatic, mainly affecting canalicular and/or ductular cells; and mixed cytotoxic/cholestatic. Our case fulfil the diagnostic criteria of cholestatic DILI: although serum AP activity was not significantly increased, the ratio between serum ALT and serum AP activities was below 2. The patient didn't reported fever, chills, abdominal pain and liver histology showed only a minimal inflammatory portal infiltrates: we can therefore more properly define the picture of our patient as pure cholestasis (in contrast to the more common form of acute cholestatic hepatitis), which can be seen mainly with hormones (estrogens, oral contraceptives) and probably arises from the inhibition of BSEP (bile salt excretory protein). The treatment with angiotensin receptor blockers (ARB), such as valsartan and candesartan, has already been linked to DILI, but in the literature there are no published report of telmisartan-induced DILI. Despite the rarity of ARB-induced DILI, patients with known risk factors (alcohol, diabetes, advanced age, female sex) deserve attention and should be monitored.

High NT-pro-BNP levels are associated with cardiac structural changes in patients with advanced liver disease

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Background and Aims: NT-pro-BNP is a pro-hormone secreted by the left atrium in presence of fluid retention. Our purpose was to evaluate NT-pro-BNP levels in patients with liver cirrhosis and to determine its potential correlation with cardiac structural changes or dysfunction.

Methods: between April 2010 and October 2011 we consecutively studied 58 patients hospitalized for liver cirrhosis of different etiologies. All patients underwent to clinical examination, abdominal ultrasound and GI endoscopy An echocardiographic assessment evaluation was performed to evaluate cardiac morpho-functional changes. NT-pro-BNP levels were determined by available commercial kit. Further, as controls, we included 23 non cirrhotic patient. All data are shown as mean ± SD or percentages. Non parametric tests were used for comparison among groups.

Results: In patients with liver cirrhosis (mean age 63 ± 11; M 72 %; viral etiology 70 %). Child-Pugh class was: A in 24 (41.3 %), B in 23 (39.6 %), C in 11 (18.9 %). Ascites was present in 32 cases (55.1 %). Median plasma creatinin level was: 0.87 mg/dl. NT-pro-BNP levels were higher in ascitic cirrhotic patients than non ascitic (414 vs. 125.5 pg/ml respectively) and controls (42 pg/ml).

Cardiac function was assessed in all patients by echocardiography. In cirrhotic patients, left ventricular ejection fraction was 62.7 ± 6.9 % as compared to controls 65.8 ± 4.2; left atrial volume (LAV) was 61.84 ± 26.3 ml as compared to controls 42.99 ± 15 ml. Left ventricular end diastolic volume (LVEDV) was higher in cirrhotic patients 90.39 ± 33.3 than in controls 78.9 ± 29.2 ml. Systolic Pulmonary Arterial Pressure (PAPs) was 30.4 ± 4.96 mmHg in cirrhotic and 28.1 ± 1.72 mmHg in controls. By analysis, we found that NT-pro-BNP was significantly higher in cirrhotic ascitic patients rather than cirrhotic non ascitic and controls ($p = 0.0001$). In addition, LAV ($p = 0.0016$), LVEDV ($p = 0.0159$), and PAPs values ($p = 0.0364$), were significantly related with NT pro BNP levels. By multivariate analysis atrial volumes, liver cirrhosis and ascites, resulted independently associated with NT-pro-BNP values ($p = 0.0001$).

Conclusion: We show that high serum levels of NT-pro-BNP have been found in ascitic cirrhotic patients. High NT-pro-BNP levels associated with increased LAV, LVEDV and PAPs values seems to be the cardiac structural changes which characterize advanced liver disease.

Pattern of drug-induced liver injury: the impact of non steroidal anti-inflammatory drugs (NSAIDs)

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Background and Aim: Drug-induced liver injury (DILI) is increasingly being recognized as a cause of clinically significant liver

disease. We aimed to evaluate the rate of severe cases of DILI on total hospital admissions and to identify drugs most commonly responsible of severe clinical course.
Methods: Between 1996 and 2011, all records of consecutive patients diagnosed as DILI seen at our tertiary referral centre were analyzed. Data were collected from in- and outpatient visit charts. Diagnosis of DILI was made when at least three of the International Consensus Criteria (J Hepatol 1990) were present. Liver damage was defined as hepatocellular, cholestatic or mixed, according to clinical and laboratory data. Liver stiffness measurement was carried out by transient elastography (Fibroscan®). All patients had regular follow-up visits every three months for at least 1 year, and were contacted to update their clinical outcomes.
Results: Out of 10,270 patients, 157 (73 males, 46 %), with a medium age of 54 years (ranging from 11 to 88) fulfilled the diagnostic criteria of DILI. One hundred and ten (70.1 %) patients were older than 40 years. Twenty nine patients (25 %) had pre-existing compensated chronic liver disease (CLD). Hepatocellular pattern was more commonly observed (53 %) followed by cholestatic (27 %) and mixed pattern (20 %). The most frequent drugs were non-steroidal anti-inflammatory drugs (NSAIDs; 33.3 %), followed by antibiotics (19.7 %), anti-diabetic drugs (13.4 %), anti-platelet agents (9.6 %) statins (9.3 %) immunosuppressant (6.7 %) followed by psychotropic drugs and herbal products. In 38 (24 %) of cases, two or more drugs were involved. Among NSAIDs, nimesulide was most frequently involved (43 %). NSAIDs were more frequently associated with hepatocellular pattern ($P = 0.006$) and signs of hepatic encephalopathy at presentation ($p = 0.02$). Patients with DILI from NSAIDs were on average younger (48.1 vs. 55.1 years, $p = 0.02$) and the duration of drug intake was lower ($p < 0.001$) as well as the average latency ($p = 0.02$). ALT values ($p = 0.02$) and eosinophil count ($p = 0.02$) were found to be higher in NSAIDs-induced liver damage compared to other drugs ($p = 0.007$). NSAIDs were involved in six cases of acute liver failure and one died while on the waiting list for OLT. The overall clinical pattern of DILI in CLD was no more severe than in other non CLD cases and none decompensated.
Conclusions: Acute liver disease induced by NSAIDs represents an important cause of hospitalization. NSAIDs are the drug class most common among patients younger than 50 years, being responsible of early and severe liver injury.

IL28-B polymorphisms of are associated with a milder histological stage at onset in primary biliary cirrhosis

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Background and Aims: Primary biliary cirrhosis (PBC) is a chronic inflammatory autoimmune liver disease that mainly targets the cholangiocytes of the interlobular bile ducts. Recent evidences showed that rs12979860 CC and rs8099917 TT genotypes of the gene coding for IL28B strongly predict spontaneous clearance of HCV infection and sustained virologic response after antiviral therapy in patients with chronic hepatitis C. Currently, there are no data regarding a potential association between IL28B polymorphisms and clinical course of PBC. We analysed the impact of IL28B polymorphisms on clinical features and natural history in a prospective cohort of PBC patients.
Patients and Methods: We collected socio-demographic, clinical, biochemical, immunological and histological data at onset, and incidence of disease progression (signs of portal hypertension at ultrasound, oesophageal varices, jaundice, ascites, hepatic encephalopathy) in a prospective cohort of 32 PBC patients. All subjects were treated with ursodeoxycholic acid at a dose of 15–25 mg/kg. IL28B genotyping for IL28B rs12979860 and rs8099917 was carried out using the TaqMan SNP genotyping allelic discrimination method (Applied Biosystems, Foster City, CA, USA).
Results: Mean age at diagnosis was 53.0 ± 12.0 years (range 32–82). All patients were female and AMA positive, and half of them was asymptomatic at disease onset. Histological findings showed an early stage disease (I-II Scheuer) in 24/32 (75.0 %). IL28B polymorphisms frequency was distributed as follows: rs12979860 CC 16 (50.0 %), CT 10 (31.3 %), TT 6 (18.7 %); rs8099917 TT 18 (56.3 %), GT 12 (37.5 %), GG 2 (6.2 %). In comparison to non-CC rs12979860 and non-TT rs8099917 groups, patients with CC genotype showed an early histological stage at onset (93.8 vs. 62.5 %, $p = 0.03$). During follow-up (mean 49 months), seven patients (21.9 %) had a disease progression without differences between patients with different IL28B genotypes.
Conclusions: In our cohort of PBC patients, the prevalence of rs12979860 CC genotype of IL28B gene was higher incidence than in matched population and was associated with a milder histological stage at onset. No polymorphism seemed to influence the clinical course of the disease.

The impact of diet on immune response in patients with HCV-related chronic hepatitis and with NAFLD

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Background and Aims: Hepatitis C virus (HCV) infection is one of the leading causes of severe liver diseases; interestingly, HCV life cycle is correlated to the host cholesterol metabolism regulating fatty acid synthesis. On the other hand, NAFLD (non-alcoholic fatty liver disease) represents another common cause of persistent liver disease leading to inflammation and fibrosis. The progression of both pathologies depends on liver metabolism. There is increasing evidence on LXRs (Liver X Receptors) as key regulators of hepatic lipogenesis and inflammation in NAFLD and HCV patients. It has also been reported that LXRs are expressed in CD4+ T cells, implying LXR-mediated regulation of Th17 cell differentiation and autoimmunity. Th17 cells, a subset of CD4+ T cells characterized by the secretion of high levels of IL-17, play an important role in both the immune response to invading pathogens and autoimmunity.
Thus LXRs, cholesterol sensors and metabolic checkpoints during inflammatory T cell differentiation, link cellular cholesterol levels to Th17 cell differentiation. Conversely, Th17 cells play an important role in several liver disease progression, including alcoholic liver disease, chronic hepatitis C and B, autoimmune liver disease and hepatocellular carcinoma. So far cholesterol may act as metabolic negative signal to restrain T cell differentiation into the Th17 subset. The aim of this study was to evaluate whether cholesterol diet composition may affect the inflammatory status in patients with HCV as compared to NAFLD.
Methods: We enrolled 10 non-diabetic patients with a clinical diagnosis of either NAFLD or chronic HCV infection and 10 age- and gender-matched healthy volunteers (HV). At the time of enrollment we collected and measured: dietary habits; routine liver tests; HCV genotyping; Body Mass Index (BMI), and plasma levels of blood glucose, cholesterol, and triglycerides. The subjects were administered with a cholesterol-lowering and hypo- or normo-caloric diet (depending on the BMI of patients) for 1 month. On day 0 and day 30,

peripheral blood mononuclear cells (PBMCs) were isolated from patients and HV, and circulating Th17 cells were monitored by flowcytometry on a FACSCanto. Real-time PCR and Western blot analysis were performed to determine hepatic expression levels of LXRs and related lipogenic and inflammatory mediators. Plasma levels of oxysterols were determined by isotope dilution gas chromatography/mass spectrometry.

Results: We found a significantly increased percentage of IL-17-positive CD4 T cells in PBMCs obtained from our cohort of patients studied compared to healthy individuals (HCV and NAFLD patients *vs* HV: 3.15 ± 1.27 and 4.23 ± 1.36 vs. 1.99 ± 0.93 %, $P < 0.001$). After cholesterol-lowering diet for 30 days, we observed a substantial suppression in the percentage of Th17 cells in PBMCs obtained from patients with chronic HCV infection (1.07 ± 0.23 %), whereas no changes were observed in NAFLD and HV (4.59 ± 1.08 vs. 1.95 ± 0.94 %). In addition, circulating Th17 cell frequency was inversely correlated with the expression of certain genes involved in cholesterol and fatty acid metabolism, such as LXRs, ABCA1, SREBP1c, from HCV patients after diet.

Conclusions: Our preliminary data on HCV patients treated with a cholesterol-lowering diet support the role of LXRs as regulators of Th17 cells in mediating autoimmunity and inflammation. These results suggest a rationale for the control of HCV immunopathogenic progression through the administration of a hypo-cholesterol diet.

Complicated coeliac disease: prevalence among coeliac patients

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Background: Coeliac disease (CD) is a chronic enteropathy characterized by an increased mortality caused by its complications, i.e. refractory CD and small bowel lymphoma. Although the prevalence of CD is known to be around 1/160, the prevalence of its complications is still unknown. This is due to the fact that patients with complicated CD are sent to referral centres and this inevitably causes a major selection bias.

Aims: To by-pass this selection bias by calculating the prevalence of complications developed in those coeliac patients directly diagnosed in each centre.

Patients and Methods: Thanks to Fondazione Associazione Italiana Celiachia, we calculated the prevalence of complicated CD among coeliac patients directly diagnosed in our centres. So, patients referred to our centres after been found to be affected by CD and/or complicated CD in other hospitals were excluded.

Results: Between Sept 1999 and Oct 2011, 15 (12 F, mean age 56 ± 14 years) out of 2228 coeliac patients developed complications (overall prevalence, 0.67 %): 6 refractory CD type I, 2 refractory CD type II, 2 ulcerative jejunal-ileitis, 3 small bowel adenocarcinomas, 1 B-lymphomas, 1 enteropathy-associated T cell lymphoma. Gluten-free diet adherence was considered to be rigorous in 12 out of 15 patients. In 13 cases the onset of complications rapidly followed the diagnosis of CD (3 ± 3 years) and in the remaining 2 cases the two diagnoses were almost at the same time. Six patients died, two of them for reasons not related to CCD.

Conclusions: Although these date are very preliminary and rough, they confirm that complications of CD are very serious conditions with a high mortality (33.3 %). They are, however, quite rare.

Modulation of P53 signaling by SERPINB3 under genotoxic stress

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SERPINB3 is a serine protease inhibitor able to inhibit apoptotic cell death and to induce epithelial to mesenchymal transition and cell proliferation. This serpin is not detectable in normal liver, but its expression increases during liver injury, with progressively higher levels in advanced liver disease and hepatocarcinoma. P53 is one of the master regulators of apoptosis under genotoxic stress and it can act directly or through its transcriptional target genes. This molecule is considered a key player in carcinogenesis, since it is inactivated in more than 50 % of tumors. In hepatocellular carcinoma caused by HBV and Aflotoxin B1 p53 is inactivated mainly by genomic mutation, but in the majority of caucasian patients with hepatocellular carcinoma the mechanisms of p53 inactivation is largely unknown.

The aim of this study was to verify the effect of SERPINB3 on p53 and its signaling pathways after Cisplatin treatment, used as genotoxic stress condition.

HepG2 cells, stably transfected with the human SERPINB3 gene (HepG2/SerpinB3) or with the plasmid vector alone (HepG2) were treated initially with Cisplatin at various concentrations (range 25–100 μM) to set up optimal experimental conditions. Cell viability was analyzed by MTT assay. The concentration of 25 μM Cisplatin was used for subsequent experiments. The expression of p53 and their target genes Bax and Noxa were analyzed at baseline and after Cisplatin treatment by Real-time PCR and protein expression, including Western blot and immunofluorescence.

HepG2/SerpinB3 cells were more resistant to Cisplatin induced apoptosis than control HepG2 cells ($p < 0.001$). Transcription and protein levels of p53 and of Bax were similar at baseline in HepG2/SerpinB3 and in control cells, while their expression was significantly lower in HepG2/SerpinB3 after Cisplatin treatment. Levels of Noxa were significantly lower both at baseline and after treatment in SERPINB3 expressing cells.

In conclusion, p53 and its signaling pathways are downregulated by SERPINB3 after Cisplatin treatment. These findings might contribute to the increased resistance to apoptotic cell death and to the higher risk of neoplastic transformation induced by this serpin.

The black esophagus

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The patient, male, 75 years old was admitted to our Internal Medicine Department for hematemesis, melena and abdominal pain started the day before the admission. He was alert, cooperative and well oriented despite he was deeply asthenic. Vital signs showed low blood pressure (BP) = 90/60 mmHg, heart rate (HR) = 90 bpm (rhythmic) and

body temperature was normal. Clinical visit demonstrated epigastric pain and dark stools were found on digital rectal examination. From the laboratory point of view a mild macrocytic anemia (hemoglobin = 11.8 g/dl) and a neutrophilic leukocytosis (15.350/ul) were found. Prothrombin time and International Normalized Ratio (PT-INR) was slightly elevated (1.53). In history: alcohol related chronic liver disease, an episode of pancreatitis over a year before admission, gallstones that underwent cholecystectomy several years before and hiatal hernia. No home therapy was taken by the patient who reported abstaining for home drinking alcohol for several months. Suddenly, few hours after admission, the patient experienced profuse hematemesis and melena complicated by hemodynamic shock (80/50 mmHg). Repeated laboratory analysis documented severe hemoglobin loss (Hg = 8.9 g/dl). Emergency treatment included intra venous (i.v.) colloid infusion (500 cc), omeprazole continuous i.v. infusion, i.v. terlipressin suspecting a bleeding from the upper gastrointestinal tract or from esophageal varices. Subsequently, the patient underwent endoscopy which demonstrated the presence of dark material growing adherent to the mucosa, starting from the upper third of the organ until the lower one. Partial removal of this material showed some areas of epithelial denudation. These areas, at the lower third, took the characteristics of an ulcer covering the entire circumference of the organ and in the contest of which stood a large exposed vessel. Stomach and duodenum appeared normal. No bioptic samples were collected due to the high hemorrhagic risk of procedures. Clinical and strumental findings suggested the diagnosis of "Black Esophagus". To date, no guidelines about the "black esophagus" management were available. Thus, according to previous literature reports, it was continued omeprazole i.v. infusion and it was introduced parenteral nutrition, wide-spectrum antibiotic coverage and antifibrinolytic therapy. After 7 days the patient repeated endoscopy that showed the presence of fibrous membranes covering the mucosa and, at the level of the lower third, the organ gradually reduced in size, until it formed a stricture. Oral feeding was restored on day 17 without the patient complained dysphagia and he was discharged on day 25.

Pseudo Budd Chiari Syndrome in decompensated liver disease

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Clinical Presentation: A 45 year old woman was admitted to our hospital due a 1 month history of abdominal pain, increase of the abdominal girth, lower limb oedema and fatigue. Her medical history was negative for major surgeries, hemotransfusions and intravenous drug abuse. She had assumed oral contraceptives during a short period about 20 years before and she denied spontaneous abortions. Notably, she acknowledged severe alcohol abuse in the last 10 years. On physical examination, jaundice, hepatosplenomegaly, ascites and lower limb oedema were noticed. Spider naevi on the chest were also observed. A diagnostic paracenthesis was performed and ascitic fluid examination was negative for spontaneous bacterial peritonitis. Abdominal ultrasound revealed hepatomegaly, enlarged caudate lobe and irregolar liver edges. The right hepatic vein was not detectable, while the left and middle ones showed monophasic low-velocity flow. MRI examination with contrast medium confirmed enlarged left and caudate lobes, with patchy enhancement of liver parenchyma in the arterial phase, and showed apparent absence of hepatic vein filling, suggesting a possible Budd-Chiari Syndrome (BCS).
Diagnostic Hypotesis: Budd Chiari syndrome in an alcoholic patient.
Diagnostic Deepening: Tests aimed to detect a possible hypercoagulable state were required and found to be normal, except for protein C deficiency and MTHFR C667T polymorphism in heterozygosis. A transjugular catheterism was carried out in order to perform a hepatic venography, to measure the hepatic pressure venous gradient and to obtain a liver biopsy. All the three hepatic veins were found to be patent, hepatic pressure venous gradient was 20 mmHg, diagnostic for severe portal hypertension, and liver histology revealed micronodular cirrhosis without pericentral congestion or other histological signs of hepatic outflow obstruction.
Diagnosis: Pseudo Budd-Chiari Syndrome in decompensated alcoholic cirrhosis.
Decision-Making: In literature, there are only few cases of pseudo Budd-Chiari Syndrome and all of these concerned patients with a mechanical compression of the hepatic vein blood flow due to anatomic abnormalities caused by enlarged cirrhotic liver. With the exception of one case, all patients had alcohol-related liver disease. Some of the described patients had a relatively good clinical evolution after alcohol withdrawal, while other patients had fatal outcomes because of severe hepatic damage related to advanced liver disease. Decompensated alcoholic cirrhosis can mime BCS. When presenting with imaging suggestive of BCS, patients with history of alcohol abuse, or with already diagnosed alcohol-related liver disease, should be properly investigated since management is very different in these two conditions.

The hydropinotherapy in some diseases of the biliary tract: preliminary results of a study on the efficacy of the therapy with a sulphate-bicarbonate mineral water

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Background: Disturbances and diseases of biliary tract are increasing in prevalence and incidence. The cholelithiasis is a worldwide disease, affecting about 10 % of people, mainly in Europe and North America. We can find clinic conditions, characteristic of a prelithiasic state, as biliary dyskinesias, mainly gallbladder's hypokinesia and functional sphincter of Oddi disorder, biliary sand, or following a cholecystectomy (post-cholecystectomy syndromes); so it is necessary to evaluate the efficacy of the therapies for these affections.
Aim: We want to do a study on the effects of hydropinotherapy with a sulphate-bicarbonate-calcium-magnesium mineral water (Acqua Santa at Italy's Chianciano Spa) in patients suffering from pain and other symptoms caused by those affections.
Methods: We enrolled 53 patients suffering from gallbladder's hypokinesia, epigastric and/or right upper quadrant pain, biliary sand (without gallstones) and previous cholecystectomy within 24 months from the beginning study, and divided the patients in two groups: the first (experimental group) did two cycles in 1 year of hydropinotherapy with Acqua Santa at Chianciano Spa, drinking 400 mL of

mineral water in the morning every day during 12 days for every cycle; the other patients (control group) followed the current pharmacological or symptomatic therapy. All patients did at every step of the study blood samples and ultrasound scan of biliary tract. At the end of the second cycle we compared the frequency of eleven main symptoms (epigastric or right upper quadrant pain, digestive troubles, biliary colic, meteorism, constipation, etc.) in both groups (experimental study) and we also performed an observational-longitudinal study in the first group on the frequency of those symptoms before the beginning of the first cycle of the therapy (T0) and at the end of the second cycle (T1).

Results: The number of the symptoms observed in all the patients was divided for the total of symptoms that would be observed if the symptoms were present in all the patients (11 symptoms × 53 patients = 583) with the following results: in the first group 45 symptoms were observed on a total of 253 (17.7 %), in the control group 120 symptoms on a total of 330 (36.4 %) (Table 1). The differences between the groups are significant at Chi-square test with a value of 23.45—P = 0.000. Furthermore the comparison in the first groups between the frequency of the symptoms observed at the start and at the end of therapy gave these results: 106 symptoms of 253 (41.89 %) at start and 45 (17.78 %) at the end; the difference was significant with the z value for the comparison between proportions (z = 5.83—P = 0.000) (Table 2).

Conclusions: The preliminary results of our research regarding the hydropinotherapy by sulphate-bicarbonate-calcium-magnesium mineral water shows a significant improvement of symptoms in patients suffering from disturbances of biliary tract, both in prelithiasis syndromes and in post-cholecystectomized patients.

Table 1 Frequency of the symptoms observed in two groups of patients

Groups of patients	Number of symptoms observed	Number of symptoms not observed	Total (1)
Experimental group (2)	45 (17.7 %)	208 (82.3 %)	253
Control group	120 (36.4 %)	210 (63.6 %)	330

(1) It is the number of symptoms if all the symptoms would be if all the symptoms would be observed in all the patients

(2) At the end of the second cycle of therapy

Table 2 Frequency of the symptoms observed in the experimental group

Time of observation	Number of symptoms observed	Number of symptoms not observed	Total (1)
T0 (2)	106 (41.89 %)	147 (58.11 %)	253
T1 (3)	45 (17.78 %)	208 (82.22 %)	253

(1) It is the number of symptoms if all the symptoms would be observed in all the patients

(2) Before the beginning of therapy

(3) At the end of the second cycle of therapy

Propionyl-L-carnitine hydrochloride in treatment of mild to moderate colonic inflammatory bowel diseases

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Aim: To assess clinical and endoscopic response to Propionyl-L-carnitine hydrochloride (PLC) in colonic inflammatory bowel disease (IBD) patients.

Methods: Patients suffering from mild to moderate ulcerative colitis (UC) or Crohn's disease (CD) colitis, with disease activity index (DAI) between 3 and 10 and under stable therapy with oral aminosalicylates, mercaptopurine or azathioprine, for at least 8 week prior to baseline assessments, were considered suitable for the enrollment. Fourteen patients were enrolled to assume PLC 2 g/day (two active tablets twice a day) orally. Clinical-endoscopic and histological activity were assessed by DAI and Histological Index (HI), respectively, following a colonoscopy performed immediately before and after a 4 week treatment. Clinical response was defined as a lowering of at least 3 points in DAI and clinical remission as a DAI score ≤ 2. Histological response was defined as an improvement of HI of at least 1 point. We used median values for the analysis. Differences Pre-Post treatment were analyzed by Wilcoxon Sign Rank test.

Results: All patients enrolled completed the study. Only one patient, despite medical prescription, assumed deflazacort 5 days before the control colonoscopy. No side effects were reported by patients during the trial. After treatment, 71 % (SE 12 %) of patients achieved clinical response, while 64 % (SE 13 %) of patients obtained remission.

Separating UC patients from CD patients, we observed a clinical response after therapy in 60 % (SE 16 %) and 100 % of UC and CD patients, respectively; furthermore 60 % (SE 16 %) of UC patients and 75 % (SE 25 %) of CD patients were in clinical remission after therapy. The median DAI was 7 (IQR: 4–8) before treatment and decreased to 2 (IQR: 1–3) ($P < 0.01$) after treatment. Stratifying by disease, only patients with UC showed a significant reduction of DAI, from a median value of 6.5 (IQR: 4–9) before treatment to a median DAI after treatment of 2 (IQR: 1–3) ($P < 0.01$). Conversely, in CD patients, although displaying a clear reduction of DAI from 7 (IQR: 5.5–7.5) before therapy to 1.5 (IQR: 0.5–2.5) after therapy, differences observed were not statistically significant ($P = 0.06$). Comprehensively, 79 % (SE 11 %) of patients showed an improvement of the HI of at least 1 point, while only one CD patient and two UC patients showed HI stability; nobody showed HI worsening. Median HI decreased from 1 (IQR: 1–2), to 0.5 (IQR: 0–1) at the endoscopic control in the whole population ($P < 0.01$), while it changed from 1 (IQR: 1–2) to 0.5 (IQR: 0–1) in UC patients ($P < 0.01$) and from 1.5 (IQR: 1–2) to 0.5 (IQR: 0–1) in CD patients (P = ns). The two sample tests of proportions showed no significant differences neither in clinical and histological response nor in clinical remission between UC and CD patients. No side effects were reported by patients neither through the treatment period nor at 4 week follow-up visit.

Conclusion: PLC improves endoscopic and histological activity of mild to moderate UC. Further studies are required to evaluate PLC efficacy in colonic CD patients.

A young woman with dysphagia

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A 18-year old girl from Ivory Coast was admitted to a gastroenterology outpatient clinic for the evaluation of a seven-month history of dysphagia for solids, chest pain, and vomiting. The symptoms had been progressive, and were worsening in frequency and intensity. She also complained asthenia and a weight loss of 5 kg over the past year. The past medical history was essentially negative; inquiry into her dietary intake found that she was strictly-vegetarian and she reported heavy menstruation bleedings. Physical examination revealed no major abnormalities. Laboratory tests revealed a severe microcytic anaemia (haemoglobin 5.7 g/dL; mean corpuscular volume 44.2 fL), with decreased iron stores (plasma ferritin 2 ng/mL). A stained film of peripheral blood showed hypochromia, microcytosis, mild poikilocytosis. A barium swallow showed a constriction of the proximal esophagus and the esophagogastroduodenoscopy (EGD) confirmed the presence of an upper oesophageal web, which was fractured using dilators. Workup for anemia, including measurement of anti-tissue transglutaminase antibodies, stool examination for occult blood, gynecological evaluation, was negative, except a mild increase of hemoglobin C in the serum. A diagnosis of Plummer-Vinson syndrome was assessed. The patient was prescribed intravenous iron supplementation, with reduction in symptoms and hemoglobin count 6 months later showed an improvement to 11.7 g/dL. Follow-up endoscopy showed the presence of new webs and a second dilatation was performed. The patient is now under endoscopic surveillance and undergoes periodic laboratory tests.

Predictive role of two biochemical scores in the diagnosis of autoimmune atrophic gastritis

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Background and Aim: Autoimmune atrophic gastritis (AAG) is burdened by high morbidity and neoplastic potential but despite this, it is often underdiagnosed. Many haematological parameters have been proposed as screening tests, but till now none of them proved to be accurate. Therefore, the aim of our study was to evaluate the predictive role of two biochemical scores to address the diagnosis.
Methods: We enrolled 139 AAG patients (103 females, mean age 60 ± 17.2 years) and 510 pathological controls (330 females, mean age 47 ± 16 years). All patients underwent EGD and diagnoses of AAG were made according to Sydney-Houston criteria. Among many biochemical parameters, hemoglobin (Hb), mean corpuscular volume (MCV), serum gastrin, vitamin B12 and cromogranine A (CgA) levels showed a significant difference between patients and controls. A logistic model indicated the importance of the alteration of each parameter and two scores were developed: the Global Score encompassed all the five variables ranging from 0 to 9, and the Simple Score considered only three parameters (Hb, gastrin, MCV) ranging from 0 to 7. ROC curve, sensitivity, specificity, accuracy, positive and negative predictive values (PPV and NPV), and costs were calculated.
Results: ROC analysis identified a best cut off of 2.5 for the Global Score and 1.5 for the Simple Score with a good reliability (AUC 0.94 vs. 0.93, respectively); the Global Score proved to be more sensitive (88.4 vs. 85.6 %) while the Simple Score showed a better specificity (95.3 vs. 94.1 %) and a better PPV (83.2 vs. 80.3 %). Finally, the Simple Score is more affordable (∼31 vs. ∼12 Euros).
Conclusions: Both scores proved to be valid tools to identify patients at increased risk to suffer from AAG. The Simple Score is cheaper and more available than the Global Score and looks suitable for an extensive application as a screening test for AAG. A prospective study is already ongoing to validate the Simple score.

Autoimmune atrophic gastritis: a clinical study on 99 consecutive patients

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Background and Aim: Autoimmune atrophic gastritis (AAG) is an immune-mediated chronic inflammation that involves the gastric body and fundus, leading to hypo-achloridria and vitamin B12 deficiency. Data on its clinical presentation and pattern are still few and fragmentary. The aim of this study was thus to perform a more detailed analysis of its frequency and clinical features, and the clues that lead to its diagnosis.
Methods: Clinical data and family history of 99 consecutive patients with AAG were recorded and analyzed. Diagnosis was based on histological grounds according to the Sydney-Huston classification and on the positivity of antiparietal cells antibodies.
Results: In the period 2007–2010, 2286 patients were first evaluated in a gastroenterology outpatient clinic. At the end of their evaluation, 99 patients (4.3 %), ratio F:M 2.6:1, mean age 59 ± 17 years, range 18–83 years, met the diagnostic criteria for AAG. The most frequent abnormality (N = 37, 37.4 %) leading to diagnosis was related to vitamin B12 deficiency (macrocytic anemia, macrocytosis without anemia, anisocytosis). Nine celiac patients (N = 9, 9.1 %) were diagnosed as having AAG because of refractory anemia, not responding to gluten free diet and having normal duodenal mucosa. The remaining patients were diagnosed because of incidental histological evidence of atrophic body gastritis (N = 34, 34.3 %), autoimmune screening (N = 9, 9.1 %), neurological abnormalities (N = 6, 6.1 %) and family history of AAG (N = 4, 4 %).
Conclusions: Our data show that AAG is more frequent than expected, it is not only a condition found in the elderly and greater attention should be paid to the diagnostic clusters described.

Baclofen in the treatment of intractable and/or persistent hiccups: case series

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Hiccup is an involuntary contraction of the diaphragm and inspiratory muscles, generating a sudden inspiration, followed by the closure of the glottis, producing the onomatopoeic sound "hic". The occurrence of hiccup is widespread, but neuronal origins of this reflex and its

physiological significance are still debated. Several factors generate hiccup, such as sparkling beverages, air deglutition, gastric distension, changes in food temperature, spicy foods, alcohol, tobacco, CNS diseases, metabolic disorders, fever, foreign body in the ear, pneumonia, lung tumour, pericardial or pleural effusion, myocardial infarction, GERD, hepatitis, gastric tumour, peritonitis, thoracic—abdominal and urologic surgery, psychogenic, chemotherapy, benzodiazepines, corticosteroids, barbiturics, morphine or hidiopathic. Hiccup lasting less than 48 h is defined "benign", while "persistent" when lasting >48 h. Hiccups is defined "intractable" when lasts more than 1 month. Generally benign hiccup is self-limiting, while persistent and intractable hiccups represent a problem both for patients, because of the limitation of quality of life, and for clinician, because of the variety of the underlying conditions and frustration for unsuccessful treatment. Anecdotal treatments include: pulling-out the tongue, pushing-up the uvula with a cold spun, swallowing granular sugar, tasting a lemon, smelling ammonia or salt, breathing in a bag, scaring the patient etc. Pharmacological treatments include: clorpromazine, metoclopramide, nifedipine, carbamazepine, marijuana or phrenic blockade.

Baclofen, a GABA-B agonist, can affect neuronal transmission of the reflex arc and it has an effect in increasing the lower oesophageal sfincter tone. A few literature data show baclofen efficacy in stopping hiccup. We report a case series of persistent hiccups successfully treated by baclofen (10 mg tid). In all patients hippcups resolved after the first 10 mg baclofen administration.

Case 1: A 23-years-old male, presented with a 5 days history of hiccup. After the first 2 days, the patient had been visited at the Emergency Dept where treatment with clorpromazine was prescribed. Despite therapy, the patient was sedated but hiccup was persisting also while sleeping. Clinical examination was unremarkable. The patient had no significant medical history excepted for smoking 10 cig/day for 4 years. Routine blood test, electrocardiography (EKG) and chest X-ray were normal. Baclofen was prescribed with remission of hiccup. Baclofen was discontinued after 2 days with no recrudescence.

Case 2: A 73-years-old woman, had a 3 days persistent hiccup. She was in the 4th postoperative day after hip replacement. Hiccup started the day after the surgery, and it was not responding to metoclopramide. Blood test, EKG and chest X-ray were normal. Baclofen was prescribed with remission of hiccup, and it was discontinued after 3 days with no recrudescence.

Case 3: A 67-years-old man, presented a 2 days persistent hiccup. He was in the 2nd postoperative day of radical prostatectomy for prostate cancer. Hiccup started a few hours after the surgery, and it was refractory to clorpromazine. Blood tests and EKG were normal. Chest X-ray was negative, and chest CT scan did not show mediastinal abnormalities. Baclofen was prescribed with remission of hiccups and it was discontinued after 2 days with no recrudescence.

Case 4: A 55-years-old man came to our observation because of 3 days persistent hiccups, nausea and vomiting. He reported chronic nimesulide use, because of ostheoarthritis. At Emergency Dept, blood test showed elevation of transaminases and cholestasys enzymes. An EGDS showed haemorrhagic gastritis (NSAIDs use). Despite supportive therapy and metoclopramide, patients could not rest because of hiccup. Baclofen was started with remission of hiccup. After 2 days, baclofen was discontinued with hiccups recidivism. The treatment was restarted successfully, and it was continued until normalization of liver enzymes. After baclofen discontinuation, no hiccup recidivism was found

Case 5: A 77-year-old man came to our observation because of an abdominal wall hematoma, occurred during heparin treatment for cardioembolic ictus. After the surgical drainage of the hematoma, the patient developed intractable hiccup. Baclofen administration was started with regression of the symptom.

Conclusions: Baclofen seems to be effective in the treatment of intractable hiccups of any origin.

A woman with rectal bleeding and cholestasis

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We present the case of a 76-year-old woman who presented to Emergency Department with recurrent rectal bleeding. She was affected by osteoporosis and she was under treatment with aspirin, 100 mg daily, for peripheral arterial disease of inferior limbs. The patient was in her usual state of health until the morning of admission, when three episodes of rectal bright-red bleeding occurred. At the moment of physical examination, she appeared alert and oriented, pale and there was no jaundice. The temperature was normal, the blood pressure 105/60 mmHg, the pulse 90 beats per minute, the respiratory rate 20 breaths per minute, and the oxygen saturation 96 % while she was breathing ambient air. She reported no abdominal or rectal pain, heartburn, and she had no nausea, vomiting or diarrhea. Cardiac examination revealed normal heart sounds and a grade 3/6 mesosystolic murmur loudest at the right upper sternal border, with irradiation into the neck. The abdomen was soft, without rebound tenderness or masses; on rectal examination was present bright-red blood and, in particular, no hemorrhoids were seen. The remainder physical examination was normal. Laboratory-test at admission showed mild pancytopenia with combined iron- and folate-deficiency anemia (haemoglobin 9.3 g/dL; hematocrit 30.4 %; MCV 90.8 fL; serum ferritin 16 μg/L; serum folate 3.29 ng/mL; white-cell 4040/mm^3; platelet 85000/mm^3), normal coagulation and renal-function tests. A nasogastric tube was placed, and gastric lavage revealed no blood in the stomach. At the time of hospitalization, a transthoracic echocardiography revealed unknown moderate aortic stenosis with conservate left ventricular systolic function. Aortic-valve stenosis can be complicated by bleeding, particularly that due to gastrointestinal angiodysplasia (Heyde's syndrome). During hospitalization, an esophagogastroduodenoscopy rouled out signs of hemorrhage and showed only hiatal hernia. A colonoscopy revealed widespread presence of clots and red blood and millimetric sessile polyps of rectum and sigma but did not show active bleeding lesions or angiodysplasia. Routine laboratory-test revealed only mild increase of alkaline phosphatase (230 U/L) and gamma-glutamyltransferase (77 U/L); the levels of total and direct bilirubin and transaminases were normal. Since the presence of cholestasis and pancytopenia, an abdominal ultrasonography was performed, showing mild splenomegaly (diameter bipolar 15.5 cm, with homogeneous parenchyma) and signs of portal hypertension, finding ectatic but patent portal vein, patent paraumbilical veins, and slight free peritoneal fluid; the size of the liver was normal, with hepatic parenchyma thinly inhomogeneous and irregular margins, without focal lesions; inferior vena cava and hepatic veins were found patent. The CT abdomen scan with contrast media enhancement confirmed the ultrasound findings and detected dilated, tortuous inferior mesenteric vein and large rectal varices. We hypothesized that rectal varices, consequent to hepatopathy, were the only apparent source of bleeding. The Child Pugh score was B. Treatment was begun with propranololo and oral tranexamic acid while the aspirin was discontinued. Regarding the etiology of the hepatopathy, the patient did not drink alcohol and the sierologies for HCV and HBV, serum copper, ceruloplasmin and α1-antitrypsin were negative; a sample of serum autoantibodies was taken. We performed noninvasive estimation of liver stiffness by transient elastography (FibroScan), that disclosed severe hepatic fibrosis (stage 4). The

patient underwent to the transjugular hepatic venous pressure measurement, and the high value (20.2 mmHg) of hepatic venous pressure gradient (HVPG) was indicative of severe sinusoidal portal hypertension. Due to the recurrent episodes of rectorrhagia and persistence of anemia, and the need for frequent blood transfusion (a total of eight units of packed red blood cells during hospitalization), along with a lack of response to betablockers and nitrates and the use of infusion of somatostatin, a transjugular intrahepatic portosystemic shunt (TIPS) procedure was performed with no complications. After the insertion of portosystemic shunt by expandable metal stent, the portocaval gradient (PCG) was 2 mmHg, the patient no longer presented rectal bleeding and blood transfusions were no further necessary. Tests for antinuclear antibodies showed positive titer (1:640) of antinuclear antibody (ANA) and (1:320) antimitochondrial antibodies (AMA). According to AMA positivity and cholestasis, diagnosis of possible primary biliary cirrhosis was established, and therapy with ursodeoxycholic acid was begun.

Management of the constipation in elderly patients

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Purpose: Chronic constipation is one of the most frequent intestinal troubles in the daily medical practice and it is strongly influenced by life conditions and diet. In industrialized Countries prevalence of constipation ranges from 10 to 20 %, increasing with age, with more than 70 % in patients of the nursing homes or the other long-term-care facilities. Two types of constipation are reported: (1) the slow transit constipation (STC), characterized by a reduction in the frequency of bowel movements less than three evacuations/week and (2) outlet obstruction (SOD) with to difficulty of emptying the rectum.
The diagnosis, obtained with intestinal transit time for the SRT and the anorectal manometry for the SOD, is fundamental for the therapeutic strategy; the SRT treatment focus on osmotic or stimulating laxatives, while for the SOD an important role is due to anorectal biofeedback.
In this study we reported preliminary data related to the management of elderly patients attending a gastroenterology unit specialized to the treatment of constipation.
Materials and Methods: From January 2010 to June 2011 we evaluated 208 consecutive patients for constipation; the degree of the constipation has been determined according to the Rome III criteria, the staircase of Bristol (constipation = type 1–3) and the staircase of Wexner (constipation $\geq$5/30). After having excluded a secondary constipation, information about diet are suggested to all the patients, prescribed therapy with fibers and osmotic laxative (lactulose, macrogol) e/o for brief irritating laxative cycles "on-demand" (senna, bisacodyl). All the patients have been invited to hold a daily diary on the characteristics of the stool and it was evaluated at 1, 3, 12 months. The patients that didn't report benefits from the treatment after 3 months, according to the results of intestinal transit time and anorectal manometry, were enrolled for biofeedback.
Results: The patients were 62 $\pm$ 18.7 years old; 84♂-124 ♀. The majority of the patients had benefit from the therapy (more frequent stool frequency, primarily made type 3–5 staircase of Bristol, reduction of the concomitant abdominal symptoms), allowing a reduction of the therapy, rarely to stopping. After a follow-up of 3 months 42/208 (20 %) patients had no benefit from the dietary and pharmacological treatment, nine of them with both anorectal manometry and colonic transit time in the normal range.
Ten patient followed a rehabilitation program of the pelvic floor with bio-beedback and physical therapy for 60 days (=20 sessions). Eight patients improved with a reduction of the abdominal symptoms, of the macrogol intake, improvement of the Wexner staircase, and mainly with a normalization of anorectal parameters normaliting the paradoxical contraction of the sphincter when straining.
Conclusion: in our series 80 % of the patients with chronic constipation have benefit with the dietary and laxative associates to the toilet training. In non-responder patients not-responder with isolated SOD or with SRT the treatment with biofeedback has allowed a meaningful improvement of the intestinal difficulties. The rehabilitation of the pelvic floor through bio-feedback seems to be effective also in the elderly patients.

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Psycological profile and health related quality of life (HRQOL) in patients with hepatocellular carcinoma (HCC)

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Background: In the field of oncology, the effectiveness of diagnostic and therapeutic program was evaluated primarily in terms of survival. In recent years, greater emphasis has been done on perceived Quality of Life (QoL), whose evaluation constitutes an integral part of patient care. (1)
It is well know that in some tumors (i.e. lung or breast) psychosocial interventions may reduce negative feelings and enhance Health Related QoL.
Studies have focused on relationship between psychopathological disorders and cancer, the analysis of personality and the behaviors related to cancer development. (2)
The Alexithymia ("emotion without word or lack of words for emotions", Sifneos 1973) is one of the most important diagnostic criteria in the field of psychosomatics (3). The theoretical assumption is that alexithymia might be considered a relatively stable personality trait characterized by a cognitive-affective deficit that declines in inadequacy of the mentalization processes and affect's dysregulation (5). It's associated with immature defense mechanisms (projection, somatization, hostility) and it's a relative stable personality trait that interacts with primary defensive organization (6). This would explain the greater vulnerability of alexithymic subjects in stress response, and development of somatic diseases such as cancer. It could be a moderator of patient's course of illness and response to treatment.
The effects of psychological variables on HRQOL of patient with HCC have been rarely evaluated as well as the interaction between physical and psychological variables in relation to HRQOL (6, 7).
The aim of this work is to evaluate the behavioral and psychological profile of a group of patients with HCC and to correlate it with the HRQOL and prognostic features.
Patients: We enrolled 32 consecutive patients with HCC (median age 71 years, range 56–82, BCLC stage: A17, B4, D3, Child A29, B3, male 23). On outpatient setting and before having information on his own clinical condition, each subject underwent administration of the

following questionnaires: SF36 for the evaluation of the HRQOL, Hamilton-D (quantitative evaluation of depression positive for scores ≥8); Symptom Check List SCL 90 for the evaluation of general psycopathologic profile (nine items, each positive for score >1), Toronto alexithymia scale (TAS) (positive if score ≥60).
The same questionnaires were further administered to a sample of 20 cirrhotics patients without HCC.
Results: SCL 90 test: 25 % of patients exhibited significant values for hostility and paranoid ideation in the HCC group and of somatization in the cirrhotic group;
TAS: In HCC group, 53.8 % of patients is positive for alexithymia and 12.5 % borderline; in cirrhotic group, 50 % is positive and 22 % borderline (HCC vs. Cirrhotic n.s.). Hamilton D: in HCC, 45.8 % and in cirrhotic group 86.3 % (p 0.001) is positive for depression. Pearson correlation test showed a positive significant association between Hamilton D and the following SCL90 items: somatization, obsession, interpersonal sensitivity, depression, anxiety, fobic anxiety. A positive association was found between alexithymic features and emotionale reactions (somatization and hostility): the patient affected by HCC would attribute to others his own feelings and intentions, assuming inadequate behaviours (*acting out*) or would display in the body and by the body the emotions complaining of somatic symptoms. SCL90, Hamilton D and TAS scores increase in Child and BCLC stage higher values. SF 36 questionnaire showed low values for physical role (M ± DS: 49 ± 45, C.I. 15.6) and emotionale role (43 ± 42, C.I. 14.5) for Child A HCC patients: these values were significantly lower than those reported for normal subjects and Child A cirrhotic patients. A possible role of alexithymia may be postulated.
Conclusions: The development of HCC does not seem to be correlated to a depressive profile of cirrhotic patients. Alexithymia seems to be a psychological marker of both cirrhosis and HCC. To our knowledge this is the first report on the psychological profile patients with HCC and on its relationship to HQoL: the results open questions on the role and the directions of psychological interventions that may improve the quality of life of patients before treatment and in the long term follow-up. This issue assumes a special importance in light of the recent employment of efficacious drugs in the treatment of advanced HCC in whose cases psychological support may favour an adequate adherence to treatment.

Clinical value of Liver and Spleen stiffness evaluation by means of Acoustic Radiation Force Impulse (ARFI) elastography

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Background and Aims: Virtual touch tissue quantification (VTTQ) based on acoustic radiation force impulse (ARFI) imaging has been developed as a noninvasive bedside method for the assessment of liver stiffness and has been described as a method for the evaluation of liver fibrosis in several clinical conditions (viral hepatitis, NAFLD and NASH). In comparison to transient elastography by Fibroscan, ARFI has no limitations depending from body mass index and allows the ultrasonographic evaluation of the liver area on which the measurement is ruled out. ARFI has also allowed to understand the presence of regional differences in liver stiffness, e.g. between left and right liver anatomic lobe, whose interest in the evaluation of liver fibrosis has not been yet well understood.
In order to get some insights into this topic, the aim of this ongoing study is to evaluate the variation of liver stiffness (LS) by ARFI elastography in a series of patients affected by chronic hepatitis and of normal subjects. The stiffness of spleen was also evaluated and compared to liver stiffness in relation to the severity of liver fibrosis.
Patients and Methods: We included in the study 35 consecutive patients of which 32 affected by HCV-related and 3 HBV-related chronic hepatitis in which liver biopsy was performed on the right lobe (evaluated according to the Metavir score). In each patient, we performed 10 valid consecutive ARFI measurements both in right lobe and in left lobe and a median value for each lobe was calculated, expressed in meters/second (m/s). We also enrolled 10 volunteers subjects, considered normal on the basis of clinical, biochemical and ultrasonographic evaluation. ARFI measurements were conducted as previously described. Data are expressed as M ± ES.
Results: there is a direct, strong correlation between the LS values assessed by means of ARFI and fibrosis both for right ($r = 0.6820$, $p < 0.00001$) and left lobe ($r = 0.7222$, $p < 0.00001$). Spleen stiffness did not correlated to metavir score ($r = 0.3447$, $p = 0.20$).

Table 1 Values of ARFI in right and left lobe in relationship to Metavir scores

	F0 (n = 10)	F1 (n = 6)	F2 (n = 4)	F3 (n = 3)	F4 (n = 14)	
Lobo dx	1.09 + 0.15	1.18 + 0.19	1.13 + 0.23	1.25 + 0.27	2.18 + 0.11	1
Lobo sin	1.2 + 0.17	1.9 + 0.22	1.80 + 0.27	1.60 + 0.31	2.80 + 0.3	2
p	0.05	0.04	0.004	0.8	0.003	

1. Right lobe: significant differences were found between F4 and all other groups; 2. left lobe: significant differences between F4 and each other group and also between F2 and F0 and between F1 and F0 groups

Conclusions: Results from this ongoing study show that ARFI elastography is highly correlated to fibrosis severity of the liver as expressed by Metavir; significant differences come from the selective evaluation of LS in right and left lobe and in contrast with some previous observation, our data seem to show a more sensitive value of LS of the left lobe rather than that of the right lobe; spleen stiffness need to be evaluated on a larger sample and may have some role in the evaluation of the risk of portal hypertension and therefore to have a more significant role in more advanced form of chronic hepatitis. In conclusion, ARFI elastography, that does not present the limits of the Fibroscan transient elastography, has a high sensitivity in the evaluation of LS and may represent a valid instrument for the study of regional differences in liver fibrosis and their role in the evolution of chronic hepatic diseases.

Epidemiology and management of hepatocellular carcinoma

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Background and Aims: Administrative data are a source for epidemiological research and study of the management of a disease in the real clinical practice. We have evaluated the data base relative to the hospitalizations for hepatocellular carcinoma (HCC) in Puglia, a region of the South Italy, in order to gain data on the main factors

affecting the survival of patients and to identify clinical areas where improvement of care would be important.

Methods: In the first part of the study, data came from the hospital discharge forms (HDF) of Puglia residents hospitalized in Puglia or out of the region with the diagnosis (ICD9-CM) of 155.0 (malignant neoplasm of liver, primary), 155.2 (malignant neoplasm of liver, not specified as primary or secondary), 155.0 and 155.2, 155.0 and/or 155.2 and/or 155.1 (malignant neoplasm of intrahepatic bile ducts), through the period 2002–2009. Afterwards both a univariate and a logistic multivariate analysis relative to the dependent variable mortality at 24 months was conducted in the index date 2004–2007 selecting the patients with diagnosis 155.0, 155.2, 155.0 and/or 155.2 >39 years age.

Results: Total cohort was represented by 10,060 pts (155.0: 53.9 %, 155.2: 18.9 %, 155.0 and 155.2: 19.1 %, 155.0 and/or 155.1 and/or 155.2: 8.1 %; % male gender 67.6; mean/SD age 69.8/11; rank age %: <40 years: 1.1, 40–64 years: 25.9, 65–74 years: 36.5, ≥75: 36.5). % of deaths within 24 months from the first finding of the diagnosis on the HDF were: 2002–2003: 64.9; 2004–2005: 61.7; 2006–2007: 61.4; 2008–2009: 60.3. 5745pts (57.1 %) underwent no procedures and interventions; 598pts had demolition surgery, 1186 pts only TACE (transarterial chemoembolization), 754 only PEI (percutaneous ethanol injection), 234 pts only RF (radiofrequency ablation), 341 pts TACE and PEI, 773pts surgery plus others proceed. except transplant, 429 pts other combinations (of which 196 transplants). 84.4 % of pts received treatments only in Puglia, 9.5 % both in and out of Puglia, 6.1 % only out of region. At univariate analysis (4279 pts of the cohort 2004–2007), significant factors affecting the survival at 24 months were: older age at the diagnosis, the aspecificity of the ICD9 CM code, the lack of any procedures, the treatment only in the region. The table shows the results of the logistic multivariate for the dependent variable mortality at 24 months.

Term	OR	95 % CI	SE	Z-Statistic	*P* Value
Age (65–74/40–64 years)	1.191	0.999–1.418	0.089	1.957	0.0503
Age (≥ 75/40–64 years)	1.4556	1.216–1.742	0.091	4.097	0.0000
Sex (F/M)	0.7614	0.658–0.880	0.074	−3.664	0.0002
Diagnosis (155.0/155.2)	0.6704	0.561–0.800	0.090	−4.409	0.0000
Diagnosis (155.0 and-or 155.2/155.2)	0.759	0.611–0.942	0.110	−2.501	0.0124
PEI (Yes/No)	0.4058	0.339–0.485	0.091	−9.861	0.0000
TACE (Yes/No)	0.6274	0.532–0.739	0.083	−5.570	0.0000
RF (Yes/No)	0.3561	0.279–0.454	0.124	−8.304	0.0000
Surgery (Yes/No)	0.3298	0.27–0.402	0.101	−10.884	0.0000
Transplant (Yes/No)	0.1083	0.054–0.214	0.349	−6.359	0.0000

Conclusions: (1) HCC administrative date analysis shows survival data widely corresponding to those of international scientific references. (2) This study shows possible areas of improvement of accessibility to care and to quality of management of HCC. (3) Main limit is related to the absence of data on the stage of the disease (e.g. BCLC classification): comparison with clinical archives may be therefore needed.

Steroid therapy in acute HCV-correlated hepatitis

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We report the case of a 71-year-old patient affected by Crohn's disease, who was infected by the hepatitis C virus likely through transfusion of RBC concentrate. He came to our attention for pancytopenia, jaundice and raised aminotransferase values. He had a history of diabetes mellitus, arterial hypertension and Crohn's disease, in treatment with mesalazine and prednisone. Two months before he had been admitted to a Gastroenterology ward for iatrogenic pancytopenia due to the administration of azathioprine for about 30 days, and had undergone transfusion of RBC concentrate. At that time, hepatitis markers were negative and aminotransferase levels normal. When he was admitted to our Unit he showed pancytopenia, cholestatic jaundice and high aminotransferase values (AST and ALT 20 times the normal values), increased ferritin and Vitamin B12 values; folates, direct and indirect Coombs test, inflammatory indexes, renal function parameters and clotting indexes were normal. Plasma protein electrophoresis demonstrated polyclonal hypergammaglobulinemia and hypoalbuminemia. Among tumor markers, Ca 19.9 was increased. Hepatitis markers were positive for anti-HCV antibodies, with HCV-RNA equal to 19918684 IU/ml, genotype 1b. Serum tests for other viruses and early CMV antigens were negative, whereas antibodies tests showed positive ANA, with a titre of 1/80 and a granular cytoplasmic pattern, as well as positive c-ANCA. Hematologic workup, including peripheral blood smears, medullary fine needle aspiration and osteomedullary biopsy, demonstrated bone marrow hypoplasia and increased $CD4^+$ lymphocytes. Total body CT showed a porcelain gallbladder, while cholangio-MRI demonstrated mild dilatation of the extra-hepatic biliary tract and no stones. Therefore, after the exclusion of a hematological or neoplastic etiology, a diagnosis of pancytopenia due to acute HCV-correlated hepatitis was made. Therapy with prednisone and mesalazine was suspended. Despite a partial improvement of the pancytopenia and hypertransaminasemia, the cholestasis and inflammatory indexes gradually increased and the liver function declined, with the appearance of declivitous edema and mild ascites. In view of the contraindications of age, Crohn's disease and pancytopenia, no antiviral therapy was administered, nor was it possible to perform liver biopsy due to the ascites. Because of a suspected overlap between autoimmune hepatitis and acute HCV-correlated hepatitis, empirical low-dose steroid therapy was started (methylprednisolone 20 mg/day i.v.), and a rapid improvement of both the liver function and pancytopenia was observed. Steroid therapy lasting 1 month was tapered and finally suspended with complete remission of the clinical picture and HCV chronicization.

The rapid response to the steroid therapy suggests a diagnosis of autoimmune hepatitis with three possible etiologies, namely the Crohn's disease, the previous treatment with azathioprine and the concomitant HCV infection. These are not mutually exclusive but could, in fact, have had a synergistic action. In fact, azathioprine is known to have a high incidence of side effects such as pancytopenia, autoimmune hepatitis and pancreatitis, in subjects affected by chronic inflammatory bowel diseases. Besides, the latter can be complicated by the onset of autoimmune hepatitis, and HCV infection can bring on autoimmune complications. We must also stress that despite standardized controls of blood donors, in a low percentage of cases transfusion-mediated HCV contagion is still possible. Finally, medullary aplasia is a rare complication of acute HCV infection and in this case it could have been fostered by the previous immunosuppressive therapy.

Comparison between conventional criterion and AKIN criteria in the definition of acute kidney injury in hospitalized patients with cirrhosis and ascites

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Background and Aims: Acute kidney injury (AKI) occurs in approximately 20 % of hospitalized cirrhotic patients. A percentage

increase in serum creatinine (sCr) of 50 % or more to a final value of sCr >1.5 mg/dl is the most commonly used criterion among hepatologists for the diagnosis of AKI (conventional criterion). Nevertheless, the Acute Kidney Injury Network (AKIN) recently developed a new consensus definition of AKI, as an absolute increase in sCr of 0.3 mg/dL or a percentage increase in sCr of 50 % or more. The aim of the study was to compare conventional criterion and AKIN criteria for the prediction of in-hospital mortality in hospitalized patients with cirrhosis and ascites.

Methods: A cohort of 233 hospitalized patients with cirrhosis and ascites was prospectively evaluated for the presence of AKI diagnosed with the two different criteria and for the subsequent prediction of in-hospital mortality.

Results: AKI, any how diagnosed, was shown to be a strong independent predictive factor for in-hospital mortality as well as MELD score and Child-Pugh score. The incidence of mortality significantly increased with severity of AKI diagnosed on the basis of AKIN criteria (no-AKI = 6.4 %, stage 1 = 29.5 %, stage2 = 60 %, stage 3 = 63.2 %). AKI progressed to a higher stage in 26.2 % of patients. The mortality was significantly higher in progressors than in non-progressors (75 vs. 22.2 %, $p < 0.001$). When compared with AKIN criteria, conventional criteria were found to be more accurate in the prediction of in-hospital mortality with a Net Reclassification Improvement (NRI) of 9.4 % ($p < 0.001$). AKIN criteria with a cut off of 1.5 mg/dl were as accurate as conventional criteria in the prediction of in-hospital mortality. We found that patients with stage 1 AKI and SCr <1.5 mg/dl had lower mortality than patients with AKI stage 1 and SCr >1.5 mg/dl (11.76 vs. 40.74 %, $p = 0.03$). Patients with stage 1 AKI and SCr <1.5 mg/dl showed a lower rate of progression than patients with stage 1 and SCr >1.5 mg/dl (5.8 vs. 40.74 %, $p = 0.01$). Furthermore stage 1 AKI improved more frequently in patients with SCr <1.5 mg/dl than in patients with SCr >1.5 mg/dl (70.59 vs. 37.03 %, $p = 0.025$) despite no specific treatment.

Conclusions: In our series of hospitalized patients with cirrhosis and ascites the common criterion seems to be more accurate than the AKIN criteria to detect the risk of in-hospital mortality. Otherwise, a cut-off of 1.5 mg/dl of SCr should be applied to the AKI stage 1 to improve the accuracy of AKIN criteria in the prediction of in-hospital mortality in these patients.

Added value of the postvascular phase at magnetic resonance imaging to diagnose intrahepatic cholangiocarcinoma in cirrhosis

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Purpose: The diagnosis of intrahepatic cholangiocellular carcinoma (ICC) in cirrhosis remains elusive at imaging, although misdiagnosis with hepatocellular carcinoma (HCC) should be prevented by lack of wash-out in the venous phase at Magnetic Resonance Imaging (MRI), which is however non diagnostic. For clinical management the differentiation between ICC and HCC is highly relevant. Aim of the present study was to evaluate the potential of MRI in the diagnosis of ICC using "hepatocyte-specific" Gadolinium-based contrast agents.

Methods: Sixteen histologically proven and retrospectively identified ICC on cirrhosis were investigated with hepatocyte-specific MRI contrast agents (6 in center 1 with Gd-EOB-DTPA and 10 in center 2 with Gd-BOPTA). The control group consisted of 41 nodules (31 HCC) imaged with Gd-EOB-DTPA. Signature of study informed consent was waived by the Ethics committee given the retrospective design.

Results: Fifteen ICC nodules (94 %) displayed enhancement defect in the hepatobiliary postvascular phase, suggesting malignancy. Thirteen ICC (81 %) showed hyperenhancement in the venous phase. Only 2 ICC nodules showed hypoenhancement in the venous phase, corresponding to wash out, in both cases preceded by rim enhancement in arterial phase. All HCC showed enhancement defect in the hepatobiliary phase, but always preceded by hypoenhancement pattern in the venous phase; notably rim enhancement in the arterial phase was never observed either in any HCC or any regenerative nodule.

Conclusions: MRI with hepatocyte-specific Gadolinium-based contrast agents showed a pattern of malignancy in almost all ICC, concurrently avoiding misdiagnosis with HCC, since the two entities in no case showed the same dynamic contrast enhancement pattern. It has therefore an added diagnostic value in patients with inconclusive findings at CT or conventional MRI.

Long-term maintenance of SVR in difficult-to-treat HCV genotypes in liver

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Background: The goal of combined HCV antiviral treatment with interferon (IFN) and ribavirin (RBV) is to achieve a sustained virological response (SVR), which must be successively maintained. SVR rates obtained in liver transplant (LT) recipients are lower than in immunocompetent patients and few data about SVR maintenance are available.

Aim: To retrospectively investigate the long-term maintenance of SVR following IFN/pegIFN+RBV therapy in LT recipients with HCV recurrence.

Methods: 340 HCV+ LT recipients with "difficult-to-treat" genotypes 1/4 who underwent antiviral therapy (when fibrosis $F \geq 2$ developed, for at least 1 year, IFN/PegIFN+RBV according to the center protocol) were retrospectively evaluated (AISF RECOLT-C database). LT was performed between 1989 and 2008.

Patients' characteristics are shown in Table 1. The Chi-square test and the Student's *t* test were used for the statistical analysis to compare data; a two-sided P value of 0.05 was considered to be statistically significant.

Results: Overall SVR rate was 25.3 % (86/340 patients), mean follow-up after the end of treatment was 7 ± 3 years (2–17 years). Among SVR patients, all but 6 (6.9 %) remained HCV RNA negative during the follow-up. Comparing patients who did not and those who maintained SVR, among all the investigated factors, treatment duration >80 % ($p = 0.026$) and the achievement of EVR ($p = 0.001$) were associated to the maintenance of SVR (Table 1). Seven (1 from SVR non maintenance) died, for causes not related to liver disease recurrence.

Table 1 Recipients' characteristics

Population's characteristic	Mean ± SD/Frequency	SVR patients' characteristic	Mean ± SD/Frequency	p value	Chi squared
BMI (kg/m^2)	25 ± 3 (15–40)	BMI (kg/m^2)	25 ± 3.5 (18–38)	0.085	
AGE (years)	54 ± 8 (19–68)	AGE (years)	54 ± 8 (19–67)	0.864	
SEX	239 M/101F	SEX	67 M/19F	0.088	2.918
Genotype	323G1/17G4	Genotype	80G1/6G4	0.487	0.484
Pre-LT treatment	65/334 (19.1 %)	Pre-LT treatment	11/59 (12.8 %)	0.935	0.007
Immunosuppressive therapy	CsA 136/FK 194/other 4	Immunosuppressive therapy	CsA 40/FK 43/other 2	0.921	0.164
Days from LT to treatment	708 ± 794 (10–5783)	Days from LT to treatment	846 ± 806 (54–4290)	0.239	
HCV-RNA ≥ 800000 IU/mL	189/296 (55.6 %)	HCV-RNA ≥ 800000 IU/mL	43/75 (50 %)	0.417	0.658
Cirrhosis (Ishak stage 5/6)	9/254 (2.8 %)	Cirrhosis (Ishak stage 5/6)	3/74 (3.5 %)	0.634	0.227
RVR	23/173 (6.8 %)	RVR	11/42 (12.8 %)	–	–
EVR	100/283 (29.4 %)	EVR	56/71 (65.1 %)	0.001	11.188
PEG-IFN	256/340 (75.3 %)	PEG-IFN	69/86 (80.2 %)	0.387	0.748
≥80 % treatment duration	215/338 (63.2 %)	≥80 % treatment duration	215/338 (63.2 %)	0.002	4.957
≥80 % IFN dose	199/322 (58.5 %)	≥80 % IFN dose	67/82 (77.9 %)	0.322	0.980
≥80 % RBV dose	135/288 (84.7 %)	≥80 % RBV dose	68/82 (79.1 %)	0.394	0.725

Conclusions: In our series of LT HCV patients, SVR was maintained for a mean time of 7 years after the end of antiviral treatment in the large majority of patients (more than 90 %). Late virological relapse was more common in patients who received a shorter treatment, not achieving EVR. These results would help in the future use of more potent antivirals in such difficult-to-treat recipients.

Susceptibility to cholesterol gallstone formation is increased in mice with deletion of the GPR30 gene, a novel estrogen receptor

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Epidemiological and clinical studies have found that the prevalence of cholesterol gallstones is markedly higher in women than in men. The use of oral contraceptives in premenopausal women and estrogen replacement therapy in postmenopausal women increase gallstone prevalence rates significantly. Estrogen therapy in men with prostatic cancer also induces similar lithogenic effects. These findings strongly indicate that the increased risk of gallstones in women compared to men is related to differences in how the liver metabolizes cholesterol in response to estrogen. We have previously established a central role for estrogen by activating estrogen receptor α (ERα), but not ERβ, in promoting gallstone formation (*Gastroenterology* 2004; 127: 239–249). However, the mechanism mediating estrogen's lithogenic actions on gallstone formation has become more complicated with the recent identification of a novel estrogen receptor, the G protein-coupled receptor 30 (GPR30). Furthermore, a new gallstone gene, *Lith18*, has been mapped to mouse chromosome 5, and it is co-localized with *Gpr30*. Our molecular and genetic data support the candidacy of *Gpr30* for *Lith18*. However, identifying the lithogenic effects of GPR30 remains a significant challenge, and it is not yet fully understood whether GPR30 acts independently from or in joint with ERα on inducing gallstone formation.

Methods: To distinguish between the lithogenic actions of GPR30 and ERα and to investigate whether estrogen can influence cholesterol gallstone formation through GPR30, we investigated gonadectomized GPR30(−/−)/ERα(−/−) and GPR30(+/+)/ERα(−/−) mice of both genders that were implanted subcutaneously with pellets releasing 17β-estradiol at 6 ug/day and fed the lithogenic diet for 12 weeks.

Results: Targeted deletion of the *ERα* gene provided a crucial way to exclude the effect of ERα on the formation of cholesterol gallstones in these mice. After 12 weeks of feeding the lithogenic diet, 17β-estradiol-treated GPR(−/−)/ERα(−/−) mice, compared with GPR(+/+)/ERα(−/−) mice, displayed significantly higher cholesterol saturation index (CSI) in gallbladder bile, more rapid cholesterol crystallization, markedly accelerated stone growth, and higher gallstone prevalence. Our discovery strongly suggests that GPR30 is a novel, selective target for the prevention and the treatment of estrogen-induced cholesterol gallstones.

Conclusions: GPR30 is also involved in estrogen-dependent lithogenic actions, working independently from ERα, as both GPR30 and ERα can work through different pathways to greatly promote the formation of estrogen-induced gallstones. Distinguishing between the lithogenic actions of GPR30 and ERα and further investigating how estrogen produces lithogenic actions via GPR30, may help to elucidate all molecular mechanisms behind the formation of estrogen-induced cholesterol gallstones.

Diagnosis of adrenal insufficiency using serum total cortisol and plasma free cortisol response after low dose short synacthen test: discrepancy exists in advanced liver disease

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Background: Adrenal Insufficiency (AI) defined by low dose short synacthen test (LDSST) in stable cirrhosis is frequent using serum total cortisol (TC). However no published data exist on directly measured plasma free cortisol (FC) after LDSST. We prospectively assessed adrenal insufficiency defined by LDSST in stable cirrhosis using TC and FC.
Methods: Patients with stable cirrhosis without shock and/or sepsis were prospectively studied using the LDSST. AI was defined by a peak-TC $\leq$ 494 mmol/L (Criterion 1) and a peak-FC $\leq$33 nmol/L (Criterion 2) 30 min after injection of 1 μg of tetracosactrin (Synacthen®).
Results: 78 consecutive patients with cirrhosis were studied (Viral: 16, Alcoholic: 41; other: 21). Basal TC (365 ± 192 mmol/L) and peak TC (571 ± 216 mmol/L) were significantly related to basal FC (26 ± 24 nmol/L) and peak FC (53 ± 34 nmol/L) respectively: for baseline values $R = 0.78$, $p < 0.001$, and for peak values $R = 0.70$, $p < 0.05$. Similar results were found considering only patients with hypoalbuminemia (albumin <25 g/L, 7 patients): for basal value $R = 0.88$, $p < 0.001$; for peak value $R = 0.89$, $p < 0.05$. Prevalence of AI was 35 % (27/78) using total cortisol (Criterion 1) and 28 % (22/78) using free cortisol (Criterion 2). There was agreement between total cortisol (Criterion 1) and free cortisol (Criterion 2) in 63 tests, in 10 AI was diagnosed only according TC (Criterion 1), and in 5 only according FC (Criterion 2): Kappa-coefficient 0.56, $p < 0.05$. In the group with discordant tests patients had more advanced liver disease (Child score: 9.17 ± 2.2 vs. 7.66 ± 1.9, $p = 0.03$), lower basal TC (237 ± 104 vs. 395 ± 196 mmol/L, $p = 0.03$), and peak TC (464 ± 121 vs. 597 ± 226 mmol/L, $p = 0.009$).
Conclusions: AI defined by LDSST is frequent in stable patients with cirrhosis, using both total cortisol and free cortisol criteria. However in patients with more advanced liver disease and/or low total cortisol level, discrepancy exists between the rates of diagnosis of AI using the total and free cortisol criteria. Thus in these patients AI should be confirmed by free cortisol measurement.

SCCA-IC predicts clinical outcome of patients HCV chronic hepatitis treated with antiviral therapy: a multicentric prospective study

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Background and Aims: The gold standard treatment for chronic hepatitis C, to prevent or delay progression to liver cirrhosis and hepatocellular carcinoma (HCC), is currently the combination of pegylated interferon-α (Peg-IFN-α) with ribavirin. The HCV genotype and a rapid virological response (RVR) have been widely recognized as the most important prognostic factors for the response to anti-viral therapy, but to optimize the cost-benefit ratio and to reduce possible side effects, additional prognostic factors are needed. Squamous cell carcinoma antigen immuno-complex (SCCA-IC) is an immuno-complex whereby IgM immunoglobulins link the serin inhibitor protease SCCA. It has been reported to be increased in the serum of patients with liver cancer. Results: In this multicentric prospective study we tested the utility of SCCA-IC as a marker of response in 103 patients (61 males and 42 females) with HCV chronic infection undergoing anti-viral therapy. Serum samples were collected at baseline before the beginning of therapy, after 4, 12, 24 and 48 weeks during treatment and at 24 weeks of follow-up. RVR, EVR, and SVR were assessed following the international guidelines. Responders with all genotypes had higher levels of SCCA-IC than non-responders. Furthermore, in responders the level of SCCA-IC showed a tendency to decrease, whereas in non-responders the SCCA-IC level appeared to remain the same at each time point. The initial value of SCCA-IC in responders was 238 AU (interquartile difference 130–556 AU); this decreased during therapy (188 AU after one month and 134 AU after 3 months) and reached the value 125 AU (70–290 AU) at the end of follow-up. In non-responders the initial value was 149 AU (86.5–306.5 AU) and decreased slightly after one (142.5 AU) and three months (115 AU), reaching the value 119 AU (82–260 AU) at the end of follow-up. These results have shown a reduction profile different between patients responders and non-responders. To evaluate the effect of SCCA-IC reduction on SVR, a logistic regression model was built with the presence of SVR as dependent variable, while the independent variables were: the class of SCCA-IC reduction after 1 month (OR = 4.82; 95 % CI 1.39–16.67; $p = 0.131$), genotype other than 1 (OR = 0.094; 95 % CI 0.21–0.42; $p = 0.002$), sex and age. Conclusions: In this study we have demonstrated that SCCA-IC seems to be an independent prognostic factor of therapeutic response in patients with chronic hepatitis C undergoing antiviral therapy. Finally, we suggest that SCCA-IC may be useful to refine patients selection, discriminating those patients that will benefit from antiviral therapy and thus optimizing the cost-benefit ratio.

Factors and mechanisms involved in the progression of hepatic fibrosis in chronic HCV infection: which role for steatosis and insulin resistance?

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Introduction: Hepatitis C virus (HCV) infection is the major cause of chronic liver disease with 170–200 million of people infected worldwide. Hepatic steatosis is a prominent feature of chronic HCV infection with a mean prevalence of about 55 %. HCV-related steatosis is chiefly virus-induced in HCV genotype 3-infection, namely viral steatosis, while host factors seem to play the major pathogenic role in HCV genotype non-3 infection, namely metabolic steatosis. Up to 80 % of patients with chronic HCV infected exhibit evidence of insulin resistance (IR). A strict association between BMI, steatosis and IR has been documented in chronic HCV infected patients. Moreover, a significant number of studies have demonstrated the important role played by IR and steatosis in the progression of the liver disease. However, the majority of these studies evaluated the role of steatosis without considering IR or viceversa and

due to the overlapping condition their independent role in the progression of liver fibrosis has not yet been known. These knowledge, as well as the mechanisms implicated in the pathogenesis, are crucial for developing new therapeutic approaches, especially in patients unresponsive to interferon-based treatment. Accordingly, the aim of this study was to evaluate separately the independent role of steatosis, IR and of both in the progression of hepatic fibrosis in HCV infected patients and the pathogenic mechanisms implicated.

Patients and Methods: 328 consecutive HCV infected patients with liver biopsy proven chronic hepatitis were enrolled in the study. Necroinflammatory activity was scored according to the Histological Activity Index (HAI) by Knodell and the fibrosis scored by Metavir. Steatosis was scored as percentage of hepatocytes affected. IR was evaluated by HOMA-IR. On the basis of a control group, patients were considered IR if they had a HOMA >2.6. HCV RNA was determined and quantified by PCR and HCV genotype by Innolipa. To evaluate separately the progression of fibrosis, chronic hepatitis C patients were divided in subgroup according to absence or presence of steatosis and IR. Thus, 4 subgroups of patients were evaluated: (a) patients without steatosis and IR (n = 72); (b) patients with only steatosis (n = 56); (c) patients with only IR (n = 69); and (d) patients with both steatosis and IR (n = 131). Moreover, considering that we had a subgroup of 124 patients of a known date of infection or with paired liver biopsy, we evaluated the annual progression rate of hepatic fibrosis according with the presence of steatosis and assuming a constant fibrosis progression rate. Univariate and multivariate analysis were performed to individuate the independent role of steatosis and IR in the progression of liver fibrosis.

Results: The median age of the overall studied population was 53 years and males were 53.4 %. The mean BMI was 26. Overt diabetes was present in 7.7 % and IR in 63 % of patients. The prevalence of HCV genotype non-3/3 was 87 %/13 %. Cirrhosis was observed in 20.5 % of cases. The prevalence of steatosis was 57 %. BMI was significantly associated with higher levels of both steatosis and IR. HCV patients of the subgroup (a) showed the lowest levels of liver fibrosis that were significantly lower than that observed in the groups (b) and (c). Patients of subgroup (b), with only steatosis, showed significantly higher levels of HAI that those of subgroups (a) and (c); there were no differences in the levels of HAI between subgroup (a) and (c). Patients of subgroup (d) with both steatosis and IR, showed an additive effect on liver fibrosis deposition. Severe fibrosis (F3–F4), at multivariate analysis, was independently associated with older age (OR 1.09, 95 % CI 1.03–1.69), steatosis (OR 2.21, 95 % CI 1.54–3.16), HAI (OR 2, 95 % CI 1.69–2.39), and HOMA-IR (OR 1.16, 95 % CI 1.01–1.31). The analysis of the subgroup with a known date of infection or with paired liver biopsy showed that the annual rate of fibrosis progression of 0.06–0.10 in patients with normal ALT or no steatosis and the estimated time to develop cirrhosis was of 40–70 years; patients with steatosis <20 %, the annual rate of fibrosis progression was 0.09–0.14 and cirrhosis expected in 30–50 years; patients with steatosis ≥20 % the observed annual rate was of 0.16–0.22 and cirrhosis expected in 18–25 years.

Conclusions: The data demonstrate that, in chronic HCV infection, steatosis and IR are independently associated with liver fibrosis progression. The simultaneous presence of both conditions causes an additive effect on liver fibrosis deposition. Different pathogenic mechanisms appear to be involved, steatosis modulates the deposition of hepatic fibrosis by inflammation, while IR by activating proteins, such as CTGF, promoting fibroblast proliferation and differentiation.

Mucinosal adenocarcinoma conditionating jejunal stenosis: a case report

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Background: Although the small bowel is one of the longest organs of the human body, less than 2 % of all the gastro-enteric tract-malignant tumors takes origin from it.

About 50 % of all small bowel malignancy involves the first or the second duodenal portion and it is represented by ADK.

Materials and Methods: A 60 years old man was admitted to our Unit because of dyspepsia, vomiting and abdominal pains. The personal anamnesis was positive for smoking, HBV-related hepatopathy. Laboratory tests showed increased values of CEA (37.9 ng/ml) and CA 19.9 (80 U/ml), EMA negative.

We decided to perform first EGDS and colonoscopy (both negative), and then PET total body with F-1-8FDG, that showed enhanced metabolic activity in the small bowel with distension of intestinal loops.

Results: In a second time the patient was submitted to Rx clisma of small-bowel and to entero-TC with contrast medium which revealed a jejunal severe stricture without c.e. but with ectasia of the proximal loops. Considering the entity of the stricture, the patient was referred to a Surgery Unit for jejunal resection.

Conclusions: The histologic examination was positive for mucinose ADK with lymphonodal metastasis (T4N1Mx). Finally the patient was referred to oncological department for chemotherapy.

Evaluation of diagnostic, therapeutic outcome and satisfaction in patients with helicobacter pylori (HP) infection

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Background: HP infection is the most common chronic human bacterial infection with up to 50 % of adults affected worldwide. HP plays an important role in generating upper gastrointestinal (GI) symptoms (dyspepsia), and diseases (chronic gastritis, peptic ulcer disease). Also, HP infection remains the most consistent risk factor for gastric cancer. Eradication of HP infection is therefore advisable in several patients, as the most promising strategy to reduce the incidence of symptoms, chronic (and atrophic) gastritis, and gastric cancer development in populations at high risk. Based on the recent Maastricht IV/Florence Consensus Report, the rising antibiotic resistance led to progressive decline of standard treatment for HP infection. This finding is a clear limitation to the overall efficacy of test-and-treat approach to the burden of HP infection worldwide.

Aim: To assess the overall diagnostic, therapeutic and compliance outcome in HP(+)ve in a tertiary referral centre in southern Italy.

Table 1

Line	Regimens	Code	Total N.	Erad. N.	Erad. Rate	VAS (mm)
1st	*Concomitant*: PPI + A1000 + C500 + T500 b.i.d. × 5 days	CM	60	55	92 %*	81.2 ± 2.0$
1st	*Hybrid Sequential*: PPI + A1000 *b.i.d.* × 7 days followed by PPI + A1000 + C500 + T500 *b.i.d.* × 7 days	HS	47	41	87 %**	86.6 ± 2.2×
1st	*Sequential*: PPI + A1000 *b.i.d.* × 5 days followed by PPI + A1000 + C500 + T500 *b.i.d.* × 5 days	S1	162	124	77 %§	91.7 ± 1.2
1st	*Triple*: PPI + A1000 + C500 *b.i.d* × 7 days	T3	68	46	68 %	89.7 ± 1.9
2nd	*Levofloxacin*: PPI + A1000 + L250 *b.i.d* × 10 days	LEVO	33	26	79 %	91.7 ± 2.7
2nd	*Sequential*: PPI + A1000 *b.i.d.* × 5 days followed by PPI + A1000 + C500 + T500 *b.i.d.* × 5 days	S2	140	88	63 %	77.4 ± 1.3°
2nd	*Tetracyclin*: PPI + A1000 + TCY250 *b.i.d* × 10 days	TCY	32	2	6 %£	84.1 ± 2.7¥
3rd	*High-dose Amoxi*: PPI + A1000 *t.i.d.* × 14 days	HDA	27	15	55 %^	87.4 ± 2.9

Legend: A = amoxicillin; C = Clarithromycin; L = Levofloxacin; PPI = Proton Pump Inhibitor; T = tinidazole; TCY = tetracyclin. Statistics: Fisher's exact test: *p = 0.001, **p = 0.03 vs. T3; £p = 0.0001 vs. all; §p = 0.02 vs. S2; ^p = 0.0001 vs. LEVO, S2. One-way ANOVA: °p = 0.0000 vs. all but CM; $p = 0.000000 vs. T3, LEVO, S1; ¥p = 0.000000 vs. LEVO, S1; ×p=0.000000 vs. S1

Methods: 5813 patients underwent UBT (75 mg ^{13}C-urea oral solution) and IRMS measurement (Helifan Instr., Medimar, IT); a total of 569 UBTs were performed in 541 outpatients (M:F = 220:321; age 50.2 ± SE1.1 vs. 49.9 ± 0.1 years, P = NS) with upper GI symptoms (n = 446, 82 %) or asymptomatic (n = 95, 18 %), randomly allocated to 1st, 2nd, or 3rd line eradication regimens. Patients' satisfaction was assessed 4 weeks after treatment using a custom-designed questionnaire with Visual Analogue Scale (VAS, 0–100 mm).

Results: (Table 1): the eradication rate was CM > HS > S1 = T3 (1st line) and LEVO > S2 ≫ TCY (2nd line). S regimen was significantly more effective as 1st than 2nd line. TCY regimen was almost uneffective. HDA was still effective as 3rd line regimen. Among the 28 patients who repeated UBT, there was no difference in VAS.

Conclusions: In our area T3 therapy for HP provides unsatisfactory eradication rate. As 1st line, S is still acceptable although less effective than other regimens. Valid regimens still exist as 2nd and 3rd lines. Due to the increasing antibiotic resistance rate, a careful selection of treatment regimens patients must be recommended as 1st, 2nd, and 3rd line regimens in specific subgroups of populations.

Expiroger 13-C-octanoic acid breath test and VAS scale to evaluate effect of "flavoured iced dessert" on digestion perception in healthy non dyspeptic volunteers

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Introduction: Digestion is a phenomenon depending on several factors, including gastric emptying and psychophysiological events. Functional foods could ameliorate digestion perception, acting on these factors. "Ferrero Gran Soleil Cappuccino", a product designed to be assumed at the end of a meal, is considered a functional food as it contains digestive herbal derivates, although its role in modifying gastric emptying and digestion perception needed further investigations.

Aims and Methods: The aim of our study was to evaluate possible changes in the rate of gastric emptying, measured with a 13C-octanoic acid breath test, and symptoms, measured with visual analogical scale (VAS), before and after ingestion of "Ferrero Gran Soleil Cappuccino" (FGSc) or "Ferrero Gran Soleil placebo" (FGSp). 9 healthy volunteers (6M–3F; 26.3 ± 4.8 mean age) were enrolled to perform 3 13C-octanoic acid breath tests with EXPIR-Oger (Sofar). They were not receiving any medication and they were negative for functional dyspepsia based on Rome III criteria. During each breath test, VAS was registered for 10 parameters (hunger, bloating, satiety, up heartburn, down heartburn, burping, stomach cramps, pain, sleepiness, general well being) to evaluate the quality of digestion at 0, 30 and 240 min after the ingestion of EXPIROger. After a baseline breath test (2 days after and up to 1 week later), subjects performed 2 other EXPIROger breath tests, one after the ingestion of "FGSc" and the other after the ingestion of "FGSp".

Results: Baseline solid gastric emptying breath test was slower (t1/2 > 120 min) in 7/9 (173.4 ± 84 mean t1/2) subjects (77.7 %). VAS scale did not differ significantly among subjects for each time point. After the ingestion of "FGSc", solid gastric emptying was reduced in 6/9 (144 ± 70.8 mean t1/2) subjects (66.6 %), although

not reaching the normality. VAS also improved at 240 min in 7/9 subjects (77.7 %) for satiety, in 8/9 (88.8 %) for bloating and general well being, in 5/9 (55.5 %) for sleepiness, unchanged for up and down heartburn, but it worsened in 3/9 (33.3 %) for burping and pain.

Conclusion: Ingestion of "FGSc", ameliorate gastric emptying, based on 13-C-octanoic acid breath test as well as VAS. More data are necessary to confirm our findings. EXPIROger 13-C-octanoic acid breath test, associated to VAS scale could be a good parameter to be analyzed while assessing digestion in healthy subjects and in evaluating functional food.

Mucosal and intestinal healing in Crohn's disease management: which relationship?

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Introduction: Crohn's disease (CD) is a chronic inflammatory process interesting the whole intestinal wall. The healing of mucosa surface lesions, called "Mucosal healing" (MH) is a new therapeutic objective in CD's management. Few information exist on relationship between MH and whole intestinal wall healing assessed by radiology.

Aims and Methods: To assess the correlation between MH assessed by endoscopy and radiologic activity assessed by CT-enterography (CT-E) or MR-enterography (MR-E).

Twenty-eight CD patients undergone CT-E or MR-E and ileo-colonoscopy (within 1 month) before and after a therapeutic intervention were enrolled (in all, 32 CT-E and 24 MR-E) A physician qualitative clinical assessment (PCA) and SES-CD were assessed. Complete MH was considered as SES-CD = 0, while relative MH as SES-CD <3. A "radiological judgment" (no lesions = 0 and severe activity = 3) was provided at any exam by an expert radiologist, based on typical CD radiological lesions. At the control, a blinded qualitative judgment of improving, stability or worsening of the disease was given by physician, radiologist and endoscopist. "Absolute agreement" was considered when radiologist, physician and endoscopist gave the same judgment about the progression, "no agreement" when they gave three different judgments (worsening vs. stability vs. improvement) while "relative agreement" for the other cases. Therapies included anti-TNF-a, azathioprine, antibiotics and steroids.

Results: Among patients with complete MH (n = 5), nobody displayed absence of radiological lesions (Radiological Remission, RR), while 60 % showed mild radiological activity (MRA). Among patients with relative MH (n = 16), only 6 % displayed RR while 50 % showed MRA. Conversely, among patients with RR (n = 6), nobody was in complete MH while 17 % showed relative MH. Among patients with MRA (n = 26), only 15 % showed complete MH while 42 % relative MH.

Radiological, endoscopic and clinical judgments showed "absolute concordance" in 36 % of the cases despite a 4 % of "complete discordance". Endoscopic and radiological judgments showed absolute concordance in 50 % of cases.

Conclusion: MH does not correspond to "radiological" or intestinal healing, as endoscopy and radiology correlate only partially. The role of MH and radiological healing in disease prognosis remains unclear.

Infliximab (IFX) acts locally on intestinal mucosa and its pharmacokinetic is different in DSS colitic mice compared to controls

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Introduction: IFX is effective in IBD but mechanisms of actions and pharmacodynamics are still not clear.

Aims and Methods: To assess whether IFX acts at intestinal mucosal level and how IFX levels change in blood, gut mucosa and stool in healthy and sick mice. To assess IFX affinity for human (hu) and murine (m) TNF-a, hu or m TNF was immuno-adsorbed on a 96 multiwell plate(30 ng/ml);incubation with decreasing concentration of IFX starting from 150 μg/ml was followed by incubation with HRP-conjugated anti-hu IgG. Plate was read at 495 nm with an Elisa reader.Hu mucosal biopsies from active IBD patients were cultured for 48 h with or w/o IFX(50 ng/ml),and supernatants were assessed for cytokines content and histology performed.IFX effect was explored in C57BL/6 mice that were divided in 2 groups:DSS group received DSS 2.5 % for 7 days.IFX or hu IgG were administered iv(5 mg/kg) at day V or by enema(300 mg/200 ml)for 3 days from day V. Healthy group received tap water and IFX iv treatment. Enema treated mice were sacrificed at day IX; iv treated mice at day V and IX, stool, serum and colon samples were collected to assess IFX and TNF levels by a specific Elisa Kit.

Results: IFX showed a good affinity for hu and m TNF-a, being affinity for hu TNF-a higher. The best affinity for TNF was for higher concentration of IFX. Same concentration of hu IgG showed very low affinity for hu and m TNF. Hu biopsies exposed to IFX showed a decrease in TNF-a content, as well as of innate and adaptive immunity cytokines. IFX-treated biopsies showed a decreased leukocytes infiltration. In DSS group IFX iv or given as enema ameliorated the severity of colitis in mice compared to controls and IgG group, by lowering the disease activity index (DAI) and the loss of body weight. At day IX a reduction of intestinal inflammatory infiltrate was observed and colon length was preserved in treated mice. At Elisa healthy mice had higher IFX levels than DSS mice in serum at day V and IX, in mucosa at day V and in stool at day IX; DSS mice had higher IFX level in stool at day V. No difference in mucosa at day IX. Sick mice loosed IFX in stool faster than healthy mice that showed higher levels in blood and in mucosa.

Conclusion: IFX is acting locally at mucosa level, as shown by incubation of IFX to hu biopsies, by the presence of IFX in blood and in mucosa.IFX as enema has a good effect on m colitis. In sick mice IFX levels are lower in the blood but higher in the stool for a more quickly elimination in stool. More data may clarify mechanisms of loss of responses to IFX and new targets for new therapies.

Gelenterum ameliorates colitis severity in DSS model of murine acute colitis, while modulating gut microbiota and intestinal mucus layer

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Introduction: Gelenterum, a gelatin powder containing Tannic Acids, is used for diarrhea in children. Few information exist on its mechanisms of action, involving gel formation and bacterial toxin sequestration. No animal model has been used to confirm its efficacy or unravel further mechanism of action.
Aims and Methods: To evaluate the effect and mechanisms of action of Gelenterum in the murine model of acute colitis by DSS.C57BL/6 mice were exposed to 2.5 % DSS, given for 8 days in tap water. At day 4, 5, 6, 7 mice received 1 or 10 mg of Gelenterum by gavage in 200 µl of tap water; control mice received water only. Body weight, occult blood test and stool consistency were measured every day and used to calculate the Disease Activity Index (DAI) to assess severity of colitis. Mice were sacrificed at day 9, colon was opened and histological degree of inflammation was assessed. To explore the direct effects on gut microbiota, stools were collected at day 0, 5 and 9. Stool and colon samples underwent microbiological assessment by culture and RT-PCR. To explore the mucus modulation colon samples were analysed at confocal microscopy at 2 photon and atomic force microscope.
Results: Gelenterum reduced DAI and body weight loss in treated mice, being 10 mg more efficacious than 1 mg dose. Gelenterum treated mice showed a longer colon. In specific culture, acinetobacteria, enterobacteria, enterococci and lactobacilli grew from stool as well as intestinal mucosa. Treated mice showed a lower concentration of enterobacteria and enterococci, no differences were found for the other strains.PCR showed similar data. At confocal microscopy, intestinal samples from healthy and treated mice displayed a similar structure in mucus layer thickness and composition, samples from placebo group had no mucus layer or a thinner stratus. Atomic force microscopy confirmed these findings, by assessing the elastic property as an indirect assessment of the mucus layer. Colon samples from healthy and treated mice showed similar elastic property while samples from placebo group had a lower elasticity.
Conclusion: Gelenterum decreased the severity of colitis in mice. It re-establishes gut homeostasis by maintaining mucus layer in gut mucosa and by re-establishing microbiota composition. Further analysis are required to better define mechanisms of action underlying these findings and more indication for gelenterum could be developed following specific studies.

Intestinal permeability in nickel allergy

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Background: The gastrointestinal tract is characterized by selective and dynamic permeability allowing the passage of nutrients and preventing the penetration of microorganisms, toxins and antigens. A derangement of intestinal permeability (IP) seems involved in the pathogenesis of several intestinal and systemic disorders. Nickel allergy (NA) has very often a gastrointestinal involvement being responsible for mild to severe abdominal symptoms.
Aim of the present study was to assess IP in patients with nickel allergy versus healthy controls (HV).
Methods: Fourteen consecutive outpatients affected by NA, assessed by cutaneous patch tests, with abdominal symptoms and 21 HV were enrolled. ^{51}Cr-EDTA absorption test was performed in all patients and HV to assess IP. After an overnight fast, pts and HV were given to drink 2.96 MBq of ^{51}Cr-EDTA in 10 ml of water; two 3-ml samples both of 24/h urine and ascites were measured by a gamma counter. Urine sample results were expressed as a percentage of administered dose and considered indicative of altered IP when ^{51}Cr-EDTA was $\geq$3 %.
Results: An IP derangement was observed in 13 out of 14 patients compared to 1 out of 21 controls (93 vs. 4.8 %, $P = 0.0001$). Patients showed an IP significantly higher than HV (6.07 ± 0.2 vs. 2.0 ± 0.3 %, $p < 0.05$).
Discussion: These preliminary results show that IP is significantly deranged in NA patients versus HV. IP can be cause of antigen penetration in the systemic circulation from the gastrointestinal tract (GI) or consequence of GI allergic involvement. Future larger studies after nickel exclusion diet are needed to confirm this preliminary results.

The best is the enemy of the good

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Introduction: The risks to develop severe adverse reactions compared with their potential benefits suggest that the statin therapy should be carefully recommended in elderly patients. Many side effects occur in course of statin therapy, mainly related to high-dose, but also induced by low-dose. Moreover, the hepatic reactions are more common in women.
Case report: A 85-year-old woman was admitted to our Medical Division for the evaluation of a clinical picture, which was occurred the week before, characterized by persistent asthenia, anorexia, jaundice, and for the increase of levels of transaminases (x3), bilirubin (x4), gamma-glutamyl transferase (GGT) (x10), and alkaline phosphatase (ALP) (x2). The medical history revealed a cholecystectomy 10 years earlier, and a hip replacement surgery for traumatic fracture 2 years earlier. Diabetes and arterial hypertension were not detected. Two week before our observation a treatment with Simvastatin 20 mg/day was prescribed for the occurrence of hypercholesterolemia (290 mg/dl), which was interrupted after few days for a suspected side effect to statins.
The viral diagnostic tests (HAV, HBV, HCV, CMV, EBV) and the tumor markers were negative. Other laboratory investigations, such as blood cell count, renal function, plasma lipid, urinalysis, coagulation tests, creatine phosphokinase, inflammation and autoimmunity (erythrocyte sedimentation rate, C-Reactive Protein, rheumatoid factor test, antinuclear antibody, anti-double strand DNA, anti-extractable nuclear antigen, anti-neutrophil cytoplasmic antibody, anti-mitochondrial antibody, anti-liver kidney microsomal type 1 antibody, anti-smooth muscle antibody) were negative. High values of aspartate transaminase (x60), alanine transaminase (50), bilirubin (x30), GGT (x10), and ALP (x2) were detected. Oesophago-gastroduodenoscopy,

thorax X-ray, abdomen ultrasound and abdomen magnetic resonance were negative.
The patient showed a severe acute cholestatic hepatitis. A therapy with Ursodeoxycholic acid 600 mg/day was prescribed. Since no improvement of the levels of bilirubin, transaminases, ALP and GGT levels were obtained, Prednisone 60 mg/day i.v was added to therapy. The clinical picture and laboratory tests showed a slow improvement; the follow-up at 1 month revealed a partial improvement of clinical picture, and a decrease of the levels of transaminases (x2) and bilirubin (x4), with no changes of the levels of ALP (x2) and GGT (x10). At discharge a decreasing-dose of steroid was prescribed, according with the laboratory tests.
The diagnosis was acute cholestatic hepatitis associated with Simvastatin.
Discussion: All statin drugs have been shown to elevate liver enzymes. At standard dose liver enzyme elevation occurs in about 0.5–2 % of users. This liver enzyme elevation is usually seen within the first 4 months of therapy. The likelihood of this elevation increases in older people and when multiple medications interact with statins. Liver enzymes are restored back to normal once the statin is stopped. However, there have also been rare reports of fulminant liver damage, possibly attributable to statins.
Although there have been reports of liver failure and hepatitis associated with statins and elevated liver enzymes, these occurrences are rare. Current studies have not been able to establish a definite link between statin use and liver disease. In our case (1) no other medications were taken in association with statin; (2) the pathological picture occurred after few days (7–10 days) from the beginning of statin therapy and; (3) a standard dose of statin was prescribed (20 mg). Moreover, the course of the illness was protracted and severe, and the improvement of the clinical and biohumoral situation was responsive to high dose (1 mg/kg/day) of steroid, suggesting an immune-mediated acute cholestatic hepatitis simvastatin-induced. In conclusion, the balance between the cardio-vascular benefits and the risk of adverse reactions in course of statin therapy (i.e. muscle problems, cognitive loss, infection, diabetes, hepatitis), which could occur especially in elderly and in women, should be carefully evaluated.

Real-time tissue elastography (HI-RTE) for the evaluation of focal liver lesions: a new application in internal medicine

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Introduction: Ultrasound elastography includes a variety of recent imaging methods capable to non-invasively assess the elastic and mechanical properties of the tissues. By measuring the deformation in response to stress, elastography can derive and display the tissue stiffness through a different color (hard tissue in blue, soft tissue in red). Recent studies confirmed its utility in breast, thyroid cancers [1] and liver fibrosis [2]; in the latter, according to a multiple regression analysis, Liver Fibrosis Index (L/F index) highly correlated with tissue stiffness and fibrosis ($r = 0.68$). Currently, however, there are no data that correlate L/F index with focal liver lesions.
Case Report: On a 55 year old man, with a history of colon cancer underwent to surgical resection 1 month before, we performed an abdominal ultrasound, with a traditional convex probe, documenting the presence of hepatomegaly with inhomogeneous and subverted echotexture by the presence of numerous hypo-isoechoic lesions with irregular margins and "target" appearance, in absence of echo color doppler signal. Based on the B-mode appearance and the patient's history, the lesions were suspected for metastases. The largest was located between the first and second hepatic segment, with the maximum diameter of 4.64 cm. Subsequently, we performed Real-time Tissue Elastography (HI-RTE), using a high frequency linear probe scanning through a right intercostal space. In the ultrasound software we put a calculation algorithm which provided the use of L/F index. After finding the right branch of the portal vein, without compression we angled the probe until the portal vein disappeared; the patient held his breath during the examination. In the action field, we set the region of interest (ROI) including a superficial lesion, and we saved a clip when the strain graph showed the typical periodic pattern. Finally, we caught the strain histogram for the suspected metastasis and we calculated L/F index. The same analysis was conducted on three other well appreciable superficial lesions and gave similar results to the first.
Discussion: The strain histogram showed an increased tissue stiffness, highlighting the nodule with a blue tint (more rigid) compared to the normal parenchyma, which was highlighted with colors from red to green. L/F index was significantly increased (4.80). The strain ratio between normal and infiltrated parenchyma was significant too. An abdominal CT with contrast medium confirmed the presence of multiple metastatic formations.
In the future, Real-time Tissue Elastography could be useful to validate the presence of neoplastic lesions, particularly in patients with contraindications to ultrasound contrast agents (e.g. heart disease) or X-ray computed tomography contrast agents (e.g. allergy, renal failure). Further studies are needed to confirm the validity of this method.

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Erytrocites cell wall defects correlate with the stage of liver disease

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Background: Anemia is frequently seen in cirrhotic patients, but spur cell anemia and acanthocytosis are particular conditions strictly related to liver impairment, which can cause hemolysis and therefore an increase in bilirubin levels. The cell wall defects which become apparent in those conditions have been related to the deficient synthesis of apolipoprotein A and B and cholesterol in course of liver cirrhosis.
Aim of this work: was to assess frequency and characteristics of these peculiar clinical conditions and their correlations with the stage of liver cirrhosis.
Materials and Methods: 55 patients (22 female and 33 male, median age 66 years, range 42–91) with established liver cirrhosis due to various etiology have been enrolled in the study after informed consent. A peripheral blood smear and full clinical and biochemical assessments were collected. Blood smears were evaluated by three independent examiners and results expressed as a semi quantitative scores for: acanthocytosis, spur cell, anisopoikilocytosis and schizocytosis.

Results: Clinical stage evaluated by Child-Pugh score subdivided patients in: 18 with class A, 13 with class B, 24 with class C. Regarding etiology, 28 patients had immune correlated disease (post viral or autoimmune); 23 were metabolic or alcoholic cirrhosis and 3 had mixed etiologies. Anemia was present in 44 patients (80 %) while erythrocytes cell wall defects were present in 21 out of 55 patients (38 %), of whom 8 (14.5 %) presented with acanthocytic cell in various degree. Statistically significant correlations were present between acanthocytosis and: total or fractionated cholesterol, apolipoproteins A & B, ($p < 0.01$). Spur cell defects correlated with apolipoproteins B ($p < 0.01$); anisopoikilocytosis with total and LDL cholesterol while schizocytosis correlate with total or fractionated cholesterol and apolipoproteins A & B ($p < 0.01$). All cell wall defects correlate with the levels of hemoglobin, bilirubin Child-Pugh score and MELD ($p < 0.01$). No correlation were present related to age, gender or etiology.
Conclusions: Anemia due to impairment of the liver synthesis of lipid protein is frequently present, especially in the milder form of spur cell anemia. These conditions strongly correlate with the stage of liver disease. Blood smear allows a more complete and easy to assess way to performed a correct clinical assessment of patients with liver cirrhosis.

The clinical presentation of potential coeliac disease

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Background: Potential coeliac disease (PCD) is a form of CD characterised by positive endomysial antibodies and a still preserved mucosal architecture of the duodenum, known to evolve into flat CD. However, the evolution into flat CD is not certain and case reports suggest that PCD can last for many years despite a gluten containing diet (GCD). The need for a gluten-free diet (GFD) is therefore questionable and it is not clear whether it is preferable to start a GFD immediately after a diagnosis of PCD or only after an endoscopic follow up showed that frank villous atrophy actually occurred.
Aims: To retrospectively study the history and both the clinical and histological evolution of PCD.
Patients and Methods: We re-evaluated the clinical notes of all the patients affected by PCD attending our clinic between Sept 1999 and Oct 2011.
Results: Between Sept 1999 and Oct 2011, we saw 47 patients with PCD (32 F, mean age 34.9 ± 15.6 years); they were all on a GCD. Symptoms leading to diagnosis were diarrhoea/weight loss (20 pts), anaemia (15 pts), familiarity (11 pts), and associated diseases (20 pts). In 23 of them a GFD was started: 12 pts were suffering from gluten-sensitive gastrointestinal symptoms and/or refused the endoscopic follow up, 5 were suffering from dermatitis herpetiformis, 4 from associated diseases and the last 2 had been found to be affected by flat CD in the past. The remaining 24 patients maintained a GCD and started a follow up: 14 of them underwent at least one histological re-evaluation that showed a flat CD in 5 of them; they were started on a GFD. Four of the 9 patients with a still preserved mucosal architecture decided to stop the follow up and started a GFD; the other 5 patients are still on a GCD. Finally, the 10 patients who have not undergone a follow up biopsy so far are in good clinical condition, despite a GCD.
Conclusions: Patients with PCD can maintain a normal duodenal mucosa for several years and their symptoms can spontaneously improve despite a GCD. These puzzling findings underline the need of further studies.

The epidemiology of potential coeliac disease

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Background: Potential coeliac disease (PCD) is considered to be a rare form of CD characterised by positive endomysial antibodies and a still preserved mucosal architecture of the duodenum despite a gluten-containing diet. Although the prevalence of CD in the general population is around 1/160, the prevalence of PCD is still unknown. Moreover, it is unclear whether this is a prodrome occurring in every patient found to be affected by flat CD or it is a distinct entity that subsequently can evolve into flat CD.
Aims: To study both the prevalence and the clinical features of PCD.
Patients and Methods: We re-evaluated all the patients directly found to be affected by CD in our clinic between Sept 1999 and Oct 2011. To study the clinical features of patients with PCD, patients with flat CD served as controls. For each patient with PCD, two controls, or at least one, matched for sex and date of born were randomly selected. Symptoms, associated diseases, familiarity and laboratory data at diagnosis were compared.
Results: Between Sept 1999 and Oct 2011, 42 patients (29 F) with PCD were diagnosed out of 238 patients with CD (overall prevalence 17.6 %). Age at diagnosis (35.6 ± 14.0 vs. 34.3 ± 13.0 years), prevalence of diarrhoea and/or weight loss (44 vs. 47 %), anaemia or minor symptoms of malabsorption (44 vs. 56 %), associated diseases (47 vs. 41 %), and familiarity for CD (31 vs. 25 %) did not differ between patients with PCD and flat CD.
Conclusions: Prevalence of PCD is higher than expected and cannot considered to be a rare form of CD. Having found no difference at all in age at diagnosis and clinical features between PCD and flat CD suggests that PCD is not a prodrome of CD but it is a separate entity that only subsequently can evolve into flat CD. This is further supported by the recent observation that, compared to flat CD, PCD is characterised by an increased frequency of DQB1*0302 and a reduced frequency of DQB1*02 homozygosity.

Dental enamel defects in coeliac disease: prevalence and correlation with clinical features

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Background: Coeliac disease (CD) is a condition well-known to be characterized by a wide spectrum of clinical manifestations. The gastrointestinal tract is far from being the only affected organ and practically any organ can be affected. Among the others, dental enamel defects and other abnormalities of the teeth and oral cavity were described [1].
Aims: To study the prevalence of enamel defects in adults with CD. To investigate a correlation between the grade of teeth lesion and clinical parameters present at the time of diagnosis of CD.
Patients: Between Oct 2010 and Sept 2011, a dental examination was performed in 54 CD patients (41 F, mean age 37 ± 13 years, mean age at diagnosis 31 ± 14 years). None of them was diagnosed

because of enamel defects; symptoms leading to diagnosis were diarrhoea/weight loss (32 pts), anaemia (19 pts), familiarity (3 pts). At the time of evaluation, they were all on a gluten-free diet. Enamel defects were classified from grade 0 to IV according to Aine [1].
Results: Enamel defects were observed in 46/54 patients (85.2 %): grade I defects were seen in 18 patients (33.3 %) grade II in 16 (29.6 %), grade III in 8 (14.8 %), and grade IV in 4 (7.4 %). We also observed that grade III and IV were more frequent in patients diagnosed with classical rather than non-classical CD (10/32 vs. 2/22). However, this was not statistically significant.
Conclusions: This study confirm that enamel defects are associated to adult CD. The exact mechanism is not clear, but nutritional disturbance like hypocalcaemia during the period of dentition, may play a role. To observe enamel defects is an opportunity to diagnose CD.

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NAFLD and CVD: a possible intriguing connection between metabolic liver impairment and the cardiovascular risk

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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is a pathological condition that from hepatic lipid accumulation can progress to non-alcoholic steatohepatitis (NASH) that, in turn, often associated with necroinflammation and fibrosis and may lead to cirrhosis and hepatocarcinoma (HCC). Since NAFLD is considered the hepatic manifestation of metabolic syndrome, one of the main cardiovascular (CVD) risk, it's crucial to understand its putative role in the onset and progression of CVD. NAFLD increases the prevalence of CVD and NAFLD patients die more frequently for heart pathologies than healthy subjects.
Mitochondrial damages play an important role in NAFLD progression and, moreover, it has been demonstrated the important role and the potential therapeutic implications of oxidative stress pathways in liver and in CVDs. We were interested to investigate the correlation between liver damage, induced by hepatic lipid accumulation, and cardiovascular risk. To this aim we created a mice model of steatosis to evaluate the relationship among markers of inflammation, oxidative stress, mitochondrial damages, lipid metabolism and the degree of liver steatosis related to cardiac and endothelial alterations.
Materials and Methods: C57BL/6J mice were fed with a High Fat Diet (HFD), known to induce liver steatosis and inflammation, whereas mice, used as control, were fed with a Low Fat Diet (LFD). Mice were sacrificed at different time points (3, 6 and 12 months) and their livers and hearts were collected.
All mice underwent routine liver tests. Body mass index, and plasma levels of blood glucose, cholesterol, and triglycerides were measured. PCR Array profiles were performed to study a panel of genes potentially involved in the modulation of lipid metabolism and genes involved in Cardiovascular risk and, finally, genes implicated in inflammation and cellular cycle.
Results: Preliminary data showed a different time in metabolism deregulation and mitochondrial dysfunctions in liver respect to the hearth tissues. Liver displayed an earlier (3 months) induction of genes involved in the control of lipogenesis and glycolysis respect to the hearth alteration highlighted in HFD treated mice (6 months). The panel of genes involved in the modulation of lipid metabolism were: Acacb, the principal orphan nuclear receptors Nr0b2, LXRs, PPARs and their targets such as FASN, Srebf1 (human SREBP1c), IRS2, Fabp4, SIRT1, SIRT3. Genes involved in Cardiovascular risk (LOX-1, Taz, IRS-1, Klf15) and implicated in inflammation and cellular cycle (Bmp4, Cdkn1a, Cdkn1b) displayed a similar behavior.
Conclusions: Our work suggests that the modulation of lipid metabolism in the liver might be used to predict a coming cardiovascular risk.

Regional body composition changes after liver transplantation-effect of insulin-resistance induced by immunosuppressive drugs?

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Background and Aims: Subjects that underwent liver transplantation (OLT) regained a quasi-normal look, normalized liver and kidney function and oral feeding. Unfortunately drugs currently used for immunosuppression can modify some metabolic pathways and share insulin resistance, overt diabetes or dislipidemia. The aim of the study was to evaluate body composition changes in patients undergoing OLT and their possible relationship with therapy.
Methods: Twenty-nine patients (16 males and 13 females; mean age 52.8 years [SD ± 10], range 21–68) submitted to OLT were prospectively enrolled in the study. All patients received tacrolimus and low-doses of steroids for immunosuppression. In all subjects body composition analysis was performed by a new dual-energy x-ray absorptiometry equipment (Lunar iDXA, GE Healthcare) after 1, 3, 6, 9 and 12 months from OLT. Fat mass (FM), non-bone lean mass (LM), bone mineral content (BMC) were assessed in whole-body and regional model (android, gynoid, upper limbs, lower limbs and trunk).
Results: Four out of 29 (13.8 %) subjects showed diabetes before OLT, and 12/29 (41.3 %) had it after surgery. Lean mass significantly increased at 3-months control, then progressively landed down to a plateau after 6-months control (Fraction of lean mass, 1-month: 70.18 [7.83], 12-month: 59.19 [7.62], $\chi^2 = 19.18$; $P = 0.001$). Total and android FM/LM slightly decreased at 3 months, but then rose up with statistically significant differences between 12-month and baseline values (TFM/TLM, 1-month: mean 0.44 [SD 0.16], 12-months: 0.72 [0.25] $\chi^2 = 19.18$; $p = 0.001$; AFM/ALM: 1-month: 0.42 [SD 0.17], 12-months: 0.87 [0.37], $\chi^2 = 22.57$, $p < 0.001$).
Fraction of fat mass [FM % = FM/(FM + LM)] paralleled to FM/LM-ratios, increasing by approximately 35 % from first month to 12 months after transplant (29.8 [7.82] to 40.8 [7.61] kg, $\chi^2 = 19.18$, $p = 0.001$). Subjects with weight gain at 3-months higher than 2 % showed AFM/ALM three times higher than other subjects (Mann–Whitney U test, $Z = -2.193$; $p = 0.032$). Insulin treatment did not significantly affect body composition, while steroid dosage was inversely associated to total and android FM/LM (Spearman's rho $= -0.326$; $p = 0.009$ and -0.472; $p < 0.001$, respectively).
Conclusions: Body composition assessment is essential in the understanding of metabolic-related disorders in OLT subjects. DXA is a valid tool at this aim and expands information emerging from the old skinfolds assessments.
Patients submitted to OLT showed significant changes in their body composition, mainly progressive increase in central distribution of fat, related to the insulin-resistance produced by calcineurin inhibitors and steroids.

Gerontology and Geriatric Medicine

Serum levels of apelin-36 are decreased in elderly hospitalized patients with heart failure

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Introduction: Apelin is an endogenous peptide, ligand for a G-protein-coupled receptor called APJ. Several functions of apelin-APJ system have emerged, the main target of its action appears to be the cardiovascular system: apelin is one of the most potent inotropes known (without causing ventricular hypertrophy), peripheral vasodilator, and is involved in fluid homeostasis, balancing the harmful effects of angiotensin II-AT1 system.
It is known that the apelin-APJ axis is down regulated in chronic heart failure (HF) and seems to be increased with favourable ventricular remodelling. Some studies show that plasma apelin concentrations are decreased in middle-aged patients with HF.
The aim of our study is to investigate the serum levels of apelin-36 in a group of old subjects with HF and to verify the involvement of apelin in the physiopathology of HF in the elderly population.
Materials and Methods: The study population consisted of a group of 30 consecutive patients aged 80 ± 7.8 years hospitalized at the Geriatric Medicine Unit, University Hospital of Messina, with an admitting diagnosis of HF, and 20 healthy control subjects. Serum apelin levels were quantified by enzyme immunoassay (ELISA) in all subjects enrolled in the study. All results were considered significant if p was <0.05.
Results: Baseline characteristics of patients are shown in the table below.

Age, mean ± SD	80 ± 7.8
Male/Female, n.	16/14
NYHA II, n. (%)	10 (33.3)
NYHA III, n. (%)	11 (36.7)
NYHA IV, n. (%)	9 (30 %)
Left Ventricular Ejection Fraction (LVEF), mean value	42.4 ± 12.2
LVEF <40 %, n. (%)	15 (50)
LVEF >40 %, n. (%)	15 (50)
Mini Mental State Examination, mean score ± SD	21.56 ± 4.44
Geriatric Depression Scale, mean score ± SD	7.35 ± 3.6
Number of preserved activities of daily living (ADL)	3.5 ± 2
Number of preserved instrumental activities of daily living (IADL)	3.81 ± 2.21
Haemoglobin (mg/dl)	11.4 ± 2.3
Creatinine (mg/dl)	1.27 ± 0.7
estimated-Glomerular Filtration Rate (ml/min) with CKD-EPI	59.5 ± 22.3
Serum sodium (mmol/l)	137 ± 3.9
Apelin (ng/ml)	0.47 ± 0.21

Mean serum values of apelin-36 in HF patients were 0.47 ± 0.21 and 0.95 ± 0.37 ng/mL in control subjects ($p < 0.0001$). According to NYHA classes mean values were 0.502 ± 0.23 ng/mL in class II, 0.505 ± 0.22 ng/mL in class III, 0.38 ± 0.16 ng/mL in class IV. We did not found differences in apelin levels in subjects with ejection fraction < or >40 %. From univariate analysis direct correlations between apelin levels and ADLs ($p = 0.0008$, $r = 0.61$), IADLs ($p = 0.008$, $r = 0.50$) were observed.
Discussion: Our patients were frail and presented cognitive impairment, depressive symptoms and disability; a direct correlation between apelin values and ADLs and IADLs was observed at univariate analysis. This study confirm that apelin levels are decreased in patients with HF even if elderly and frail; since apelin represents a potential and promising novel therapeutic target for patients with HF, geriatric patients should be considered for future clinical trials.

Duration of post-operative delirium as an independent predictor of 1-year mortality after surgical repair in a population of orthogeriatric patients

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Background and Aim: Delirium is typically considered a transient clinical condition that may complicate the course of many chronic diseases and surgical procedures among frail elderly patients. However, recent studies have suggested that delirium may persist for several hours or even days. Persistent delirium (PerD), as opposed to delirium itself, seems to be an independent predictor of poor clinical and functional outcomes. However, the prognostic implication of PerD remains still unclear. The aim of our study is to assess the prevalence of PerD in a population of elderly patients undergoing hip fracture (HF) surgical repair, and to investigate whether it is an independent predictor of 1-year mortality.
Materials and Methods: We considered 396 patients consecutively discharged after HF surgical repair from the Orthogeriatric Unit (OGU) of San Gerardo University Hospital, during the period March 2007–December 2011. Baseline characteristics, time from admission to surgery, and occurrence of complications were evaluated. The presence of post-operative delirium and its duration were assessed with a retrospective chart-based review method of medical and nursing notes. We calculate a normalized post-operative delirium index (NPDI), ranging from 0 (absence of delirium) to 1 (persistent delirium for all the post-operative phase), according to the formula: duration of incident delirium (days)/length of post-operative stay (days). Statistical analyses were performed with PASW Statistics 18.
Results: Patients were divided in two groups according to the outcome "1-year mortality": alive (group 1, n = 305) and dead at 1-year (group 2, n = 91). Patients in the group 2 were significantly older, more frequently dependent in activities of daily living (ADL) and demented before HF, and carried more comorbid conditions than those in group 1. In addition, they experienced more frequently delay in surgery (>48 h from admission), had higher rates of PerD, and a longer length of stay than their counterparts. We performed a logistic regression analysis, with 1-year mortality as the dependent variable, adjusting for age, gender, and Charlson Comorbidity Index (CCI). The multivariate regression showed that independent predictors of poor outcome were pre-fracture cognitive impairment, a time from admission to surgery longer than 2 days, dependence in ADL, and PerD. In particular, there was a linear relationship between duration of delirium and 1-year mortality, i.e. the longer the duration of delirium, the greater the mortality risk.

Conclusion: PerD is a strong independent predictor of 1-year mortality among elderly patients undergoing HF surgical repair. Therefore, prevention and prompt resolution of delirium are mandatory for physicians and nurse staff in order to reduce mortality among these frail patients.

Table Logistic regression analysis (univariate and multivariate models) of 396 patients from OGU, with 1-year mortality as the dependent variable, adjusting for age, gender, CCI, and drugs

Characteristics	Univariate model			Multivariate model		
	OR	95 % CI	P	OR	95 % CI	P
Pre-fracture cognitive impairment (yes/no)	2.12	1.30–3.48	.003	4.48	1.76–11.17	.002
Time from admission to surgery ≤2 days	Ref.	–	–	Ref.	–	–
Time from admission to surgery >2 days	2.36	1.41–3.96	.001	2.84	1.54–5.23	.001
NPDI = 0	Ref.	–	–	Ref.	–	–
NPDI 0.01–0.25	1.14	0.61–2.13	.675	6.35	2.41–16.66	<.001
NPDI 0.25–0.50	1.89	1.06–3.36	.030	18.26	6.22–53.68	<.001
NPDI >0.50	7.42	4.20–13.10	<.001	36.09	12.45–104.61	<.001
Functional status, ADL 5–6	Ref.	–	–	Ref.	–	–
Functional status, ADL 0–4	4.02	2.21–7.31	<.001	2.57	1.05–6.28	.039

A study on functional decline in depressive older adult. Changes related with depressive symptoms

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A lot of precedent studies has proved that depression in older people is associated with a physical and functional decline.
We want, in this retrospective study, to compare the changes of depression symptoms; particularly if the change of depression scores, or the remission of depressive symptoms, in older person, is associated with a change in autonomy and ability.
Methods: We have chosen a random champion of 100 old people aged about 60, out of 351 patients examined in our geriatric department, during the year 2009–2010.
Geriatric depression scale (GDS) and instrumental and basic activities of daily living (IADL and ADL) and MMSE were measured in all patients in the first visit and checked after 6–10 months.
58 patients were depressed and 48 + 8 were treated with pharmacological therapy and specialized help.
The association of GDS changes score or the conversion to e non depressed status were compared with the changes of ADL and IADL scores.
We found out that 44 patients (78 %) on those who had improved their depressed status, had improved their ability tests too (in the 70 % of cases); 28 were no depressed.
An improvement of GDS score not only in patients with pharmacological therapy, was significantly associated with improvement of ADL and IADL scores.
The 83 %of the other patients with improvement of their GDS score, had an improvement in the basic and instrumental activities.
To conclude, we can assert that in depressed older persons, an improvement of the depression status was associated with a reduction of the functional decline.

Effect of homotaurine in patients with Alzheimer's disease

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Introduction: The progressive accumulation of the Aβ-amyloid plays a central role in the genesis of Alzheimer's disease and it was long understood that Aβ had to be assembled into extracellular amyloid fibrils to exert its cytotoxic effects. This process could be modulated by molecular chaperones which inhibit or accelerate the amyloid formation. The enzyme Acetylcholinesterase (AChE) induces Aβ fibrils formation, forming a stable complex highly neurotoxic. Ensuing structural damage in some brain areas such as the hippocampus, as revealed by magnetic resonance imaging, may be associated with, or even precede, clinical symptoms.
Current therapies for Alzheimer's disease (AD) are symptomatic with limited impact on the disease itself. Treatment that slows or stops disease progression remains an unmet need. Interventions that protect against Aβ-induced neurotoxicity may have therapeutic value for the treatment of AD.
Taurine, 2-aminoethane sulfonic acid, is one of the most abundant free aminoacids in the brain where it may play a role as an osmoregulator, antioxidant, neuromodulator or may control calcium influx. It has been also described that taurine may induce an increase in conductance upon binding to $GABA_A$ receptors. Taurine prevents the neurotoxicity of beta-amyloid peptide and that the neuroprotection is related to the activation of $GABA_A$ receptors.
Homotaurine is a small, orally-administered compound that binds to soluble Aβ and reduces amyloid aggregation and subsequent deposition. **In vitro**, homotaurine provides neuroprotection against Aβ-induced neurotoxicity in neuronal and mouse organotypic hippocampal cultures, and reverses Aβ-induced long-term potentiation (LTP) inhibition in rat hippocampus, in part, through activation of β-aminobutyric acid A (GABA-A) receptors. **In vivo**, homotaurine produced dose-dependent reductions of Aβ in the brain of transgenic mice (hAPP-TgCRND8). Clinical studies showed that homotaurine was safe and tolerable. In mild-to-moderate AD patients homotaurine also reduced Aβ levels in CSF.
The aim of the study was to assess the clinical efficacy, safety, and disease-modification effects of homotaurine in MCI (Mild Cognitive Impairment) and in mild-to-severe Alzheimer's disease (AD).
Matherials and Methods: A total of 66 people aged 65–80 were enrolled: 22 with MCI, 24 with mild cognitive decline, in treatment with AcheI (Acetylcholinesterase inhibitors), 20 with moderate-severe cognitive decline, in treatment with AcheI + Memantine. Patients were divided into two groups: one group (Group I-Homotaurine) in treatment with Homotaurine 50 mg and previous therapy, one group (Group II-Non Homotaurine) with only their previous therapy. All patients were followed for 6 months. A complete neuropsychological examination was conducted at baseline (T0) and 6 month later (T1). Outcomes measures were Mini-Mental State Examination (MMSE), Activities of Daily Living (ADL), Neuropsychiatry Inventory (NPI), Geriatric Depression Scale (GDS).
Results: Statistically, data have proved as the Group I-Homotaurine Group, showed an unchanged cognitive framework: the CDR average score at T0 does not differ significantly from the average score at T1 ($T0 = 1.15 \pm 1.06$; $T1 = 1.3 \pm 1.1$; $p > 0.05$). Instead, the Group II-Non Homotaurine, has showed an advance of a cognitive impairment: this group has recorded a statistically significant increase of the CDR ($T0 = 0.9 \pm 0.3$; $T1 = 1.36 \pm 0.5$; $p < 0.05$).

MMSE showed an average score decrease of 0.23 ± 3.06 unit in Group I-Homotaurine, while, Group II-Non Homotaurine showed a greater score decrease (1.65 ± 2.31 unit).
Moreover GDS revealed an average score decrease of 0.8 ± 2.44 unit in Group I-Homotaurine, while, Group II-Non Homotaurine revealed an average score increase of 1 ± 1.62 unit.
Conclusions: Homotaurine seems to be able to slows the rate of cognitive decline and against depression associated with Alzheimer's disease.

Cognitive performance and mood in patients with hypovitaminosis D: a preliminary study

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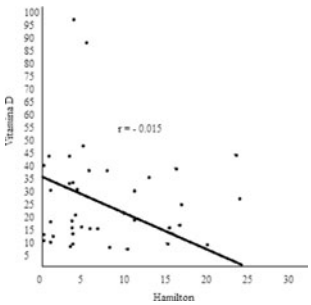
Background: Besides its main role in increasing calcium bowel absorption and promoting bone mineralization, vitamin D exerts relevant pleiotropic effects on several tissues. Low serum levels of vitamin D are correlated with higher risk of infections, cardiovascular diseases, cancer, autoimmune and neurological disorders. Few studies have been conducted in order to investigate whether vitamin D is involved in depressive and cognitive disorders.
Vitamin D may be neuroprotective as it influences neurogenesis, calcium homeostasis, neurotrophic factors expression, detoxification and amyloid-β clearance. Vitamin D receptors (VDR) have been identified in multiple human brain areas, most implicated in the pathophysiology of depression. While recent laboratory-based studies have substantially advanced our understanding of the effects of vitamin D in the brain. However it remains unclear how vitamin D may be involved in mood regulation and with the onset of cognitive impairment. Few epidemiologic studies about vitamin D, cognitive impairment and depression have been conducted, and they produced inconsistent results because of methodological limitations. Current evidence have not definitely demonstrated if vitamin D deficiency could be a risk factor for depression and cognitive impairment or whether vitamin D supplementation therapy may be useful for these conditions.
Aims: This study was aimed to investigate the association between vitamin D levels, depression and cognitive impairment.
Materials and Methods: 35 subjects aged between 50 and 75 and of both genders, were divided into 2 groups according to normal D3 vitaminosis (>30 ng/ml) and D3 hypovitaminosis (<30 ng/ml) and were evaluated according to the presence of depression and cognitive impairment. Vitamin D values were normalised through $\log_{10}$ transformation. Cognitive status was investigated by the administration of Milan Overall Dementia Assessment, a standardized test able to detect subjects with early-stage cognitive impairment. Depressive symptoms were assessed by Hamilton Scale.
Results: In the normo-vitaminic group we found an average $\log_{10}$ vitamin D plasma values of 1.6 ± 0.14 versus 1.14 ± 0.16 of the hypovitaminosis group ($p < 0.0001$). The cognitive evaluation of the normo-vitaminic group (aged 62.7 ± 9, M/F:4/13) showed the following results: Orientation Test: 34.5 ± 1.17; Autonomy Scale: 14.7 ± 0.58; Neuropsychological Tests: 40.9 ± 6; Clock Drawing Test: 3.6 ± 2.4; Hamilton Scale: 7.11 ± 6.2; the following results were found in the hypovitaminosis group (aged 66.6 ± 7, M/F:8/16): Orientation Test: 34.5 ± 0.9; Autonomy Scale: 14.6 ± 0.8; Neuropsychological Tests: 41.4 ± 5; Clock Drawing Test: 4.9 ± 2.3; HamiltonScale: 8.38 ± 7. Continuous variables were compared by Student's *T* test: no differences were found between the two groups nor in gender by χ^2-test.
The bivariate regression analysis showed no correlations between vitamin D values and the score of the cognitive tests. However we observed a linear negative trend between increased Hamilton scale score and lower plasma values of vitamin D, even if there is not statistical significance ($r = -0.015$).
Conclusions: Our study suggests that low vitamin D levels are not associated with the onset of depression and cognitive impairment. The small study sample size could explain the lack of statistical significance of our results.
A clinical study by us is still in progress, in order to investigate whether vitamin D supplementation may improve cognitive functioning and mood in the patients with low plasma vitamin D levels.



Graph of correlation between Hamilton score and plasma levels of vitamin D

Bisphosphonates related osteonecrosis of the jaws in patients affected with osteoporosis: clinical characteristics of a series of 33 cases

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Bisphosphonates (BPs) are currently the chief drugs for the prevention/treatment of osteoporosis; over the past two decades, the therapy with BPs has become the main clinical intervention for postmenopausal osteoporosis, thanks to their huge benefits for accumulation in the skeleton, selective suppression of osteoclast activity and retardation of bone resorption. For osteopenia/osteoporosis, BP oral formulations are based on alendronate, risendronate and ibandronate; intra-muscular one by pamindronate, zoledronic acid, clodronate, and intravenous one by zoledronic acid. Alendronate is the commonest oral BP prescribed to prevent or to treat osteoporosis.
Osteoporosis, being a chronic disease, requires generally long-term administration of efficacious drugs such as the BPs; taking into account the benefits of their prolonged use, compared with their side effects, BPs have been believed to have a safety profile in the treatment of osteoporosis.
Nowadays, the occurrence of an important comorbidity as BPs related osteonecrosis of the jaws (BRONJ), is much less clear in osteoporosis patients treated with BP, differently from cancer subjects who are characterised by a strong evidence of association.
Primary endpoints of this study on 33 BRONJ cases are to observe the clinicopathological features, the local and systemic risk factors, the time of exposure in osteoporotic patients with BRONJ.
Between January 2005 and June 2012, 33 patients with BRONJ assuming BPs for the treatment of osteoporosis and referred to our clinical centre were considered in the study. Other causes of

osteonecrosis (dental or primary bone disease) were excluded by clinical and radiological assessment.
All patients were female (mean age ± standard deviation 71.06 ± 10.32; range 47–84 years).
With respect to the type of BP, 21 (63.6 %) patients used alendronate; 3 (9.1 %) alendronate and clodronate in different time; 2 (6.1) clodronate; 1 (3.0 %) ibandronate; 1 (3.0 %) pamidronate; 3 (9.1 %) risendronate; 2 (6.1) zoledronate.
Twenty seven (81.8 %) patients are treated with BF per os, 2 (6.1 %) with BF per os + i.m.; one case (3.0 %) per i.m route and 3 (9.1 %) per i.v. due to an off label use.
The duration of bisphosphonate therapy at presentation ranged from 2 to 240 months (mean time ± standard deviation 67.87 ± 53.47.
Eleven patients (33.3 %) presented systemic risk factors for BRONJ, singly or in association (e.g. diabetes mellitus, hypertension/hyperlipidemia/hypercholesterolemia, HCV-related liver disease, other cardiac diseases) and 3 (9.1 %) were in therapy with corticosteroids.
Dentoalveolar surgery, such as tooth extraction, was the most common triggering factor for BRONJ (28/33 patients; 84.8 %); two cases occurred in patients with ill-fitting dentures (6.1 %) and other two cases occurred in patients with periodontal chronic diseases and abscess (6.1 %). Finally, for 1 patient no local risk factors for BRONJ was recognized.
The mandible was affected more commonly (17 lesions, 51.5 %) than the maxilla (10 lesions, 30.3 %), and six patients (18.2 %) presented multiple BRONJ events.
The most frequent sign at presentation was bone exposure, frequently associated with pain and suppuration. In eight cases (24.2 %), it was made diagnosis of BRONJ without bone exposure.
Panoramic radiograms and computed tomographic (CT) scans were available for all patients and usually showed mixed radiolucent/radiopaque lesions, consistent with osteonecrosis, alterations of bone architecture with loss of medullar bone, trabeculation, or increased bone density.
In conclusion, our observation confirms the existence of the risk, although low, of BRONJ in osteoporotic patients and that it is important to know how it may be predicted and possibly minimized, especially in presence of known systemic and local-dental risks.

Impact of therapy with DPP-4 inhibitors in the elderly: a prospective cohort study

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Background and Aims: Saxagliptin is an oral antihyperglycemic of the dipeptidyl peptidase-4 (DPP-4) inhibitor class. The aim of this study was to analyze impact of therapy with DPP-4 Inhibitors in elder patients, especially on risk of cognitive impairment (COG) and cerebrovascular events (CER) and survival rate (SURV).
Materials and Methods: DPP-4 inhibitors were investigated in diabetic patients over a period of 60 months using a prospective cohort study with three parallel groups: metformin 500 mg/thrice a day (MET), saxagliptin 100 mg/day plus metformin 500 mg/twice a day (COMB) and saxagliptin 100 mg/day (SAX). A Mini Mental State Examination (MMSE) was measured every 6 months. Cerebrovascular events were assessed by yearly visit and consulting clinical databases.
Result: A total of 430 patients were randomly assigned to the three groups. Saxagliptin and metformin were safe and well tolerated in the daily subministrations. COMB group showed a very significant reduction of incidence of cerebrovascular events (RR 0.56 CI 0.23–0.94) and an improvement in survival rate ($p < 0.05$). No significant differences were seen in cognitive impairment relative risk (RR 0.9 CI 0.5–1.7).
Conclusion: Combined therapy with saxagliptin plus metformin appears to decrease significantly risk of cerebrovascular disease, improving the survival rate. These findings will be useful in patient selection in future clinical trials with sitagliptin in long term studies.

Behavioural disorders and Alzheimer disease

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Background: In literature several studies have analyzed the relationship between Alzheimer disease (AD) and behavioural disorders. However, few authors have investigated the relationship between psychosis and AD.
Objective: Aim of this study was to evaluate the prevalence of risk factors and predictors of psychosis and aggression in an elderly population affected by AD.
Population and Methods: We randomly selected 166 free-living subjects (57 M, 109 F), aged 58–92 years (mean 77.8 years), affected by AD according to DSM-IV. Among those patients 71 subjects (26 M, 45 F) presented behavioural disorders. Cognitive function was evaluated by Mini Mental State Examination (MMSE), Prose Memory test (PMT), Matrix test (MT), Clock Drawing test (CDT), Fluency Verbal test (FVT) and Apraxia Constructive test (ACT). The degree of AD was ascertained with the Global Deterioration Scale. Depression was evaluated with Geriatric Depression Scale (GDS), Cornell Scale for Depression in Dementia (CDS) and Hamilton Depression Rating Scale (HDS). Behavioural disorders were analyzed with Neuropsychiatric Inventory (NPI). Comorbid conditions were recorded.
Results: The scores of MMSE, PMT, CDT, MT, FVT, ACT were significantly lower in the group of patients with behavioural disorders with respect to the unaffected ones ($p < 0.006$, <0.05, <0.0005, <0.05, <0.05, <0.005, respectively). Considering the Global Deterioration Scale it was observed a higher score in subjects with behavioural disorders ($p < 0.05$). Among the patients with behavioural disorders, the prevalence of depression was 87 % and that of insomnia 67.6 % while it was 75 and 9.1 % in those without such disorders ($p < 0.0008$ and $p < 0.0005$, respectively). Then, according to multivariate analysis it was observed always a strong and significant association of behavioural disturbances with insomnia ($p < 0.0005$) and CDT ($p < 0.03$).
Conclusions: According to our results we could predict the onset of behavioural disorders in aged patients with AD through the detection of insomnia and by means of CDT. This could help the physician in the management of elderly with AD, treating insomnia prior to administer antipsychotic drugs.

New insights in management of pain in the elderly

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The amount of persons aged 65 years and over is rising throughout western countries. Prevalence of pain increases with advancing age but observational studies have shown persistent under-treatment of painful conditions in older people. There are specific challenges in managing pain in the elderly. In fact senescence itself causes physiological changes that alter the pharmacokinetics and pharmacodynamics of analgesics, reducing their therapeutic index and intensifying the risk of toxicity and drug interactions. Furthermore, poorly controlled pain in geriatric patients leads to cognitive impairment, depression and mood disturbance and reduces quality of life and activities of daily living. Pain assessment is the basis of pain treatment, since pain that is not identified cannot be treated. Self-report is considered the gold standard for the diagnosis of pain. Visual analogical scale (VAS) still is one of the most commonly used tool in the clinical setting. Other tools developed for assessing non-verbal pain are based on observation of modifications in behavioural and functional spheres, including sleep and physical activity. An example is the Pain Assessment in Advanced Dementia (PAINAD) a scale of five items. Proposed classifications distinguish mild, moderate and severe pain, neuropathic, non-neuropathic and mixed pain, cancer and non-cancer pain, acute, subacute and chronic pain. Chronic pain itself can be divided into three types of pain syndromes: pain for excess of nociceptive inputs, neuropathic pain and dysfunctional pain. Presence of neuropathic pain is essential to be revealed in clinical settings, since it requires an appropriate treatment and does not respond well to common analgesics such as anti-inflammatory drugs. Current treatment guidelines almost universally promote a 'start low and go slow' approach to analgesic dosing in older subjects, above all in the treatment of frail older patients. The WHO's (World Health Organization) three-step guideline to pain management recommends the use of nonopioids for mild to moderate pain (with or without adjuvants) and opioids (with or without nonopioids and adjuvants) for moderate to severe pain. Adjuvant analgesics are drugs developed for purposes other than analgesia but are however useful for alleviating pain. Common examples are antidepressants, anticonvulsants, local anesthetics and muscle relaxants. The most common approach in treatment of pain consists of the employment of regularly given oral analgesics. Paracetamol is a simple analgesic recommended as the drug of choice for the treatment of mild to moderate pain and in association with opioids in more severe pain. Geriatric patients present higher risk of developing toxicity from non steroidal anti-inflammatory drugs (NSAIDs), so the overall safety of these drugs in frail elderlies should be considered. When older patients have obvious contraindications to NSAIDs, clear signs of toxicity from these agents or evidence that pain is no longer controlled with this class of medications, opioids should be prescribed. Several opioids are available. They differ extensively with respect to analgesic potency and adverse effects among the elderly. Adverse reactions with opioids use include nausea, vomiting, constipation, sedation, impaired judgement, impaired psychomotor function and respiratory depression. Cancer is a leading cause of pain. For the management of cancer pain, the WHO stepwise model is widely accepted. Treatments should be multimodal, with attention given to the co-morbidities of pain as well as the global health status of the patient. Musculoskeletal pain in the elderly is frequent and disabling. Conditions causing rheumatic pain, such as osteoarthritis, are, for the most part, not fully curable, so pain control is vital in order to maintain quality of life. Pain management should be adapted to the individual patient and will likely include a combination of both non-pharmacological and pharmacological interventions. Helpful non-pharmacological strategies include massage, topical agents, heat and cold packs, cognitive strategies, education of the patient and attention to healthy life habits (weight control and regular physical activity). Moderate to severe non-cancer pain in older people arises frequently from peripheral vascular disease, ulcers, coronary artery disease and other conditions such as diabetes and stroke. As curative treatment is often impossible, management goal is usually palliative. Since pharmacological management of pain in the elderly is complicated by a lack of clinical investigations conducted in geriatric populations, further research is needed into the properties of analgesics in frail older people to notify rational prescribing in this group.

Urinary stone risk factors as nutritional markers in bedridden inpatients on artificial nutrition

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Introduction: In the last decades the number of old multiple-disease patients is rising. Malnutrition and immobilization are crucial challenges for clinicians because of the relevant fallout on a clinical, social, economical and health care point of view. It is still unclear what are the best scores and/or instrumental/laboratory tests to assess nutritional status in this setting of frail, multiple-disease elderly. In the adult subject the urinary factors of lithogenic risk are considered as an adequate dietetic-metabolic profile and there are data suggesting that both unbalanced diet and bed resting are risk factors for nephrolithiasis. Data in the elderly population, both hospitalized or community-living, are still lacking.
Aim: To assess the urinary factors of lithogenic risk in multiple-disease bedridden patients receiving either parenteral nutrition or tube enteral feeding and to verify their role as nutritional markers.
Materials and Methods: At the Internal Medicine and Critical Subacute Care ward of Parma University Hospital, Italy, 49 patients receiving artificial nutrition (20 on parenteral nutrition (TPN), 14 M, 6 F, average age 80 $\pm$ 6 years; 29 on tube feeding (TF), 16 M, 13 F, average age 81 $\pm$ 9 years), completely bedridden and unable to eat orally, and 19 healthy controls (CTRL) (9 M, 10 F, average age 80 $\pm$ 5 years) were enrolled. All subjects undertook a urine 12-h sample collection for the determination of the complete lithogenic risk profile (volume, pH, creatinine, Na, K, Cl, Ca, P, Mg, uric acid, ammonium, oxalate, sulphate, urea, citrate, supersaturation for calcium oxalate, uric acid and struvite).
Results: Patients receiving artificial nutrition, either on TPN or on TF, showed significantly lower values of many urinary lithogenic risk factors than controls, both promoters and inhibitors (for example Ca 43 $\pm$ 37 vs. 95 $\pm$ 58 mg $p < 0.001$, sulphate 3.8 $\pm$ 2.8 vs. 8.1 $\pm$ 3.7 mM $p < 0.001$, urea 6.8 $\pm$ 4.3 vs. 9 $\pm$ 3.5 g $p = 0.05$, ammonium 7.6 $\pm$ 7 vs. 13.7 $\pm$ 7 mEq $p = 0.002$, citrate 131 $\pm$ 93 vs. 261 $\pm$ 114 mg $p < 0.001$, K 16 $\pm$ 9 vs. 23.3 $\pm$ 9.7 mEq $p = 0.005$). Also creatinuria, corrected for creatininaemia, resulted significantly lower (297 $\pm$ 170 vs. 527 $\pm$ 143 mg $p < 0.001$). These differences were confirmed even in the analysis of controls versus the subgroups parenteral nutrition and enteral nutrition. Supersaturation values resulted normal in all groups. The comparison of urinary profiles in parenteral nutrition and tube feeding did not show differences, except higher pH and lower phosphorus and ammonium and higher volume in the TF group than in the TPN group

(pH 6.8 ± 0.9 vs. 6.2 ± 0.8, p = 0.01; P 191 ± 160 vs. 337 ± 306, p = 0.035, ammonium 5.4 ± 4 vs. 11 ± 9 mEq p = 0.006, volume 731 ± 380 vs. 521 ± 300 ml, p = 0.049).
Conclusions: These data suggest that elderly, frail, bedridden multiple-diagnosis patients receiving artificial nutrition do not show an elevation of their lithogenic risk, showing on the other hand low values of the urinary factors excretion. Urinary dietetic-metabolic parameters appear therefore very useful in the nutritional status assessment also in this particular type of severely malnourished patient.

A retrospective observational parallel-group study about readmission, prognosis and quality of life in patients with dementia on artificial nutrition

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Introduction: Dementia is a disease with a high prevalence in the elderly population. The effects of total enteral nutrition with tube in patients with advanced dementia are controversial. The clinical trend, chronic and progressive, of the disease often makes it difficult to establish clinical course and prognosis.
Aim: To evaluate in patients with dementia discharged from hospital with or without tube feeding: (1) rate of survival, (2) rate of readmission, (3) quality of life (QoL) as perceived by the caregiver.
Materials and Methods: At the Internal Medicine and Critical Subacute Care ward of Parma University Hospital, Italy, 240 patients with dementia were consecutively enrolled within a period of 6 months. 44 patients were excluded because dead during the hospitalization. The remaining 196 (M 68, F 128, age 82 ± 8 years) underwent FAST (Functional Assessment Stages) and CDR (Clinical Dementia Ratio) score calculation and nutritional evaluation. Total enteral nutrition through PEG (percutaneous endoscopic gastrostomy) was administered to patients not able to eat orally for any reason and with a life expectancy greater than 30 days. After about 12 months from the hospital discharge, survival, re-hospitalization and quality of life through a telephonic interview with the caregiver were assessed.
Results: PEG was placed in 59 patients (PEG group), while 137 patients maintained oral nutrition (oral group). Average follow-up was 17 ± 6 months (range 8–26). 38 patients of the PEG group (67 %) died (median of survival 7.5 months) versus 51 patients of the oral group (37 %) (p = 0.0001—Kaplan-Maier survival curve). However, since FAST and CDR scores were significantly worse in the PEG group than in oral group (FAST 7a vs. 6b, p < 0.0001, CDR 3 vs. 2, p = 0.0004), the survival within the two groups did not result statistically different after correcting the mortality rate for the disease severity. The two scores resulted strongly correlated one with another (rho = 0.862, p < 0.0001). Readmission rate was not different among the two groups (29 % in both). In both groups the caregiver defined the QoL of the patients as good in 55 %, acceptable in 25 % and poor in 20 %.
Conclusions: In our population enteral nutrition is associated with a poor prognosis quoad vitam, but this difference is not confirmed after correction for dementia severity. This suggests that perhaps in clinical practice enteral nutrition through tube is undertook too late in the disease course. Finally, there does not seem to be differences in readmission rate and quality of life as perceived by the caregiver.

Sonic hedgehog therapy increases the regenerative capacities of the aging skeletal muscle

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Sonic hedgehog (Shh) is a morphogen regulating crucial mechanisms of muscle development during embryogenesis. We have previously shown that the Shh signaling pathway is post-natally recapitulated after injury and during regeneration of the adult skeletal muscle and plays an important regulatory role on both angiogenesis and myogenesis after skeletal muscle injury. Here, we demonstrate that in aged mice (18-month-old), there is a significant impairment of the upregulation of the Shh pathway that physiologically occurs in the young skeletal muscle after mechanical and toxic injury. We also show that intramuscular therapy with a plasmid encoding the human Shh gene (phShh) increases the regenerative capacities of the aged muscle after injury. Indeed, Shh therapy increases the number of MyoD and Myf-5-positive cells in the site of regeneration, enhances the number of regenerating myofibers, and reduces fibrosis. At the molecular level, phShh treatment increases the upregulation of the prototypical myogenic and angiogenic factors IGF-1 and VEGF. These data demonstrate that Shh increases regeneration after injury in the aged skeletal muscle, thus suggesting that the manipulation of the Shh pathway may be useful for the treatment of muscular diseases in the elderly.

Diagnostic accuracy of bedside abdominal ultrasonography and chest X-ray for pleural effusion in elderly bedridden patients

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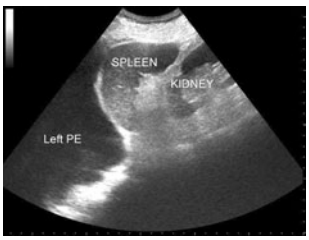
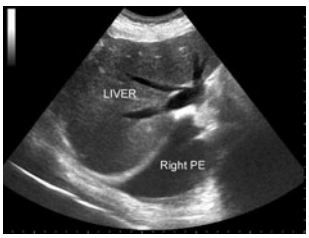
Aim: In hospitalized elderly patients is frequent pleural effusion (PE) from various causes, but is difficult to carry out medical history, physical examination and diagnostic procedures because of delirium, inability of the voluntary control of breathing, supine obligatory. Bedside abdominal ultrasonography (US) can detect the presence of fluid adjacent to the diaphragm. Therefore, we retrospectively evalued the accuracy of US and chest X-ray (CX), performed for various indications, for the diagnosis of PE.
Methods: We reviewed the medical records of patients in our geriatric division for various acute conditions in 2011. Thus, we selected 51 consecutive bedridden patients (mean age 79.4, range 65–100 years, males 29, females 22) submitted to US, CX and subsequently thoracic Computed Tomography (CT) within 3 days. Assuming CT as the gold standard, we evaluated the diagnostic accuracy of US and CX for pleural effusion (102 half-chests).
Results: In the sample examined, the pleural effusion was present on CT in 42/102 half-chest: 16 bilateral, 6 right, 4 left. The results of CX and US are reported in the Table.

Table

	CX	US
POSITIVES	24	37
NEGATIVES	78	65
True positives	22	33
False positives	2	4
True negatives	58	56
False negatives	20	9
TOTAL	102	102
Sensitivity (%)	52.3	78.5
Specificity (%)	96.6	93.3
Positive predictive value	0.91	0.89
Negative predictive value	0.74	0.86
Accuracy (%)	78.4	87.2
Likelihood ratio for positive test result	15.71	11.78
Likelihood ratio for negative test result	0.49	0.22
Pre-test probability (prevalence)	0.41	0.41
Pos*t* test probability (%)	0.91	0.89





Conclusions: Abdominal US, although not aimed to thoracic diseases, has showed a good diagnostic accuracy for PE, higher than the CX. Therefore, US results in a more reliable method to detect the presence of PE in bedridden elderly patients. Based on our results, abdominal US, routinely focused also on the half-chests, may be have better diagnostic accuracy, but this must be evaluated through a prospective study of large sample.

Coffee intake and mild cognitive impairment (MCI): prospective study on a large cohort of elderly Italian subjects

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Mild cognitive impairment (MCI) describes non-demented aged persons with mild memory- or cognitive impairment that may be an early stage of Alzheimer's disease, but that otherwise cannot be accounted for by another specific medical or psychiatric condition. As no effective clinical treatment exists for age-related neurodegenerative disorders, the identification and management of factors potentially influencing the development of MCI may be crucial for prevention of MCI and dementia. In the last years, some cross-sectional and longitudinal studies provided evidence that caffeine use or coffee consumption is associated with better cognitive functioning, suggesting that coffee could have major public health implications. In this study, we investigated the association between coffee consumption and incident MCI in a population-based prospective study of Italian elderly non demented subjects.

We analysed data from 5632 subjects aged 65–84 years who participated in the 1° and 2° survey of the "Italian Longitudinal Study on Aging" (ILSA). MCI was defined as the criteria by Petersen. Coffee consumption was assessed at baseline in 1992 using a self-administered questionnaire and reported as number of cups/day. All the statistical analyses were adjusted for age, gender and other clinical and socio-demographic factors that may contribute to MCI, such as education, CAD, stroke, hypertension, packs of cigarettes/year, MMSE, GDS, tee consumption.

During a mean follow-up of 3.5 years, 105 subjects were diagnosed as having MCI. We found that cognitively normal elderly individuals who modified increasing in time their habits in coffee drinking (>1 cup of coffee/day) had about two times higher rate of MCI compared to those who changed habits reducing in time the coffee intake (<1 cup of coffee/day) and about one and half time higher rate of MCI in comparison with those with constant habits in coffee drinking (just 1 cup of coffee/day). Moreover who habitually never or rarely consumed coffee (less than 1 cup of coffee/day) had a higher rate of incident MCI than those who habitually consumed up to 2 cups of coffee/day. Finally, no significant association was observed between who habitually consumed higher levels of coffee consumption (>2 cups of coffee/day) and incident MCI in comparison with those who never or rarely consumed coffee. The association between coffee consumption and MCI was not modified after adjustment for the other risk factors.

The results of this prospective study suggested that subjects who never or rarely consumed coffee or changed their habits in time increasing coffee intake per day had a higher risk of developing

incident MCI. However, additional prospective studies on coffee consumption and mild cognitive impairment incidence are warranted to confirm our findings.

Self perceived hearing impairment, mild cognitive impairment and frailty in Italian elderly population (ILSA study)

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Recent evidences concerning aging and auditory communication focused on questions about age-related differences in peripheral hearing, central auditory processing, and cognitive processing. However the relationship between peripheral and/or auditory dysfunctions and mild cognitive impairment (MCI) and its role in evolution of the natural history of Alzheimer's disease is still unclear. As well it should be better understood as these phenomena could have their effect on the determinism of frailty in the elderly. However, these conditions are difficult to assess because they are often excluded from the operational criteria for assessing frailty. MCI is at present the most widely used term to indicate non-demented aged persons with no significant disability and a mild memory or cognitive impairment which cannot be explained by any recognized medical or psychiatric condition. Although physical frailty may represent a true risk factor for cognitive impairment, the biological basis of the association remains unknown. It may be that physical frailty, MCI, and AD may share an underlying pathogenesis. For example, several factors that are related to physical frailty are also related to cognitive impairment, including inflammatory markers, diabetes mellitus, congestive heart failure, and stroke. Given that vascular findings are common and have functional consequences in older persons, further investigation of the influence of vascular factors on cognitive-physical relationships is warranted. Vascular risks factors are associated also with central auditory processing skill directly and indirectly by other pathologies typical of elderly people. Furthermore prevalence punctual estimates for amnestic type MCI (aMCI) and frailty (by Fried L. criteria) were evaluated according to the procedures of complex surveys in a large population-based elderly Italian cohort (ILSA). They were about 3 and 7 % respectively. Out of 5632, the ILSA study population, 34 elderly individuals have reported several degrees of hearing impairment. Despite their sensory deficit, 13 individuals performed neuropsychological tests and 2 were affected by aMCI (prevalence rate about 5 times higher than those without a hearing impairment), while 12 individuals were evaluated for frailty according to Fried operationalized criteria and 3 were frail (prevalence rate about 3.5 times higher than those without a hearing impairment). The purpose of the present paper is to emphasize how auditory and cognitive processing, from lower-level sensory processes (peripheral "site-of-lesion"') to higher-level (central "site-of-lesion") cognitive processes, interact possibly conditioning the natural history of dementia; to suggest how new knowledge about age-related changes in audition and cognition could be useful in understanding the relationship between cognitive impairment and frailty in the elderly.

HIV and aging: assessment of cognitive function, nutritional status and functional ability in elderly HIV-positive women

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Background and Aims: The number of older adults living with HIV infection is growing. The combination of aging with HIV may place some older adults at increased risk for a variety of poor health outcomes including cognitive impairment. The aim of this study was to define aging-associated alterations of neuropsychological profile and to evaluate the prevalence of malnutrition and interference in everyday functioning in older HIV-positive women.
Methods: We examined a sample of 20 HIV-positive women aged 65 years or older (mean age = 72.7, SD = 5.08) and 21 HIV-negative women (mean age = 74, SD = 5.26) matched for age (±1 year). Psychometric and functional assessments were carried out using the following scales: Mini Mental State Examination (MMSE), Geriatric Depression Scale (GDS-15), Trail Making Test parts A and B (TMT A and B), two word fluency tests, Rey list, Short Story Test, Clock Drawing Test, Basic Activities of Daily Living (BADL) and Instrumental Activities of Daily Living (IADL). Nutritional status was evaluated using the Mini Nutritional Assessment (MNA) and bioelectrical impedance analysis.
Finally in the HIV-positive group HIV disease severity or treatment differences between patients with and without neurocognitive disorders, including years of HIV infection, AIDS diagnosis, combination antiretroviral therapies (cART) status, nadir and current CD4 counts, HIV RNA in plasma, Veteran Aging Cohort Study (VACS) Index, Central Nervous System penetration-effectiveness (CPE) score and medication adherence, were examined.
Results were expressed as "raw scores" and as "equivalent scores" by relating "raw scores" to reference rank categories.
Results: HIV-positive women evidenced neuropsychological impairment at disproportionately higher levels particularly in the domains of executive functions, psychomotor speed, verbal learning and memory. The HIV-positive group had lower "raw scores" than seronegative one for TMT B ($p = 0.024$), TMT B-A ($p = 0.011$), Clock Drawing Test ($p = 0.043$) and Short Story Test ($p = 0.016$). A larger proportion of HIV seropositive patients had pathological "equivalent scores" than HIV-negative women and the difference was statistically significant for TMT B-A ($p = 0.043$), Phonemic Fluency Test ($p = 0.028$), Rey list ($p = 0.021$) and Short Story Test ($p = 0.02$). Among HIV-positive group lower current CD4 count (<500 cells/μl) appeared as an important marker of depression ($p = 0.02$). A VACS Index higher than 42 was associated with impaired executive functions ($p = 0.04$). TMT A was positively associated with duration of infection in this group ($p = 0.07$). Main effects of medication adherence were observed on verbal memory ($p = 0.055$). HIV-infected women were at heightened risk for malnutrition (MNA; $p = 0.021$). Finally HIV-positive group evidenced lower self-reported rates of declines in BADL ($p = 0.04$) and IADL ($p = 0.0044$).
Conclusion: Elderly HIV-positive women have worse cognitive performances than age-matched women without HIV and display a "subcortical" cognitive profile of executive dysfunction, slowing in

speed of processing, deficient verbal learning and memory. Executive dysfunctions are associated with worse prognostic index in the seropositive group. Cognitive dysfunction without functional repercussion in daily life is the most frequent subtype observed in HIV-positive patients. HIV-positive women are at heightened risk for malnutrition and need to be carefully assessed.

Cognitive impairment and hypercalcemia: a case report

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A 65-year-old man was introduced to our Day Service because of an increase difficulty with walking and because of frequent falls. He was affected by arterial hypertension treated with a sartan and a calcium channel blocker, hypercholesterolemia treated with a statin, adenocarcinoma of the prostate treated with radiotherapy and bicalutamide, cognitive deficit treated with piracetam and renal lithiasis. He was under therapy with acetylsalicylic acid and with a proton-pump inhibitor, too. Physical examination and neurological examination were normal except for a mild bilateral trembling of the hands. The arterial blood pressure was 130/90 mmHg and hearth frequency was 72 beats per minute, rhythmic. His cognitive deficit (memory deficit, disorientation, language disturbance, numerical ability and visuoprassic deficit) began 3 years ago; it was progressive but fluctuating. He was suspicious and frequently failed to recognize familiar persons. We administered mini mental state examination (MMSE: 20/30; MMSE Adjusted for age and years of formal education: 18/30) and clock drawing test (CDT: 2/5). These tests confirmed a moderate cognitive deficit (CD). He was dependent in dressing (Index of Independence in Activities of Daily Living, ADL: 5/6), in managing finances, in shopping and in managing medications (Index of Independence in Instrumental Activities of Daily Living, IADL: 3/5). Laboratory data revealed normal values of folate (2.5 mg/dl), vitamin B12 (481 pg/ml) and thyroid function tests (FT3 3.1 pg/ml; FT4 1.18 ng/dl; TSH 0.60 μUI/ml), but revealed also a chronic kidney failure (creatinine 1.4 mg/dl; urea 29.4 mg/dl), hypercalcemia (12.9 mg/dl) and hypophosphatemia (2.5 mg/dl). Vitamin D-total level (8 ng/ml) and Urine Microscopic Exam were normal. A Nuclear magnetic resonance (NMR) of the brain made before and after administration of contrast agent, showed atheromasia of carotid siphons, a diffuse subcortical ischemic vascular disease, not recent lacunar infarcts of basal ganglia and thalamus and a diffuse cortical and subcortical brain atrophy. A Tc-99 m Total Body Nuclear Bone Scan made 4 months ago showed an increased symmetric uptake of the tracer in both shoulders, in both coxofemoral joints and in some spine metamers, suggesting a probably arthropathy. It did not show any sign of bone metastasis and so we decided to dose paratormone (PTH) level, that was high (409.9 pg/ml). After that, a thyroid ultrasound revealed a not vascularized 3 mm nodule in the left lobe and a large, well encapsulated hypoechoic mass of 10 × 6 mm in the inferior aspect of the right lobe of thyroid; the color Doppler images showed a marked vascularity with an arc of vessels around the lesion. So this lesion could be an autonomous nodule of the thyroid gland or a parathyroid adenoma, but the normal values of thyroid function tests were suggestive for the second hypothesis. A computed tomography (CT) of the neck and mediastinum confirmed the presence of a mass of 11 × 6 mm in the same localization of the ultrasound exam. After that, a Tc-99 m sestamibi parathyroid scan showed a focal area of persistent increased uptake within the inferior aspect of the right thyroid gland, while no abnormal activity was identified elsewhere in the neck or mediastinum; this aspect was compatible with a parathyroid adenoma. So the patient was admitted to the hospital to receive surgical resection of the right inferior parathyroid adenoma. Following surgery, the serum calcium and phosphorus values returned to normal. Two months after surgery, the patient showed an improved cognitive function with a MMSE score of 25/30 and a MMSE score Adjusted for age and years of formal education of 23/30; the clock drawing test was improved (CDT: 4/5), too. He became independent in dressing (ADL: 6/6), while he continued to be dependent in managing finances, shopping and managing medications (IADL: 3/5). He began to recognize familiar persons, too. So, in conclusion, we can affirm that the dementia was secondary to primary hyperparathyroidism.

The impact of cognitive level on disability in an aged population with Alzheimer disease

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Background: Alzheimer disease (AD) is an age-associated illness characterized by a severe and progressive impairment of cognition. Few papers have pointed the impact of AD on disability in elderly.
Objective: The aim of the study was to evaluate the correlation between cognition and disability in aged people with AD and, secondly, the relationship of depression with cognition and disability.
Population and Methods: We randomly selected 166 free-living subjects (57 M, 109 F), aged 58–92 years. Cognitive function was evaluated by Mini Mental State Examination (MMSE), Prose Memory test (PMT), Matrix test (MT), Clock Drawing test (CDT), Fluency Verbal test (FVT) and Apraxia Constructive test (ACT). Depression was evaluated with Geriatric Depression Scale (GDS), Cornell Scale for Depression in Dementia (CDS) and Hamilton Depression Rating Scale (HDS). Disability was studied with index of Activities of Daily Living (ADL), Instrumental Activities of Daily Living score (IADL) and Barthel's Index.
Results: We have demonstrated a significant positive correlation of MMSE, PMT, CDT, ACT, MT and FVT with ADL ($p < 0.0005$, <0.007, <0.0005, <0.0005, <0.0005 and <0.02, respectively). The association of those tests was positive also with IADL ($p < 0.0005$, <0.0005, <0.005, <0.01, <0.0005 and <0.05, respectively). A significant positive correlation of Barthel's Index with MMSE ($p < 0.05$), PMT ($p < 0.005$), ACT ($p < 0.05$) and MT ($p < 0.04$) was observed.
Considering depression and cognition it has been observed that GDS and HDS are negatively associated with MMSE ($p < 0.006$ and $p < 0.05$, respectively), CDT ($p < 0.04$ and $p < 0.05$), MT ($p < 0.03$ and $p < 0.02$), FVT ($p < 0.04$ and $p < 0.007$) and ACT ($p < 0.02$ and $p < 0.005$). GDS is inversely related to PMT ($p < 0.02$), while no correlation was found between HDS and PMT. A significant negative association of CDS with MT ($p < 0.05$) and ACT ($p < 0.05$) was observed.
Finally, IADL was inversely related to GDS ($p < 0.04$).
Conclusions: Our study has shown that, in aged population, the seriousness of Alzheimer dementia is responsible for increasing disability; moreover the degree of depression has impact on AD and disability.

Cardio-metabolic risk factors and inflammation are associated with late-onset depression

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Background and Aims: Several pieces of evidence suggest a close association between late-onset mood disorders and vascular diseases. This association is potentially bidirectional, and the underlying mechanisms are still poorly understood. Cardio-metabolic risk factors clustering in metabolic syndrome (MetS) have been demonstrated to affect mood regardless of the presence of brain vascular lesions. MetS-related chronic micro-inflammation could play a crucial role in the onset of depressive symptoms, as suggested by experimental and clinical investigations. The aims of this study are to investigate the associations between late-onset depressive symptoms, MetS and its single features and inflammation.
Materials and Methods: We excluded subjects with clinical atherosclerotic diseases, dementia, early onset depressive disorders, psychiatric comorbidities, acute or chronic pain, current treatment with antidepressant and anti-inflammatory agents. Physical parameters, standard blood analytes and high-sensitivity C-reactive protein (hsCRP) were assessed. MetS was diagnosed according to NCEP ATP-III criteria. Fifteen-item Geriatric Depression Scale (GDS) was administered to detect depressive symptoms. RESULTS: 105 elderly outpatients (mean age: 69.8 $\pm$ 5.2 years; M/F 44/61) were randomly enrolled. The subjects were divided into three groups (G) according to the GDS score: G1 (GDS: 0–5): without depression; G2 (GDS: 6–10): mild depression; G3 (GDS: 1–15): clinical depression. The comparative analysis across the groups showed that subjects with higher GDS score had higher prevalence of MetS ($p < 0.0001$) and higher prevalence and severity of all MetS traits: central obesity ($p < 0.0001$), blood hypertension ($p = 0.032$), low HDL cholesterol ($p = 0.001$), high triglycerides ($p = 0.006$) and impaired blood glucose ($p = 0.011$). Log_{10}hsCRP values steadily increased across GDS groups ($p < 0.0001$). At the bivariate regression analysis GDS score was correlated with MetS ($r = 0.656$; $p < 0.0001$), waist circumference ($r = 0.345$; $p < 0.0001$), hypertension ($r = 0.200$; $p = 0.020$), HDLc ($r = 0.336$; $p < 0.0001$), fasting blood glucose ($r = 0.531$; $p < 0.0001$), diabetes ($r = 0.236$; $p = 0.008$), log_{10}hsCRP ($r = 0.656$; $p < 0.0001$). At the multivariate analysis, after adjustment for sex, age, education, current smoking, use of anti-platelet, anti-hypertensive, lipid-lowering and anti-diabetic agents, we found that MetS ($B = 4.211$; 95 % CI: 2.440–5.981; $p < 0.0001$), fasting blood glucose ($B = 0.051$; 95 % CI: 0.018–0.084; $p = 0.003$) and log_{10}hsCRP ($B = 7.187$; 95 % CI: 3.987–10.387; $p < 0.0001$) persisted as strong independent predictors of higher GDS score. As shown in the Figure, by dividing log_{10}hsCRP values into tertiles (T), GDS score increased at the upper tertiles, overall when MetS was present. CONCLUSIONS: We found that MetS and hsCRP are independently associated with late onset depressive symptoms. The only single MetS component that predicted higher GDS score was fasting blood glucose, regardless of the presence of diabetes. These results suggest that the number of metabolic abnormalities could exert cumulative effects on mood regulation, in the elderly with low probability of cerebral vascular lesions. These effects are largely enhanced by chronic micro-inflammation.

The use of rivastagmine in behavioural disturbances of post traumatic dementias

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The Dementia Pugilistica (DP) affects about 10-15% of professional boxer and it is associated with a chronic brain injury called "punch drunk syndrome". The DP syndrome consists of extrapyramidal and cerebellar signs and symptoms, associated or not, with cognitive and behavioural abnormalities.
The neuropathological picture discloses a severe frontotemporal dysfunction as a result of diffuse axonal injury which breaks frontal-temporal circuits as well as the cortical and subcortical ones, generally caused by blunt, lacerative brain injuries.
We reported the clinical case of a 78- year-old-patient, ex boxer, affected with arterial hypertension, dyslipidemia with carotid atheromasia, megaloblastic anemia, benign prostatic hyperplasia, a medium degree/extent retinal angiosclerosis. He started as an amateur boxer at the age of 16 becoming a professional one at the age of 21.
The patient came to our attention in our outpatients'clinic because of a symptomatology characterized by verbal aggression, anxiety, irritability, auditory hallucinations, sleep disorders and mnesic gaps. In particular, caregiver related that these symptoms had been getting worse in the last months.
The patient was evaluated with a multidimensional cognitive test of first level that showed a cognitive impairment, especially in those items concerning attention and calculation, registration, recall and inthe ability to perform complex commands (Mini Mental State Examination, roughly 20/30; corrected according to age and schooling = 19,3/30). The patient showed also some dependence in basic life activities (ADL 3/6) and in some instrumental activities (IADL 3/5).
Results: Important neuropsychiatric alterations came out, such as frequent episodes of hallucinations, agitation, aggression, anxiety and insomnia (NPI 72/144, BEHAVE- AD 25). The evaluation of walking and balance highlighted dysmetria and slight postural instability (Tinetti scale 7/28).
A brain RMN revealed enlargement of the 3° and lateral ventricles, cortico-subcortical atrophy and presence of cavum septi pellucidi. A Single Photon Emission Computed Tomography showed mild hypoperfusion of the frontal lobes bilaterally. Basing on these data and considering patient's past we diagnosed a DP.
The most frequently affected areas in patients with traumatic brain injury are the frontal lobes and the hippocampus, more exposed than other brain structures to the trauma effects because of the their close contact with particularly blunt bone protuberances.
The damage of these areas can cause problems in attentional as well as mnesic functions, connectable to the injury of the entorhinal cortex and the hippocampus system, with prevalent involvment of cholinergic pathways and partial saving of dopaminergic and noradrenergic pathways.
The involvment of these areas and of the close limbic system causes, in addition to the alteration of the cognitive functions, BPSD which strongly affected the performance effectiveness of the subject, with prevalent involvment of cholinergic pathways and parttial preservation of dopaminergic and noradrenergic ones. Achei was consequently prescribed: a rivastigmine plaster with a 4,6 mg/die

dosage, brought one month later to 9,5 mg/die, for the proved inhibitory action of butirrilcholinesterase, an enzyme largely present in the limbic system, an area well known for its action in the behaviour control.After three months, we repeated the evaluation that showed a slight improvement of cognitive and behavioral symptoms (NPI 56/144, BHEAVE_AD 18/75). After six months, we observed an additional improvement of BPSD with resolution of hallucinations and increase in MMSE (MMSE 21,3/30; NPI 32/144; BEHAVE-AD 11/75).
Conclusions: This case demonstrates as the use of rivastigmine, also in patients with chronic traumatic brain injury, is useful in the management of behavioral disorders linked to cognitive impairment.

Infective Diseases

Cat scratch disease…when the diagnosis sneaks around

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Generalized lymphadenopathy may be the indicator of infectious, immune and neoplastic diseases. Where a biopsy is needed, the differential diagnosis relies almost exclusively on histology, inevitably overshadowing the anamnesis, clinical, laboratory and instrumental data, in the presumption of the superiority of a "direct" diagnosis rather than an "indirect" diagnosis. We are describing the case of a 17 year old young man with a procedure that led to the diagnosis of "cat scratch disease" mainly through specific serological investigation. The patient complained severe pain and swelling in the right armpit for about a month before our observation. Only mild general weakness was associated. On medical advice he had taken an anti-inflammatory therapy in the previous 2 weeks with remission of painful symptoms but persistence of the swelling. Physical examination showed a bulky, movable lymph node with a tender texture in the right armpit and numerous bilateral small lympho nodes in cervical and inguinal region, movable and painless. Autoantibodies, serology for viruses, bacteria and toxoplasma were negative. Mycobacteria in the urine were absent. The search for IgM anti-Bartonella Henselae was positive at a dilution of 1:1024. Ultrasound exam confirmed a bulky and inhomogeneous lymph node (47 × 20 mm) with increased vascularity. Also it showed numerous oval lymph nodes smaller than 20 mm (18 mm in left laterocervical region and 17 mm in the right inguinal region). To better characterize this lymphadenopathy, a CT-total body was performed that showed enlarged lymph nodes with a diameter of 20 mm in the interaortocaval region, in the root of the mesentery and bilateral iliac region. The presence of disseminated lymphadenopathy associated to a scarcity of clinical manifestations (the patient did not remember any skin manifestations that occurred after contact with cats) imposed the suspicion of lymphoma. However, the laboratory positivity for Bartonella and a history of having played with stray cats the month before, needed a differential diagnosis of Bartonella infection. A histological examination of the armpit lymph node biopsy was fundamental. This one showed a diffuse follicular hyperplasia with confluent follicles similar to "geographical map" characterized by histiocytic predominant component like a "starry sky". Also foci of necrosis with neutrophils, macrophages and epithelioid cells were present. The immunohistochemical study showed a segment B preserved with follicles bcl2 negative, and higher growth fraction in follicles, with preservation of the polarization. Myeloperoxidase was positive in granulocytic component. The search for acid-fast bacilli and the search for mycetes with the Grocott stain were negative. Histological diagnosis was compatible with "cat scratch disease". Therefore, for a week, therapy with azithromycin (500 mg/day orally) was initiated which determined gradual reduction of lymph nodes. After 6 months the patient continues follow up in our clinic with progressive improvement of the clinical condition. In this case, histology, commonly considered diagnostic by itself, would exclude a malignant disease and only a few infectious agents on the basis of specific stains. Supplemented by a thorough history, by serological results (antibody specific to Bartonella) it lead us to a precise diagnosis.

A rare case of tuberculous pericarditis

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Background: Tuberculosis is the most important worldwide cause of pericardial disease; in developing countries with a high prevalence of disease, tuberculous pericarditis is the common form of pericarditis and it is often associated with HIV infection. In industrialized nations, the incidence of tuberculous pericarditis has decreased but it remains a dangerous disease with a high mortality (20–40 %) if untreated. It presents clinically in three forms: pericardial effusion (80 % of cases), constrictive pericarditis (5 % of cases) and effusive-constrictive pericarditis (15 % of cases). The onset may be abrupt, resembling acute idiopathic pericarditis, with weight loss, cough, dyspnoea, chest pain, ankle oedema, fever, tachycardia, anorexia and night sweats. Physical examination usually shows fever, tachycardia, pericardial friction rub, hepatomegaly, ascites, peripheral oedema and weak heart sounds. The X ray shows cardiomegaly, sometimes a pleural effusion. Pulmonary infiltrates or calcification are present rarely. The tuberculin skin test (PPD) may be negative (30 %) for patient's anergy. The definitive diagnosis is based on the demonstration of tubercle bacilli in pericardial fluid or biopsy. However the sensitivity of pericardial biopsy is low and a negative biopsy does not exclude tuberculous pericarditis. PCR in the pericardial fluid has a higher sensitivity but may be prone to contamination and false positive. Indirect methods for diagnosis include evaluation of elevated levels of adenosine deaminase activity (ADA) in pericardial fluid. Alternative tests include pericardial lysozyme and IFN (sensitivity 89 % and specificity 98 %). A response to anti tuberculous drugs also makes the diagnosis probable in those countries with a low prevalence of disease. The treatment is usually an initial four drug regimen: isoniazid (300 mg orally once daily), rifampicin (600 mg once daily), pyrazinamide (15–30 mg/kg per day in a single dose), ethambutol (15–25 mg/kg per day once daily), or streptomycin (20–40 mg/kg intramuscularly once daily). After a regimen of 8 weeks, the patient should be switched to a two drug regimen (isoniazid + rifampicin) to complete a 6 month course of therapy. Corticosteroid therapy has a recommendation class IIa. Pericardiectomy is reserved to patients with constrictive pericarditis after 4–8 weeks of therapy, in association with corticosteroid therapy.
Case Report: A 73-year-old man was admitted with weight loss (15 kg) weakness and anorexia. He had hypertension and hyperuricemia. There was already a pleuric effusion on chest X ray 2 months before the admittance to hospital and a chest TC showed a pericardial effusion as well, with microlinfoadenopaties in mediastinum. On physical examination, he was apyretic and pale. We confirmed pericardial effusion on X ray which showed an enlarged cardiac silhouette. On echocardiography, there was a moderate pericardial

effusion with multiple fibrin strands and bridging towards visceral pericardium with a good cardiac function. Tumoral markers were negative and rheumatologic markers too. He had good renal, hepatic and thyroid function. The ESR was 5 mm/h, leucocyte count was 9130./mm^3, CRP was 0.68 mg/dl and β2 M 2.70 mg/dl (1,8). The PPD was positive. The elevated levels of INF were suggestive for probable diagnosis of tuberculosis (9.91 U/ml with a cut-off of 0.35). HIV was negative. We could so exclude other causes of pericardial effusion and started antituberculous therapy with isoniazid, rifampicin and pyrazinamide. Clinical improvement occurred after the initiation of antituberculosis chemotherapy. The pericardial effusion decreased after therapy.

Discussion: Persistent and recurrent pericardial effusion, weight loss, anorexia, echocardiographic pattern and the dosage of INF suggested tuberculous origin of pericarditis in our patient. A definitive diagnosis of pericardial tuberculosis may be made by a colture or histological demonstration, however it's difficult for the low yield of the bacillus in the pericardial fluid. So we conclude that tuberculosis should be considered as a possibility in many cases of persistent and recurrent pericardial effusion associated with prolonged anorexia and weight loss. Before diagnosis could be certain, it could be necessary to make a presumptive diagnosis and start antituberculous treatment, because cardiac tamponade can occur in acute phase and constrictive pericarditis may develop later.

A re-searched conversion

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We are referred a 59-years-old patient, hypertensive, who is used to smoking 20 cigarettes a day and suffers from Chronic Obstructive Pulmonary Disease (COPD). He is being kept under medical supervision for hyperpyrexia and possible bronchopneumonia.

Physical examination revealed reduced vesicular murmur in the left medial-basal segment, along with dullness on percussion and septic fever (max body temperature 40.7 °C).

Hematochemical tests revealed alteration of the following parameters: WBC 17820/μL, Neutrophils 91.6 %, ferritin 8106 ng/mL, natremia 122 mEq/L, ESR 76, APC 35.80 mg/dL, fibrinogen 896 mg/dL, ***Alpha 1*** 10.4 %, ***Alpha-2*** 22.1 %, SGOT 112 U/L, gamma-glutamyl transpeptidase 166 U/L, arterial blood gas tests within reference range.

Chest radiograph revealed non-homogeneous pulmonary shadow in the left lower lobe apicoposterior segment, as confirmed by CT scan. Empiric antibiotic treatment was performed using macrolides, fluoroquinolones, and semisynthetic penicillins, resulting in a complete remission of fever after the fifth day of treatment, and in a subsequent fever spike on the tenth day, the latter coming to clinical resolution 2 days afterwards.

Subsequently, culture, microbiological, and antibody tests were performed in order to search for microorganisms usually responsible for pneumonia. All tests proved negative, except for reported slightly Legionella pneumophila urine antigen positive, even if negative antibodies had been detected (IgG 9.13 and IgM 4.05, with reference standards >70 and >45 respectively).

Notwithstanding antibodies towards Legionella were initially reported negative, clinical and radiological pictures, hematochemical tests, and the slightly positive urine antigen led us to re-assess the antibody concentration level. Accordingly, 10 days after the first assessment, a new sample was tested in order to search for antibodies towards Legionella in blood serum in order to reveal any possible positive IgG.

IgG seroconversion, which after 10 days revealed a more than four-fold increase in the initial rate, has led us to diagnose legionella pneumophila pneumonia. In conclusion, this report stress the importance of searching for specific antibodies after 7–15 days despite any prior negative-reported test result.

Insidious staphylococcal toxic shock syndrome: a clinical case

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Case Report: A 69 years woman, arrived in the emergency room for dyspnea, pale skin, right leg severe pain, tachycardia (108/min), and hypotension 80/60 mmHg). She is hospitalized in the internal medicine department after blood tests and instrumental emergency (ECG, CT chest and abdomen). In medical history of this patient: diabetes mellitus complicated by neuropathy, severe obesity, autoimmune hemolytic anemia, single kidney for malignancy 20 years ago with chronic renal failure III° K.DOQI. In home therapy for many years with corticosteroids for autoimmune hemolytic anemia, as well as insulin, furosemide, olmesartan, allopurinol. One month before admission, she was admitted for surgical drainage and removal of an abdominal wall abscess. Physical examination evidenced a large cavity deriving from abscess had, many bullous lesions on the right leg and edema of legs. Diagnostic studies performed: serological infective test and blood cultures. Abnormal tests are: G.B. 15.120, N 90 %, HB 10.4, PLT 148000 → 89000, GGT 181, LDH 338, VES: 116, PCR: 42, Creat: 2.1, Urea: 131. Liquid abscess cultures: positive for methicillin-resistant Staphylococcus aureus, EGA: pH 7.35, pO2 56, pCO" 35, lat 4.9. (septic shock for SIRS criteria). TC Total body: lung, kidney, mediastinum, abdominal organs normal for age 'and body shape. Doppler right leg: absence of stenosis or venous thrombosis. The therapy set was vancomycin 750 mg die continuous infusion in 24 h, levofloxacin 500 mg × 2/die, fluconazole 400 mg/die, dexamethasone 4 mg × 2/die, dopamine. The third day After 3 days of hospitalization she had supraventricular tachycardia, with pharmacological cardioversion. After 13 days of progressive improvement and 5 days of clinical stabilization which made it possible to expect a future discharge, the patient presented a new sudden clinical worsening with dyspnea, hypotension and death.

Conclusion: Staphylococcal toxic shock syndrome (**TSS**) is a potentially fatal illness caused by a bacterial toxin. The causative bacteria include Staphylococcus aureus and Streptococcus pyogenes. Symptoms of toxic shock syndrome vary depending on the implied causes. TSS resulting from Staphylococcus aureus infection typically manifests in non healthy individuals with high fever, accompanied by low blood pressure, malaise and confusion, which can rapidly progress to stupor, coma, and multiple organ failure. The characteristic rash, often seen early in the course of illness, look like a sunburn and can involve any region of the body including lips, mouth, eyes, palms and soles. Among patients with septic shock who receive appropriate initial antibiotic treatment, the acquisition of infection within the intensive care unit and severity of illness seems to be the most important determinants of clinical outcome. Logistic-regression analysis identified three variables as independent predictors of mortality: presentation with septic shock, infection with methicillin-resistant S. aureus, and initial inadequate antimicrobial treatment. More than half of patients with SAB have MRSA strains. Presentation with septic shock and inappropriate empirical therapy are generally associated with increased mortality.

This case report teaches to always fear a fresh outbreak of septic shock, even after several days of clinical improvement and especially when, as in the case our patient is necessary to maintain a chronic steroid therapy for a preexisting autoimmune disease.

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Aneurysms in patient with tuberculosis aortitis

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Background: Tuberculous aortitis (TA) is a rare entity that is suggestive of disseminated tuberculosis. It can be associated with aneurysm formation or perforation of adjacent structures in about half of the cases.
Case Report: A 78-year-old-man, with a previous history of tuberculosis, was admitted to our department with loss of weight (over 5 kg in 3 months). He had wright sovraclavear lymphadenopathy and laboratory results showed important inflammatory markers, with Hb 9.8 g/dl, ESR 120 mm/h and PCR 5.7 mg/dl. ANCA antibodies were absent. Mantoux reaction resulted strongly positive. A thoracic and abdomen TC showed a thickening about thoraco-abdominal aorta picking up contrast, compatible with aortitis. The exam also showed the presence of infrarenal aorta and common iliac artery aneurysms of about 4 and 2.2 cm respectively. Serology for HIV and syphilis were non reactive. Even if broncocoltural exams were negative, the patient began therapy with ethambutol (for 2 months), pyrazinamide (for 4 months), isoniazid and rifampin (for 6 months). The therapy was well tolerated and at the end of this period the patient showed a general and laboratory improvement.
Conclusions: Our case suggests the importance of a timely diagnosis of TA and its consequences because an early chemotherapy for disseminated tuberculosis can sometimes avoid surgical treatment of aneurysms.

Atypical presentation of invasive candidiasis

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We report an unusual case of endovascular invasive candidiasis in a 78 years-old man with recent positioning of Bentall-prothesis device, admitted to our hospital for one-week history of foot pain due to peripheral leg embolization and acute hemorrhage as consequence of mycotic aneurysm due to blood isolation of *Candida albicans*.
The patient performed a six-weeks of intravenous caspofungin (50 mg iv daily), associated to Daptomycin (500 mg iv daily) and Rifampicin (600 mg iv daily) and was submitted to artery embolization with resolution of feet pain and upper leg hemorrhage. After 3 weeks, during lifelong suppressive fluconazole therapy, the patient performed a CT-scan that showed an asymptomatic ischemic cerebral area and a trans-esophageal echocardiography showed a new abscess and an aortic valve vegetation. On the basis of the aforementioned a possible therapeutic failure is hypothesized.
Candidemia is the fourth most common cause of nosocomial bloodstream infections in the United States and in much of the developed world. Invasive candidiasis has a significant impact on patient outcome, and the attributable mortality is about the 47 %. *C. albicans* accounts for the 63 % of all cases of candidemia, followed by *C. glabrata* and, in some hospitals, *C. tropicalis*. However, in recent years, non-albicans species have been isolated more frequently and are associated with higher mortality and complication rates than *C. albicans*, including breakthrough candidemia during antifungal therapy.
Candida species are an increasing cause of sepsis among non neutropenic patients receiving intensive care. As the number of devices is escalating, there is an increasing proportion of devices-related infections caused by *Candida spp*; this fungus forms biofilm on the surface of synthetic materials, which facilitates adhesion of the organism to devices and makes them relatively refractory to medical therapy.
In conclusion, *Candida* IE should be classified as an emerging infectious disease, usually involving people with intravascular prosthetic devices, and associated with substantial related morbidity and mortality. The diagnosis of *Candida* phrostetic valve endocarditis (PVE) is difficult and usually delayed, because endocardial vegetations become evident at echocardiography investigation even several months from an initial episode of early postoperative candidemia. Once *Candida* PVE is diagnosed, a combined medical and surgical approach is required for optimal therapy. With the continued expansion of medical and surgical techniques, it is expected that an increasing number of these infections will occur.

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Granulomatosous cystitis: from Sri Lanka to Naples

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In June 2011 a 54 years old man from Sri Lanka was admitted to our department because of a type 2 Mellitus Diabetes in poor glycemic control, alcoholic liver disease and tabagism. Furthermore in the last 7 months he had presented asthenia, weight loss (−10 kg), fever, macroscopic haematuria and strangury and had been treated for cystitis with many cycles of antibiotics, meanly Ciprofloxacin, without any improvement.

The patients was referred to urologists that suspected bladder neoplasia. At admission, he presented hypotension, sinus tachycardia, fever (37.4 °C), muscle hypotrophy, hyperglycemia (230 mg/dl) and high levels of inflammatory markers (ESR > 100; C-RP 3.03 mg/dl; fibrinogen 686 mg/dl). Renal ultrasonography showed right hydronephrosis and polypoid lesion of the bladder, suggestive for neoplasia; pelvic CT and cystoscopy confirmed the ultrasonographic findings.
Unexpectedly, histology of bladder biopsy revealed granulomatosous cystitis, but not neoplastic cells.
NMR and total body CT showed submucosal and muscular thickening of the ureter and bladder, compatible with chronic inflammation and a swelling lymph node in the right paravesical area; urine and blood coltures were repeatedly negative.
Considering the place of origin of the patient and his previous work as seaman, we hypothesised a Schistosome infection and treated the patient with Praziquantel without any improvement.
Subsequently, on the basis of a strongly positive Tubercolin skin test, and a positive Elispot assay, considering risk factors for Tuberculosis (birth-place, smoking and alcohol habits), and despite the severe comorbidities, mainly liver disease, diabetes and risk for neuropathy, in October 2011 the patient was started on specific antituberculosis therapy with Rifampicina, Isoniazide, Pirazinamide and, for the first 2 months, Etambutolo. After 2 weeks of therapy, fever and urinary symptoms disappeared, asthenia decreased and the pathological laboratory data improved.
The interest of this case is that, at the onset, the disease mimicked a bladder's neoplasia that was not confirmed by histology of bladder biopsy. Indeed genitourinary disease is the most common form of extrapulmonary tuberculosis with usual involvement of kidney, but not of ureter and bladder only. Moreover genitourinary tuberculosis develops after a pulmonary primary complex and/or in the contest of a miliary tuberculosis, clinical events not presented by our patient. Microbiologic diagnosis is not easy because tuberculosis mycobacteria can be excreated intermittently; indeed our cultures resulted repeatedly negative. Furthermore the risk of multidrug resistance, due to previous use of other antibiotics, and communication difficulties (the patient did not speak Italian or English) are other relevant factors that make medicine for immigrant a real challenge.
At present, after 8 months of therapy that has been well tolerated, the patient does not present urinary or systemic symptoms and his general conditions have improved significantly. Therefore, using a "ex juvantibus" criterion we can conclude that he has been affected by an atypical form of urinary tuberculosis with granulomatosous phlogosis of the right ureter and bladder.

Who turned off the light? Case report of sudden decrease of visual acuity

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Case Presentation: A 49 years old woman presented an increasing decrease in visual acuity in right eye since 10 days; she was visited in a service of ophthalmology, and a complete ophthalmologic examination was done. There was no abnormalities in left eye; in right eye, in posterior segment was present a deep focal white para-macular infiltrate in the retina, and an associated vitritis with fluffy balls in vitreous body, consistent with an endophthalmitis. The patient was hospitalized, with a probable diagnosis of infective endophthalmitis. An empiric antimicrobial therapy with ceftazidime and piperacillin/tazobactam was started.
In her past medical history there was nothing significant; 3 weeks before the onset of symptoms, she was hospitalized 3 days in a service of urology for a renal colic with evidence of urolithiasis of left ureter, with position of a stent; she presented fever, and a course of 7 days of antibiotic therapy with ciprofloxacin 500 mg bid was done, with complete recovery of symptoms. No coltural research was performed.
In following days after the beginning of antimicrobial therapy, no improvement was observed at fundoscopy; the characteristics of lesions were susceptible for Candida endophthalmitis. An infectious diseases visit was performed, and antifungal therapy with voriconazole was started (400 mg bid the first day, then 200 mg bid); antimicrobial therapy was changed into piperacillin/tazobactam 4.5 g qid and linezolid 600 mg bid.
Sierology for CMV, *Toxoplasma gondii*, *Toxocara canis*, HIV were performed and resulted negative; no increase in ESR and CRP was observed.
A second opinion in a Regional Reference Center of Ophthalmology confirmed the suspicion of Candida endophthalmitis, so antimicrobial therapy was stopped, and intravitreal administration of 5 μg of Amfotericin B was done.
After 10 days of treatment, a mild improvement in fundoscopy examination was observed, with reduction of vitreous body involvement.
Patient continued voriconazole for 3 weeks, then switched to fluconazole 200 mg qd for further 12 weeks. At the end of antifungal therapy, no sign of vitritis and chorioretinitis was present, but visual acuity resulted significantly decreased (3/10) as a consequence of marginal involvement of macula.
Discussion: Endophthalmitis is a rare but well known complication of Candida blood stream infection (BSI), even in non-neutropenic patients. Fundoscopy of Candida endophthalmitis present typical features, that even in absence of coltural confirmation may be suggestive for diagnosis. In the case described, no sign of BSI or other sites of Candida infection has been observed; probably, during the procedure of ureteral stenting, a transient fungemia occurred, and has been responsible of endophthalmitis. Fundoscopic aspect and a good response to systemic antifungal therapy can confirm the diagnosis of Candida endophthalmitis.
In literature, some cases of Candida endophthalmitis after urinary tract infections (UTI) are described. Unfortunately no coltural exam was performed to confirm presence of Candida UTI.
Antifungal therapy may be effective and control adequately endophthalmitis, without recurring to vitrectomy, but drugs with a good penetration in eye must be used; azoles, in particular voriconazole and fluconazole, have pharmacokinetic characteristics ideal for long-course treatment required for candida endophthalmitis.

Sports Medicine

Cardiac arrest in an amateur athlete on the tennis court

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Introduction: Professional sport was tragically marked by numerous sudden deaths during sporting events, but recent statistics show that

84 % of cases occur in amateur athletes. Exercise-related cardiac arrest (CCA) is linked to two factors: a triggering event (hypoxia, lactic acidosis, increased body temperature, electrolyte abnormalities) and a bad not recognized heart, mainly coronary atherosclerosis disease.

Case Report: We managed a case of sudden CCA by ventricular fibrillation (VF) in a 38-year-old male caused by myocardial infarction on the tennis court, followed by post-anoxic coma. Patient was unconscious, Glasgow Coma Score (GCS) was 3 and there was no breathing activity. The ECG monitor showed a VF (Fig. 1). Three shock at 360 J were delivered, continuing CardioPulmonary Resuscitation (CPR) appeared a bradycardia with a progressive reduction of mydriasis (Fig. 2) and a weak carotid pulse became palpable (Fig. 3). Soon the rhythm became sinus, heart rate of 150 b./min, narrow complex (Fig. 4). Patient began to breathe spontaneously, GCS improved to 6, an oxygen saturation of 98 % was achieved with assisted ventilation. In the Emergency room there was a rapid recovery of all cognitive functions with GCS 15, **G**lasgow **O**utcome **S**cale (GOS): 5, good recovery, remaining only mnesic lacunae of the episode. ECG showed an acute inferior infarction.

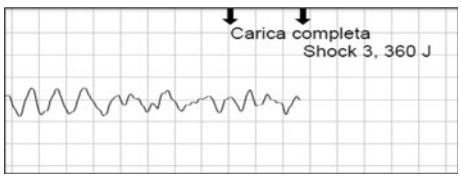

Fig. 1 VF pre-shock

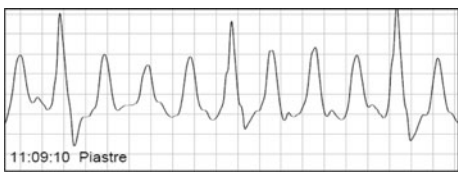

Fig. 2 Post-shock, continuing CPR

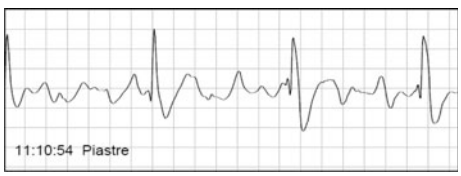

Fig. 3 Bradycardia with palpable pulse

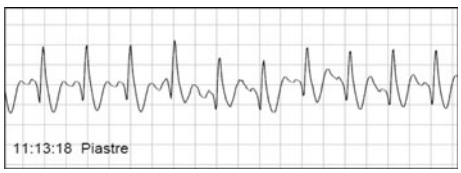

Fig. 4 Sinus rhythm, GCS 6, pupils reactive to light

Discussion: This patient had no history of myocardial ischemia. ACC was caused by an underlying atherosclerotic coronary artery disease. Post-anoxic brain injury is very serious in these cases. We ascribe rapid brain's improvement instead observed in our case, to the strength of "chain of survival", that are actions linking a victim of CCA with survival, and to high quality CPR performed by **A.R.E.S. 118-REGIONE LAZIO** advanced life support (ALS) team. Death in sport both amateur and professional is still a challenge to be overcome: single visit or multiple clinical findings do not yet ensure the tranquility of being able to play without fear that the heart stops without warning.

Conclusions: CCA on the tennis court is a witnessed event: high rate of bystander CPR, speed of rescuers and high quality CPR may increase survival rate and improve neurological outcomes. A rapid cardiac defibrillation could save many lives during sport. A good preventive action is achieved providing the sports facilities of emergency equipment and increasing the presence of qualified staff on the sideline.

Reference

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Importance of hydration in maintaining an correct body water balance during the exercise as prescription program

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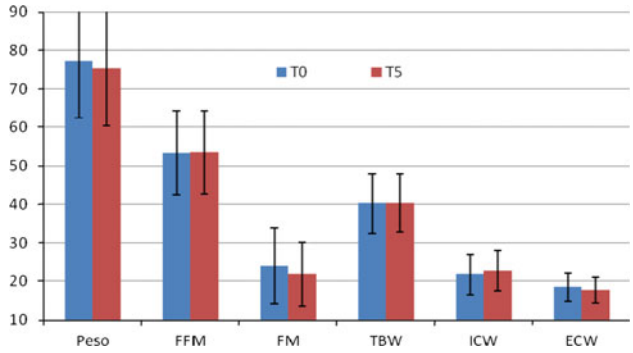
Introduction: Epidemiological studies, clinical and laboratory provided many evidences on the relevance of a correct hydration during a regular Physical Exercise (PE). An incorrect body composition and hydration can also enhance cardiovascular risks. At present few data are available about the hydration and body composition after a short period of PE prescribed as therapy. This study is aimed to investigate this concern in a small group of hypertensive patients following an Exercise as Prescription Program based on the ACSM guidelines.

Methods: Thirteen (8 male and 5 female, aged 58 years) hypertensive patients, were submitted to an individual exercise training at moderate effort (3–4 METS). The Bioimpedance analysis (BIA), as non-invasive method for the body composition and body water analysis, was carried out at the beginning (T0) and after 5 months (T5) of physical exercise. In the same session and following the AHA guidelines an Echocardiographic exam was performed for each subject in order to evaluate the morphological and functional myocardial parameters.

Results: All data are expressed as mean and standard deviation. After 5 months of PE the bioelectrical data (Rz, Xc, PA) have shown an evident increase of Intra Cellular Water (T0: 21.79 $\pm$ 5.29 L, T5: 22.70 $\pm$ 5.28 L) values with a parallel decrease of the Extra Cellular Water (T0: 18.44 $\pm$ 3.60 L, T5: 17.67 $\pm$ 3.33 L) resulting both in none substantial change of the Total Body Water. Similarly there was an evident reduction of body weight (T0: 77.25 $\pm$ 14.80 kg, T5: 75.31 $\pm$ 14.97 kg) due to the Fat Mass values (T0: 23.99 $\pm$ 9.89 kg, T5: 21.86 $\pm$ 8.34 kg). The Echocardiographic systo-diastolic parameter didn't show any statistical differences after 5 months of PE.

Conclusion: The results are suggestive for an early physiological improvement of the water distribution after a short period of regular exercise as prescription therapy inducing an enhancement of water into the active (Intra cellular) compartment. The BIA exam can timely identify this behaviour not evaluable by the anthropometrics parameters.



Blood pressure behavior during exercise in young athletes

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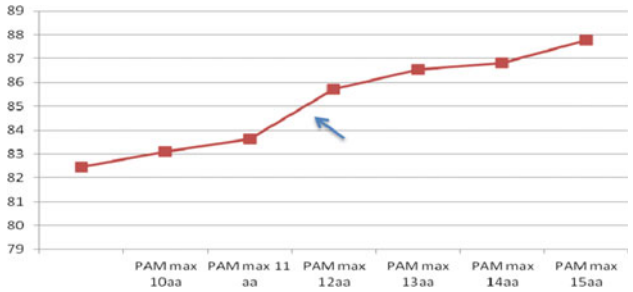
Introduction: The behavior of blood pressure in young is normally related to growth and sexual maturation. This study was aimed to evaluate the blood pressure values in a group of young athletes, at rest and during exercise, in order to evaluate any possible relationship with age and anthropometrics parameters (BMI and BSA)in them.
Materials and Methods: a sample of 300 (100 female and 200 male) young athletes, aged between 9 and 15 years, followed for the eligibility, was investigated. Systolic (SBP) and Diastolic blood pressure (DBP) at rest, at the apex of the effort and at the 4'min of recovery, by sphygmomanometer, were measured in addition to the mean arterial pressure (MAP) and BMI and body surface area.
Results: All data obtained were expressed as mean ± SD. Either BSA and BMI showed a gradual variation without any significant differences for year, with exclusion of the period between 11 and 12 years (17.69 ± 2.25 vs. 18, 79 ± 2.39, $p < 0.05$).The mean SBP at rest increased with age while the DBP showed a progressive increase of values, with the exception of 10 and 11 years. The MAP at rest showed a progressive increase over the years with significant difference between 11 and 12 years (75.81 ± 5.54 vs. 78.22 ± 7.27, $p < 0.05$) and between 14 and 15 years (79.43 ± 6.53 vs. 81.42 ± 6.89, $p < 0.05$). The averaged values of The SBP at the peak of the effort gradually increased every year, while a slight enhancement of the DBP with age, was observed, despite an important decrease of the values between 13 and 15 years. The MAP at the peak of the effort increased over the years with a significant difference between 11 and 12 years (83.62 ± 6.04 vs. 85.71 ± 6.59, $p < 0.05$). At the 4′ of the recovery the SBP showed a progressive increase with age; DBP did not follow the trend of systolic pressure, showing a trend toward a gradual increase between 9 and 13 years and between 14 and 15 years and a decrease between 13 and 14 years. The MAP values increased over the years, with significant enhancement between 12 and 13 years (76.7 ± 5.77 vs. 78.26 ± 5.65, $p < 0.05$) and between 14 and 15 years (78.39 ± 5.6 vs. 79.8 ± 5.62, $p < 0.05$).
Conclusions: In young athletes the is a progressive increase of blood pressure and anthropometric parameters despite not significant, with the exception of the period of 11 and 12 years. The main parameters involved are MAP and SBP, showing a significant increase between 11 and 12 years at rest and at the peak of the effort. On the contrary, the DBP globally increase during the growth, even if any significativity was yearly observed.



A long term sport activity and myocardial performance in breast cancer women

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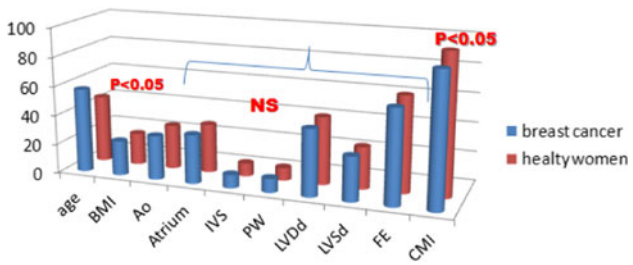
Purpose: The beneficial effects of the exercise as prescription in cancer is well known, however few information are now available on the cardiovascular performance when competitive sport is regularly practiced. The study was aimed to evaluate in a group of breast cancer women (BCW), the effects of dragon boat sport on the myocardial performance during a 4 years follow up study.
Methods: Since 2006 to 2010, 1 year after the diagnosis of breast cancer, a group of 30 regularly trained(Dragon- Boat) women, without metastasis, has been followed at Sport Medicine Center in Florence, Italy. They were yearly submitted to a maximal cardiopulmonary test and to an 2D echocardiographic exam evaluating morphological and functional cardiac parameters in addition to Heart Rate (HR) and Blood Pressure (BP) values measured at rest and at the end of the effort. All data were compared (T-Student Test) to a group of competitive healthy women (HW).
Results: At the end of the 4 follow-up years all the echo parameters were within the normal range in both groups. (Fig 1) Despite CMi and BMI were significantly higher in HW than in BCW, the EF resulted to be similar. After 4 years of training in BC group the HR at rest was lower (78.12 ± 13) than at the beginning (80.7 ± 11.7) of the study. Systolic and Diastolic BP were comparable to the healthy athletes normal values.
Conclusions: The results obtained are suggestive for a beneficial effect of sports activity in breast cancer with an excellent exercise tolerance. A long term competitive sport activity does not seem to have any negative impact on the myocardial performance in them.



Cardiac arrest in an asymptomatic professional volleyball player

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A professional volleyball player come to our Sports Medicine Division to perform for the first time the pre-participation screening for competitive sport eligibility, non mandatory in his homeland. He refers to be healthy, completely asymptomatic, and denies previous syncopal episodes or palpitations, particularly during sports activities. In addition, he also denies a family history of sudden death or cardiomyopathies. The release of the sport eligibility requires: spirometry, urine test (both normal) and a maximal cardiovascular test. This test was interrupted for muscular exhaustion after 8 min at a maximal heart rate of 179 bpm, without any cardiovascular symptom. During the test, a normal blood pressure response, no ventricular repolarization abnormalities or arrhythmias, were also observed. However, in the recovery phase of the test, we detected some ventricular ectopic beats (VEB), isolated, with a right bundle branch block morphology and superior axis. Considering these findings, to complete the diagnostic process, a color doppler echocardiography was requested, while a 24-h ECG was positioned at the end of the visit.
In the same afternoon, during the warming up with his team, after a few minutes of low intensity running, the patient became unconscious and fell down. A CPR was immediately performed by the team's physiotherapist while was called the emergency. The ambulance came in 18 min, and ALS procedures were started. The finding of a VF, allowed to perform three defibrillations until the re-establishment of sinus rhythm, which was associated with the appearance of normal breathing and pulse. Further, epinephrine (2 mg) and atropine (1 mg) were administered, and the athlete, still unconscious, was intubated.
In the Emergency Department (ED), the athlete arrived unconscious, intubated, in spontaneous breathing, BP 130/80, HR 120 bpm (no ECG repolarization abnormalities), Glasgow Coma Score 3. Midazolam and amiodarone were administered, then the patient was quickly transferred in the Cardiac Intensive Care Unit. During the hospitalization, telemetry ECG reported only the presence of isolated monomorphic VEB. Considering the characteristics of the case presentation the main diagnostic hypotheses were: myocarditis, a heart attack in normal coronary arteries, anomalous origin of coronary arteries, arrhythmogenic right ventricular dysplasia (ARVC), hypertrophic cardiomyopathy, a cardiac channelopathy.
To clarify and restrict the field of diagnostic hypotheses, all necessary investigations were performed. Both blood tests in the ED and those performed later showed a troponin peak of 9.9 μg/l with slight rise of inflammatory markers, CK-MB, AST and ALT. All these indicators showed a quick normalization. The toxicological screening and serology for viruses associated with myocarditis were negative. The echocardiography showed an important "akinesis of the apical-lateral segment and middle segments of the lateral wall; left ventricle moderately dilated with systolic function at lower limits (EDV 89 ml/m, EF 52 %), mild mitral valve prolapse". Cardiac MRI showed "normal biventricular size and function, no signs of myocardial edema, no fibroadipose infiltration, marked thinning and akinesis of the myocardial wall in apical region and adjacent areas. After contrast (gadolinium), apical left ventricular late enhancement extended to adjacent areas of the anterior wall and septum, which appeared very thinned". Once excluded myocarditis, ARVC and the main cardiomyopathies, to complete the diagnostic process a cardiac catheterization with endomyocardial biopsy and coronary angiography was carried out. The first evaluation demonstrated "biventricular dilatation with moderate depression of systolic function, angiographically normal coronary arteries", while histology was compatible with myocardial ischemia–reperfusion damage. Coronary angio-CT showed no abnormality. Hence, despite the large number of instrumental evaluation, a clear diagnosis was not reached, and the patient was discharged after the positioning of an ICD, with the probable diagnosis of "cardiac arrest caused by a VF in professional athlete. Congenital Aneurysm (?) of the left ventricle apex". The Italian legislation for competitive sport does not allow the issue of sport eligibility in athletes with ICDs. For this reason, the athlete returned to his homeland, where, once repositioned the ICD in abdomen, was able to restart playing professionally. At present, the athlete is asymptomatic and the ICD never discharged.

Water-versus land-based exercise in elderly subjects: effects on dynamic balance, physical performance and body composition

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Background: The development and progression of sarcopenia is a complex and multi-factorial process. A growing body of evidence indicates that physical activity in elderly can slow the loss of skeletal muscle and function. Among exercise modalities, water-based protocols are suggested for subjects in whom a lower joint stress is recommended, however, limited data are available about their actual effects in maintaining muscle mass and physical fitness. The novelty of this paper consists in the comparison of two physical activity protocols, training at the same rate of perceived exertion: a group performing a physical activity protocol in thermal water versus a land-based exercise group. In addition, advanced techniques of body composition assessment were also performed such as dual-energy X-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT).
Objective: To determine the effect on physical function and body composition of a 24-week structured physical activity protocol, carried out in thermal water and on land in a group of healthy elderly.
Methods: Fifty-nine subjects (29 male, 30 female; age 71.2 ± 5.4 years) were recruited and randomly allocated among three groups: Aquatic Group (AG), Land Group (LG) and Control Group (CG). During a 6-month period, subjects of the first two groups followed a twice-a-week exercise intervention, with each session lasting 1 h. Exercise intensity was monitored using Borg's Scale (RPE): all activities were performed on a range between 13 and 16 RPE, quantified as "somewhat hard" and "hard" as perceived effort.
Results: Knee-extension strength appeared maintained in AG and LG. Grip strength increased in LG by 26.1 %. Back Scratch test revealed a significant improvement in AG (+25.8 %), while Sit & Reach test improved in all groups. Timed Up & Go test was reduced in AG (−19.3 %) and LG (−12.6 %). Finally, data obtained from DXA and pQTC demonstrated that AG reduced total fat mass by 4 % and dominant forearm fat by 9.16 %; in addition, calf muscle density increased by 1.8 %.
Conclusion: Both water- and land-based activities, performed at the same rate of perceived exertion, were beneficial in maintaining strength and improving lower-body flexibility. Moreover, aquatic exercise appeared a better activity to increase upper-body flexibility, dynamic balance and promote weight loss. Exercise in thermal swimming pools, monitoring RPE, should be considered a useful tool to enhance physical performance and body composition in healthy elderly.

Crucial role of catalase in redox homeostasis of endothelial cells treated with sera from athletes conducting moderate or strenuous aerobic exercise

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The balance between production of reactive oxygen species (ROS) and the activation of antioxidant defense systems is important for human physiology and to control cellular homeostasis. The ROS giovano an important role in the processes of signaling, but their excessive production generates oxidative stress, which, in turn, can cause damage to cellular constituents, such as DNA, proteins and lipids, especially when it occurs in the presence of reduced activity antioxidant enzyme. We have previously shown that aerobic exercise has beneficial effects on tissue and cellular homeostasis in humans, in particular, that different types of exercise induce different molecular effects and that aerobic exercise is the best protocol compared to all'anaerobico and mixed. It is well known that even regular exercise reduces oxidative stress, intense physical activity can produce opposite effects. A vigorous exercise can in fact be associated with accumulation of free radicals and result in clinical conditions such as overtraining syndrome and chronic fatigue syndrome, which affect both the athletes that the general population.

Currently, have not been fully studied the effects of different operating loads on markers of oxidative stress and the response of human cells to different volumes of exercise.

Therefore, in this study, we tested the hypothesis that different workloads of an aerobic exercise program could undermine the beneficial effects of exercise, comparing the same type of athletes practicing sports but at different volumes.

The study has provided a first phase in which they were carried out assays of markers oxidants and antioxidants on the sera of two groups of triathletes trained at different laden work (triathletes "moderate" and "vigorous") and a phase in vitro in which a line of human endothelial cells, and not exposed to oxidative stress, have been conditioned with the serum of the two groups of athletes.

Although no differences were observed in functional and hemodynamic parameters between the two groups, significant differences were found in some oxidative stress markers in their serum.

In particular, TBARS and the activity of SOD was similar in both groups, but the moderate triathletes showed higher serum levels of NO and lower catalase activity than the Triathletes vigorous. The endothelial cells conditioned with the serum of the moderate triathletes (mT-ECs) showed, in addition, a greater survival and proliferation, and less senescence, endothelial cells treated with the serum of triathletes vigorous (ST-ECs), both before and after induction of oxidative stress (H2O2). These effects were dependent on catalase, as demonstrated by inhibition of the enzymatic activity by the 3-amino-1,2,4-triazole (ATZ). After induction of oxidative stress the activity of SIRT1, a key regulator of the response to oxidative stress was significantly increased in mT-ECs but not in the sT-ECs. In addition, the mT-ECs requiring less catalase activity as compared to sTECs to counteract the effects of an equal amount of TBARS after administration of H2O2.

This study demonstrates that the beneficial effects associated with aerobic exercise are deleted when the exercise is performed at higher workloads. Furthermore, we suggest that the activity of serum catalase, might be a good indicator of oxidative stress, and as such can be a valuable tool to supervise the changes in the volume of exercise to avoid the overtraining syndrome, and in understanding the molecular mechanisms involved in determining the effectiveness of exercise in humans.

Resting right ventricle performance assessment in young athletes: a comparison between 3D and 2D echocardiographic study

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Introduction: Right Ventricle (RV) ejection fraction (EF) of young athletes, where the onset of the "athletes heart" is not yet recognizable, is currently assessed by 2D-RV area change. The role of a 3D-RV function assessment is not well investigated in these subjects. The study aims to analyze RV function in young athletes from different kind of sports by these two methods. Methods: 25 young trained athletes (20 soccers, 5 basketball) aged 20 $\pm$ 3 years matched with 20 sedentary controls, were studied by 2D and 3D-RV methods (Image Arena, Tomtec) measuring either RV diastolic (RVDV) and systolic (RVSV) volumes, or EF. Data were compared by ANOVA test.
Results: All the EF, RVDV and RVSV values resulted within the normal range. However 3D-RV volumes were slightly higher in athletes (RVDV: 106.14 $\pm$ 30.3 ml; RVSV: 50.74 $\pm$ 15.25 ml) than in sedentary (88.0 $\pm$ 41.36 ml; 40.67 $\pm$ 23.96 ml). On the contrary the 2D volumes resulted to be lower in athletes, even if not significantly, (RVDV: 43.40 $\pm$ 13.11; RVSV: 21.13 $\pm$ 6.5) than in sedentary (45.33 $\pm$ 14.05 ml; vs. 22.0 $\pm$ 7.8 ml). The EF values, by the two methods, were slightly but not significantly lower in athletes (3D-RV: 52.10 $\pm$ 6.4;2D-AC: 50.865 $\pm$ 6.5) than in sedentary(3D RV:55.61 $\pm$ 7.4 ml; 2D AC: 52.0 $\pm$ 4.0 ml). Significant differences were on the contrary found comparing 3D-RV and 2D-AC volumes within each group (RVDV: $p = .001$ for athletes and $p < .001$ for controls, RVSV: $p < .04$ for athletes and $p < .001$ for controls) None significant difference for the EF was found. Conclusions: Despite the normal range of RV chamber values is currently unknown in case of young athletes, the results support the hypothesis that 2D and 3D methods cannot be considered completely overlapped. The higher values found by 3D are suggestive for a more accurate analysis than 2D.

Obesity and related diseases: the paradigm of inactivity and physical exercise

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The definition of obesity has remained the same over the years: an excess of adipose tissue in the body; but the condition which defines the parameters of obesity has undergone numerous changes rather restrictive (i.e. the "normal" body weight or waist circumference), given the consequences that obesity has on global health.

The adipose tissue, initially considered as a passive container of fat, has become the active protagonist of a series of clinical conditions pre-pathological or frankly pathological (metabolic syndrome to type 2 diabetes, endothelial dysfunction to coronary artery disease) getting in the inflammation and the cytokine system their "primum movens".

Enzymatic activities responsible for the maintenance or the imbalance of body weight (non-exercise activity thermogenesis or NEAT), were recently discovered: the NEAT explains the metabolic needs other than exercise, because it is the energy expended for everything that is not sleeping, nor moving large muscle groups: for example NEAT include the act of writing, of typing, blinking, or just keep your posture upright and chew. Thus NEAT (that teleologically increases with overfeeding and decreases with underfeeding) can explain the energy requirements needed by a person who is not totally resting, doing justice to those who have always maintained their fat by eating very little, and still the envy for who eats a lot remaining thin, even without practicing any exercise.

The purpose of this review is also to examine the role of sedentary behaviors (particularly the long-sitting) on mortality, cardiovascular disease, type 2 diabetes, the metabolic syndrome and obesity. Recent epidemiological studies strongly suggest that the time spent sitting can have a significant direct relationship with each of those medical concerns. There is need for further studies to distinguish between the effects of molecular, physiological and clinical effects of sitting (inactivity physiology) from the effect of structured physical activity (exercise physiology). It was found that any kind of short but frequent muscle contractions during the day may be needed to avoid short-circuit of unhealthy molecular signals, causing metabolic diseases. One of the first series of controlled studies is on the cellular regulation of lipoprotein lipase (LPL) in skeletal muscle; in these studies LPL raised its levels in low-intensity, intermittent activities, during all the days of the week. Experimentally, reducing time for deambulation had a much greater negative effect on the regulation of LPL, compared to the positive effect of adding vigorous exercise three times during the week.

Other studies on inactivity physiology are beginning to raise a new problem, of great importance for public health: people who do not practice any exercise could become even more metabolically unfit in the coming years, if they will limit the practice of spontaneous physical activity intermittently during the day. Thus, a terrible worry for the future is the growing numbers of people unaware of insidious danger to be sitting too long, and not using their benefits to maintain muscle intermittent activity throughout the day. This global trend is likely to continue, given the increasing availability of personal computers, TV, automation in the household, transport and any other future inventions.

In summary, the most powerful mechanism to eliminate the specific risk factors of metabolic diseases is achieved by maintaining a high volume of daily intermittent low intensity activities (posture and gait), besides the usual guidelines that promote the well-documented 150 min/week of moderate physical activity during leisure time. The new public health policy should rather limit the time of sitting (such as a prescription medicine) and advise the most forms of intermittent muscle activity. Only an agreement between the family medicine, occupational medicine and sports medicine will help the solution of this problem in the contemporary society.

Effects of agonistic physical activity on the activation of Wnt/β-catenin signaling

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Introduction: The beneficial effects of physical activity on bone seem to be mediated by osteocytes, that are the main source of sclerostin, an inhibitor of Wnt/β-catenin signaling and also a source of RANKL.

Objectives: The aim of our study was to evaluate Wnt/β-catenin signaling, the OPG/RANKL system and bone turnover markers in a group of sportsmen.

Methods: Fifteen soccer players from the Italian Serie D league were studied and compared with an equal number of sex- and age-matched control subjects. In September at the beginning of the season, we measured serum concentrations of: calcium, phosphorus, creatinine, 25-OH vitamin D (25OHD), parathyroid hormone (PTH), bone alkaline phosphatase (B-ALP), carboxy-terminal telopeptide of type I collagen (CTX), osteoprotegerin (OPG), RANKL, Dkk-1, sclerostin and β-catenin. The dosages were repeated, solely for the group of footballers, after 3 months. In all subjects, bone status was assessed by QUS measurements of the right calcaneus using the Achilles Ultrasound Express device, a dry system using a coupling ultrasound gel, that provides the Stiffness Index.

Results: The sportsmen had significantly higher levels of 25OHD, creatinine and Stiffness index. There were no significant differences between groups in serum levels of calcium, phosphorus, PTH, sclerostin, Dkk-1, β-catenin, OPG, B-ALP and CTX, whereas levels of RANKL were higher in the sportsmen than controls. Moreover after 3 months of sporting activity we observed a significant reduction of sclerostin levels and an increase in β-catenin and B-ALP (Table 1).

Table 1 Biochemical parameters at baseline and after 3 months in the sportsmen group

	Baseline	After 3 months	p
Sclerostin (pmol/l)	52.2 ± 9.9	45.6 ± 8.9	<0.05
Beta-catenin (pg/ml)	4.74 ± 1.27	5.76 ± 1.18	<0.05
DKK-1 (pmol/l)	8.06 ± 1.87	8.21 ± 3.70	ns
OPG (pmol/l)	1.86 ± 0.41	1.87 ± 0.95	ns
RANKL (pmol/l)	1.002 ± 0.693	0.986 ± 0.591	ns
B-ALP (ng/ml)	14.47 ± 6.64	22.48 ± 12.81	<0.05
CTX (ng/ml)	0.697 ± 0.127	0.711 ± 0.313	ns

Data are expressed as mean ± SD. ns: not significant

Conclusions: This is the first study to evaluate OPG/RANKL system and Wnt/β-catenin signaling in a group of sportsmen during their sports season. Even if it is necessary to increase the sample size, our data could contribute to a better understanding of the crucial role of osteocytes in response to mechanical loading.

Exercise might improve cardiovascular autonomic regulation in adolescents with type 1 diabetes

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Introduction: Type 1 diabetes represents a recognized risk factor for total and cardiovascular mortality largely through complications stemming from early atherosclerosis and changes impairing endothelial function; on average diagnosis occurs in young children, therefore allowing more time for the occurrence of complications. Diabetes complications are beneficially affected by modern therapeutic regimes aiming at reducing glucose variability and HbA1c levels by either multiple insulin injections or insulin pump. The therapeutic aim is to maintain an optimal glycemic profile minimizing glycemic oscillations and preventing complications but even with the most intense therapies it

is in real life rare to obtain levels of Hb1Ac better than about 8 %, way above the normal range. The addition of a moderate exercise program may be of particular interest because it has the recognized capacity to improve insulin sensitivity, thus representing a potentially interesting component of diabetes treatment without the risks of glycemic instability associated with intense exercise.
Regarding autonomic neuropathy (the presence of which is frequently overlooked although it may increase the mortality risk up to threefold) we recently reported that in a population of children and adolescents with type 1 diabetes, in spite of optimal therapeutic regimen and in absence of clinical signs of complications, early alterations of autonomic regulation (i.e. a reduction of baroreflex gain and an increase of the frequency component of systolic arterial pressure oscillations) were present and they appeared to worsen over time in spite of maintained optimal insulin therapy (Hypertension 2009;54:987–994).
Objective: Considering that adolescence is a critical age for the maintenance of spontaneous physical activity with a large dropout rate and that consequently changes in exercise routines might have relevance in treatment of adolescents with type 1 diabetes mellitus, we sought to assess whether modifications to weekly exercise habits might occur in these patients and if such variations would be accompanied by alterations in autonomic profile.
Methods: In this observational study we examined 77 patients (age 15.0 $\pm$ 0.6 years) who in addition to a tailored optimal insulin treatment were invited to perform at least 1 h a day of moderate, aerobic exercise, as suggested by recent guidelines. Patients were studied at baseline (T0) and after 15.8 $\pm$ 0.7 months (T1). They were divided into three subgroups according to increased, unchanged, and diminished total estimated weekly METs (METabolic equivalents) between T0 and T1. Autonomic profile was evaluated by assessing spontaneous baroreflex gain and low frequency oscillation in arterial pressure using spectral analysis of RR interval and SAP (Systolic Arterial Pressure) time series.
Results: Insulin therapy and biochemical data were similar among the 3 groups at T0 and T1 while BMI (Body Mass Index) standard deviation score was slightly reduced ($p < 0.04$) and markers of autonomic performance were improved (alpha index, from 17 $\pm$ 1 to 20 $\pm$ 2 ms/mmHg, $p < 0.002$) in the group who increased the amount of exercise (from 1627 $\pm$ 250 to 3582 $\pm$ 448 METs/min/week, $p \ll 0.001$). Furthermore the change in total weekly METs significantly correlates with changes of key indices of autonomic regulation.
Conclusions: The potential capacity of relatively modest increments of spontaneous leisure physical activity to reduce signs of autonomic dysregulation in young patients with type 1 diabetes devoid of clinical signs of complications seems supported by this observational investigation. Extrapolating from our findings we may hypothesize that the combination of autonomic evaluation with standardized noninvasive techniques and careful planning of exercise opportunities might help reduce the incidence of a severe complication like cardiac autonomic neuropathy, which is frequently overlooked until symptoms emerge from subclinical levels.
We conclude suggesting that a more formal test of the introduction of moderate loads of exercise as an adjunct to type 1 diabetes therapy in adolescents may be warranted. Potentially beneficial autonomic effects could be evaluated with analysis of RR interval and SAP variability that may be appraised as a component of the diagnostic portfolio of the modern treatment of type 1 diabetes.

Carotid intima-media thickness in master athletes

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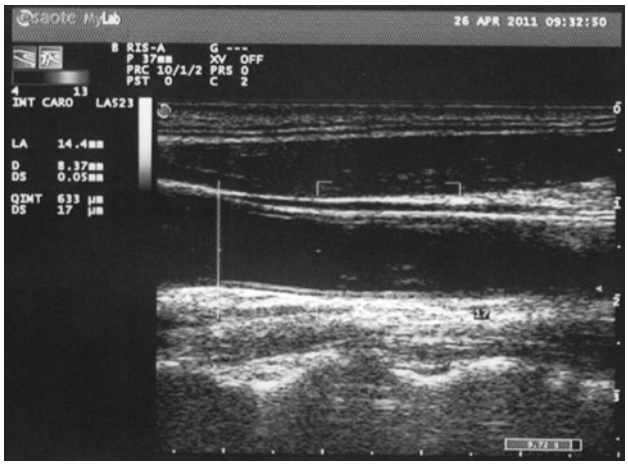
Purpose: While the effects on heart of regular physical activity (PA) and sport in adult athletes is well known, on the contrary the impact on peripheral vessels are not yet completely clarified. This study aims to evaluate a possible relationship between carotid intima-media thickness (IMT) peak systolic blood pressure (SBP), mean arterial pressure (MAP), body mass index (BMI), age and time of training in master athletes (MA).
Methods: A sample of 100 MA(aged 50.0 $\pm$ 6.7 years) and 51 sedentaries (S) (aged 51.1 $\pm$ 5.7), without cardiovascular risks factors were enrolled. By a questionnaire the weekly hours of sports activity was evaluated (at least 7.0 $\pm$ 2.6 h/w) in addition to the BMI. During an echographic 2D exam a dedicated software (QIMT-Esaote) evaluated the IMT absolute and mean value in left and right common carotids. A treadmill modified Bruce test, was also provided. The heart rate, blood pressure at rest, at peak of the effort (PE)and after 4' min of recovery and the MAP calculation were measured.
Results: In both groups left IMT values resulted to be higher than right side(MA: 635 $\pm$ 104 vs. 614 $\pm$ 104, average IMT 624 $\pm$ 92; S: 633 $\pm$ 78 vs. 622 $\pm$ 90, average IMT 627 $\pm$ 78).A slight relationship between IMT and SBP at the PE was found in both groups (MA: R 0.28 $p < 0.01$; S: R 0.32 p 0.02) as well as between IMT and mean arterial pressure at rest and at the PE in MA (rest R 0.25 p 0.01; PE: R 0.23 p 0.02).A mild relationship between IMT and age was confirmed in both groups (MA: R 0.30 $p < 0.01$; S: R 0.30 p 0.03) while no relationships between IMT/BMI and IMT/weekly time of training was found.
Conclusion: The study confirms the role of age in the wall carotid thickening. The progressive increase of SBP seems to have an impact on the enlargement of carotid wall mainly when the PE SBP values are high. The PA does not seems to have any effects in reducing carotid thickening in similar subjects for age and vascular risk factors.



Relationship between work-out and vascular function in professional soccer players

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To study the changes of some vascular parameters in different work-out modalities, we evaluated the vascular adaptation in a professional soccer players team at the beginning of the season (T_0), after the predominantly anaerobic work out (T_1) and after the aerobic/anaerobic work out (T_2).
Twenty-four professional soccer players (age 21.7 $\pm$ 5.4 years; weight 70.3 $\pm$ 6.6 kg), no smokers, no affected by thyroide and/or cardiovascular diseases, were enrolled. The vascular function was

evaluated by Pulse wave analysis (PWV), used to generate a corresponding central (ascending aortic) waveform with a generalized transfer function and RHI as measured with a semi-plethysmographic method that, using the principle of peripheral arterial tonometry with a finger probe assessed digital volume changes accompanying pulse waves. Moreover, brachial artery function as vascular strain (VS), compliance (VC) and stiffness index β were evaluated. In 2-tailed tests, a value of $P < 0.05$ was considered statistically significant and calculated with a standard statistical package.
About the vascular changes, in the phase T_1 we observed an increase of the systolic blood pressure (25 %; $P = 0.004$) and of the pulse pressure (9 %; $P = 0.003$) versus phase T_0 associated with the appearance of vascular disfunction like demonstrated by the significant increase of the stiffness (0.35 ± 0.13 T_1 vs. 0.26 ± 0.08 T_0; $P = 0.004$), decrease of the VS (5.12 ± 1.24 % T_1 vs. 6.81 ± 2.27 % T_0; $P = 0.044$) and of the VC (46.4 ± 12.5 $mmHg^{-1}/cm$ T_1 vs. 57.5 ± 15.1 $mmHg^{-1}/cm$ T_0; $P = 0.130$). Always in the phase T_1 we noted, not significant, increase of the PWV and a decrease of the RHI. In the phase T_2 we observed a return to the basal vascular data.
These results demonstrate for the first time that in a same professional sport team different training methods induce different cardio-vascular adaptations, in particular the anaerobic/aerobic work-out improves the vascular function.

Cardiac modification during a championship in professional soccer players

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The functional and morphological atrial adaptations in a soccer players professional team were evaluated during a regular season in the beginning of the season (T_0), after the predominantly anaerobic work out (T_1) and after the aerobic/anaerobic work out (T_2).
Twenty-four athletes (21.7 ± 5.4 years; 70.3 ± 6.6 kg) no smokers, without cardiovascular diseases, were enrolled. Anthropometric data, blood pressure (BP) and heart rate were evaluated early in the morning. Echocardiograms were obtained to evaluate left atrial volume indexed by body surface (AVI), mitral functional area, atrial ejection force, wave peak A and E, left ventricular mass (LVM) according to Devereux's formula indexed by body surface (LMVI).
In the phase T_1 we observed an increase of the systolic BP (25 %; $P = 0.004$) and of the pulse pressure (9 %; $P = 0.003$) versus phase T_0. During T_1 there was a significant increase of PWd (0.95 ± 0.10 cm T_1 vs. 0.88 ± 0.11 cm T_0; $P = 0.000$) and IVSd (1.09 ± 0.09 cm T_1 vs. 0.93 ± 0.11 cm T_0 vs; $P < 0.000$) and a not significant increase of the LVTDd which determined an increase of the LMVI (115.70 ± 12.76 g/m^2 T_1 vs. 101.29 ± 13.98 g/m^2 T_0; $P = 0.0001$) and of the stroke work +8 % in T_1 and +23 % in T_2, $P = 0.010$. Similarly, in T_1 we observed a significant increase of the AVI (35.27 ± 10.88 ml/m^2 T_1 vs. 28.08 ± 6.36 ml/m^2 T0 $P = 0.058$), mitral functional area (4.13 ± 0.44 cm^2 T_1 vs. 3.91 ± 0.49 cm^2 T0; $P = 0.001$) and atrial ejection force +43 % ($P = 0.001$). There was an apparent worsening of the diastolic function (E/A 1.90 ± 0.41 T_1 vs. 2.27 ± 0.42 T_0; $P < 0.0001$), determined by an increase tardive ventricular filling (wave A, 0.47 ± 0.08 m/s T_1 vs. 0.41 ± 0.06 m/s T_0; $P = 0.003$). In T_2 we noted a reduction of the atrial diameters and atrial contribute to the ventricular filling with an improvement of the diastolic function.
The cardiac changes during an agonistic season are dynamic and strictly correlated to the different training ways.

Morphologic and functional cardiac modifications in adolescent soccer players

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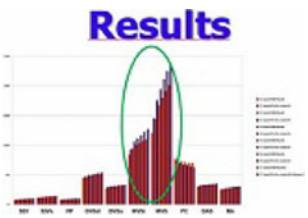
Purpose: Almost all the study on athlete's heart have been carried out on adult players; for this reason there are limited data on the cardiac adaptations to exercise during adolescence. The study sought to describe the modification and the evolution of cardiac morphology and function in athletes compare to controls.
Methods: 40 highly trained male soccer players and 47 less trained controls, were evaluated in the study from the age of 12–17 years old. Once a year every athlete underwent 2D echocardiography evaluating the Left Ventricle (LV) systolic and diastolic dimensions, inter ventricular septum (IVS) and Posterior Wall (PW) thickness and Cardiac mass Index (CMI). This last parameter was also compared to BSA growth in both groups, to evaluate a possible correlation.
Results: The data indicates a significant increase in absolute values of all the echocardiographic parameters examined ($p < 0.05$) in adolescent highly trained soccer players compared to less trained controls, especially in CMI. No correlations between CMI and BSA growth has been found.
Conclusion: Our data indicates an early cardiac remodeling especially in highly trained athletes. The results are suggestive intensive training has no eventual influence on BSA growth. While it is a decisive factor for LVM growth.



Neuroendocrine and psychological assessment in a 14-days guinness scuba dive

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Background: Environmental stresses occur in scuba diving, due to raised partial pressure of oxygen, increased ambient pressure, cold stress, higher breathing resistance, increased resistance to movement and added weight and drag of diving equipment. However at present few data are available on stress hormones in recreational scuba divers. Moreover stress, anxiety and panic attack could be involved in injuries and fatalities occurring during this activity. In this connection the ability to control anxiety in not trained scuba divers as well as the ability to manage stressful situations in experienced divers are demonstrated to be the best solution to prevent accidents. In 2005 our group already evaluated physiological and psychological stress parameters in 2 professional trained scuba divers, using a unique physiopathologic model, offered by the guinness 240 h scuba dive. The present study represent the second step of the same project performed 2 years later in 6 professional trained scuba divers.

Aim: To evaluate both physiological and psychological stress parameters in 6 professional trained scuba divers, using a unique physiopathologic model, offered by the guinness 14 days scuba dive.
Methods: A total of 6 healthy scuba dive masters, 3 male (aged 28, 34 and 40 years-old), and 3 female (aged 31, 36 and 26 years-old) lived for 360 h (14 days) on a wall-less platform anchored to the seabed at a depth of 8–10 m (22–28 feet). The "Abyss Project" took place in Cala Feola, NW off the Italian Island of Ponza in the central Tyrrhenian Sea. The temperature of seawater varied between 24 and 26 °C. The 6 subjects lived on a 49-square meter platform furnished with table, chairs, sofa, bikes and treadmills. They could also watch a special waterproof TV, read books or play cards, crosswords, sudoku and pool. The 6 divers were divided into 3 pairs. Each pair had a minimally floating diving bell to be used as private room.
In this dry chamber, the medical team carried out regular tests on a daily basis (blood pressure, oxygen levels, heart rate control, skin condition and blood sample collection). Psychological assessment was also performed using the State and Trait Anxiety Inventory and the Zung self-rating depression scale. A fourth diving bell was used as a common room where they cooked, ate and took care of their underwater gear. The study subjects spent 74 % of their time in the water using special diving suits and full-face breathing masks.
Results: Confirming our previous data (1), cortisol and prolactin showed physiological pulsatile secretion in all scuba divers; thyroid hormones, testosterone, DHEAS, sexual hormones and IGF-I did not show significant inter-days differences in respect to physiological fluctuation in controls subjects. At the start of the study, no subjects showed high levels of state anxiety, trait anxiety and current depression. The score of the psychometric scales remained steady during the diving period and no subjects showed anxiety and/or depression during the time of observation. No subjects showed panic symptoms.
Conclusions: The present study shows that, although the long-time diving, the well trained professional divers did not develop stress hormon's abnormalities and/or anxiety and depression; no subject discontinued the diving due to occurred psychological distress or systemic events. The present report shows that the long-term diving permanence is possible, at least in well trained scuba-divers.

Reference

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Effects of exercise training on endothelial dysfunction and wave reflection indexes in subjects with metabolic syndrome

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The metabolic syndrome (MS) is a cluster of risk factors for cardiovascular disease (CVD) and all the components of the syndrome are likely to be associated to impaired arterial vasoactivity and stiffness, now recognized as early markers of atherosclerosis burden. It is clearly established that adequate amounts of regular physical activity (PA) are an effective CVD prevention and treatment for subjects with type 2 diabetes mellitus and MS. The study investigated, in 20 patients (13 females, mean age 51 ± 9 years) affected by MS, the effects of a 2 session/week mixed (aerobic-resistance) 3 months physical training on brachial-artery flow-mediated vasoactivity (FMV), assessed by two-dimensional ultrasonography, on aortic arterial stiffness, measured as central augmentation index (AIx)(index of timing and amplitude of reflected pulse waveform), by means of an applanation tonometry-based method, and skin microvascular reactivity, evaluated by laser-Doppler flowmeter. Twenty age- and sex-matched MS patients, who were examined twice at 3 months interval in the absence of exercise training, served as controls. Exercise training was followed by a significant reduction in body mass index (from 34.8 ± 4.7 to 33.9 ± 5 kg/m^2, $p < 0.05$) and fat mass (from 41.6 ± 5.2 to 38.7 ± 6.4 %, $p < 0.05$) and by an improvement of cardiorespiratory fitness (VO_{2max} from 18.7 ± 8.0 to 29.7 ± 8.8 mL kg^{-1} min^{-1}, $p < 0.05$) and upper and lower body and chest muscle strength. Rest flow and peak flow and the area under the curve after postocclusive reactive hyperemia (AH), at skin laser-Doppler examination, increased significantly after PA (from 1593 ± 665 to 2661 ± 1270 U/s, $p < 0.05$). AIx was not significantly modified by exercise training (from 13 % to 12 %, $p = 0.56$). Nevertheless the magnitude of AH improvement, observed after PA was inversely associated with the relative AIx changes (Pearson's R 0.67, $p = 0.03$). Brachial FMV increased after PA from 9.9 ± 5.2 to 12.2 ± 4.6 % (p: NS). Also metabolic parameters (glycemia, glycosylated haemoglobin, triglycerides and HDL-cholesterol) improved even if not significantly. No significant variations were recorded in the parameters under study in the control group. Our results seem to indicate that moderate aerobic-resistance training improves microvascular endothelial dependent vasorelaxation and large vessel stiffness in sedentary patients with MS and support the importance of addressing lifestyle modifications as a first-line therapeutic approach for reduce the high CVD risk associated to MS.

A catastrophic "promenade": a case report of exercise-induced purpura!!

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Introduction: Exercise-induced vasculitis is an underestimated erythematous, urticarial or purpuric lesions developing on the lower legs in healthy subjects after a strenuous muscular activity as running or climbing, especially in hot weather. Recently it has also been described in golfers and hikers. Our report describe the case of an exercise-induced vasculitis in a young bar-woman no affected with Schamberg disease but struck by her hobby of walking!!!
Clinical Case: A 26-year-old female patient otherwise healthy came to our observation because of onset of purpura to her lower limbs associated with intense itching onset at history after a very proud and long "promenade" in Paris during her last holiday. The patient denied any drug intake and her prior medical history was irrelevant, except for similar episode complained 3 years before as effect of a strenuous walking in London. Clinical examination displayed on her legs a few patches and pinpoint erythematous-purpuric macules and papules, irregularly shaped, measuring around 1 cm in diameter and partly persistent under diascopy; some lesions had resolved leaving slight hyperpigmentation. The lesions were asymptomatic with occasional burning sensation before their appearance. Laboratory investigations including full blood examination, coagulation times, thyroid and rheumatic tests, antinuclear antibodies, pharyngeal and vaginal swabs, urine culture, urea breath test and serology for viruses were negative or within normal values. Chest X rays, electrocardiogram, ovarian and

adrenal glands ultrasounds, lower limbs doppler ultrasonography displayed no abnormalities. A biopsy specimen from a lesion demonstrated orthokeratosic hyperkeratosis, with some focal vacuolar degeneration of the basal membrane and a mostly lymphocytic perivascular mononuclear infiltrate with scanty leukocytoclasis of neutrophils in the superficial dermis, vessels hyperplasia and endothelial swelling with some extravasated erythrocytes. Direct immunofluorescence demonstrated granular IgM and C3 deposits at the dermoepidermal junction and C3 in superficial dermal vessels. A diagnosis of leukocytoclastic vasculitis was done. Meanwhile, the patient referred clinical improvement with resolution of the eruption during summertime, when she stopped swimming, then followed by a prompt relapse in autumn, just a few weeks after the resumption of her training program. A therapy with oral diosmine and esperidine has been established and the patient was advised to wear elastic socks (medium graduated compression). After 2 months of therapy the lesions partially subsided on clinical examination, displaying only slightly hyperpigmented postinflammatory maculae, and no evidence of new lesions.

Discussion: Exercise-induced vasculitis is an under-recognized and frequently misdiagnosed disease which affects healthy subjects following a strenuous effort as long distance running or hiking. It has also been described in jogging, step aerobics, body building, and recently in a series of golfers. Females seem to be affected more than males. Clinical features are itchy or burning, erythematous, urticarial or purpuric lesions, typically worsened by high temperatures. There is a neither abdominal nor systemic symptom. Usually the lesions fade spontaneously after some days, with frequently relapses during similar exercise. It is often misdiagnosed as allergic reaction. Histology showed aspects of leukocytoclastic vasculitis with immunologic deposits at direct immunofluorescence. Although etiology is still unknown, a main role might be played by the heat produced by big muscle groups, especially in wet warm weather or climate. In such conditions heat-regulation mechanisms are deficient and muscular hyperthermia may develop and reach temperatures even higher than 41 °C inducing damage of muscle fibres. In addition anaerobiosis increasing lactic acid load, may worse tissue damage. Complement activation has also been reported to occur in association with prolonged exercise and it can be due to a non-specific immune response to muscle cell inflammation caused by prolonged physical activity. Cytokine release and changes in the expression of adhesion molecules may contribute to inflammation and complement activation.

Need for a tool: handling professional soccer players biochemical data

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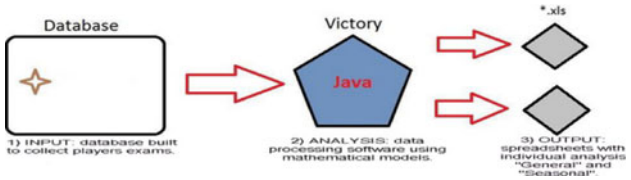
Purpose: According to Italian regulation, professional athletes undergo to a periodical biochemical parameters evaluation addressed to maintain health. A software toolkit analyzes biochemical parameters focused on monitoring of Least Significant Change (LSC) for hematological variables.

Method: Since January 2008 to July 2011, 81 professional soccer players blood samples were collected. According to quality standard reference Clinical Laboratory, a dedicated software ("Victory") allows the user retrieving LSC in the team's athletes. LSC = $2.77(CVi^2 + CVa^2)^{1/2}$ equation, including every athlete's data, derived from soccer seasonal training period. The software identifies hematological values exceeded the LSC values.

Results: Standard hematological mean team values (2009/2010), examined considering ethnicity, age and role, were within the normal range (Hb 15.2 ± 0.6 g/dL, min 13.9, max 16.6; HcT 43.0 ± 1.9 %, min 41.0, max 49.0; MCV 87.3 ± 3.0 fL, min 82.0, max 93.5; reticulocytes number 0.0433 ± 0.0128 × 10^{12}/L, min 0.0186, max 0.0732). In parallel the LSC for Hb (5.80 %), HT (8.20 %) and MCV (2.41 %) and reticulocytes count (17.96 %) resulted to be normal, with the exclusion of soccer players data exceed LSC value in consequence of the training period at the same work load. In the 6.2 % of the all samples investigated for each athlete, the hematological variation was over the LSC.

Conclusion: The software retrieves epidemiological information based on the physiological changes of the hematological parameters occurring during the seasonal competitions. It can therefore be propose to clarify several clinical questions related to regular training or to risk factors particularly if in presence of different work load or recurrent injuries.



Functional assessment of cardiovascular performance after a short period of Exercise as Prescription: an evaluation by 6 min walking test

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Introduction: It is note as Exercise as Prescription represents a therapy in several chronic diseases with a progressive improvement of the cardiovascular performance that is normally evaluated by the cardiopulmonary test. More recently the employment of the 6 Minute Walking Test (6MWT) for a regular evaluation of this aspect has been spread. The study is aimed to verify the role of the 6MWT in predicting the progressive improvement of the heart performance.

Methods: Eleven (6 male and 5 female, aged 59 years) hypertensive patients, were enrolled for Exercise Prescription as therapy program. At the beginning (T0) and after 5 months (T5) of regular exercise, at least three times a week at moderate intensity (corresponding to 3–4 METS of effort or to 6 of Rate of Perceived Exertion CR-10 Scale) a 6MWTest was carried out to evaluate some hemodynamic parameters. Among them: walking meters (m), Peak Heart Rate (PHR), Peak Respiratory Rate (PRR), Systolic and Diastolic blood pressure (SBP, DBP). In the same session and following the AHA guidelines an Echocardiographic exam was performed to obtain the morphological and functional systo-diastolic myocardial parameters.

Results: data are expressed as mean and standard deviation. After 5 months of physical exercise there was a trend toward a progressive enhancement of the distance covered during 6 min (T0: 567.27 ± 66.65 m, T5: 599.09 ± 81.42 m). The PHR values remained around 135 beats per minute (T0: 134.36 ± 12.13 b/min, T5: 136.00 ± 10.30 b/min), PRR resulted, on the contrary to be similar that at the onset of the exercise (T0: 30.00 ± 4.38 r/min, T5: 31.45 ± 4.95 r/min). The SBP was higher at T5: 143.64 ± 12.67 mmHg than at T0: 137.73 ± 14.89 mmHg, while the DBP mean values were lower at T0 (75.27 ± 7.80 mmHg) than at T5 (70.91 ± 5.84 mmHg).The Echocardiographic systo-diastolic parameters didn't show any statistical differences after 5 months of physical exercise.

Conclusion: A short period of exercise as prescription improves the effort tolerance showed by the HR response at the peak of the exercise. The 6 MWT seems to be a sensible test to detect this aspect, much more than echo parameters whose modifications need a longer period of observation. Otherwise the lung's response to the exercise

does not seem to be apparently easy estimated in presence of exercise program at moderate intensity.

Effects of structured physical activity in overweight patients with type 2 diabetes: the role of oxidative stress in disease progression

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Background: Oxidative stress is recognized as a key participant in the development of diabetic complications.
Purpose: The aim of our study is to rate the efficacy of the physical activity on metabolic, functional and oxidative parameters in patients with type 2 diabetes mellitus (T2DM) and also to prove the role of cardiopulmonary exercise testing (CPET) in the management of the diabetic patient.
Research Design and Methods: We selected twenty male patient with T2DM, overweight (body mass index $\geq$ 25 kg/m^2), aged 40–70 years, with at least 2 years of disease, without diabetes-specific complications. They were randomly divided into an intervention group, which followed a supervised physical activity in the hospital, and into a control group, remained sedentary. The exercise protocol included both aerobic and resistance training, performed twice a week for 6 months. Patients were subjected to medical examination, biochemical investigation and maximal CPET with ramp mode (20 watt/min). Investigation of oxidative stress parameters was also performed, consisting of plasma oxidized phospholipids assay and analysis of lymphocyte gene expression with real-time PCR and western blot. These investigations were carried out at time zero (T_0) and after 6 months (T_6).
Results: In the investigation group only, we obtained:

- 1.5 percent reduction in waist circumference with significant difference from control group ($p = 0.05$)
- 14.6 percent increase in anaerobic threshold with significant difference from control group ($p = 0.02$)
- 12 percent improvement in maximum aerobic capacity, changing from 1552 ml/min to 1737 ml/min ($p = 0.008$) with significant ($p = 0.001$) difference from control group, that moved from 1782 ml/min to 1605 ml/min.
- Reduction of the following plasmatic oxidized phospholipids: lysophosphatidylcholine$_{16}$ ($p = 0.05$), lysophosphatidylcholine$_{18}$ ($p = 0.03$) and 1-palmitoyl-oxovaleroil-phosphatidylcholine ($p = 0.05$)
- Nonsignificant variation in the expression of the following antioxidant genes: Nrf2, heme oxygenase-1, γ-glutamylcysteine ligase, phospholipase A_2-associated lipoprotein.

Conclusions: The CPET allowed to customize the physical activity that was effective in reducing oxidative stress and, therefore, in slowing the progression of the disease. The cardiorespiratory fitness increased with mainly benefits in muscles. The lack of improvement of other metabolic parameters suggests that physical activity must be conducted for a period greater than 6 months and at least three times a week, so that the beneficial effects obtained from the single training session does not exhaust.

Oncology

An association study of two SNPs in the SPARC and EGF genes with hepatocellular carcinoma

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Background: Hepatocellular carcinoma (HCC) is one of the most frequent cause of cancer-related deaths worldwide. HCC has a variable incidence depending primarily on the local environmental risk factors. However today it is clear that also genetic background has role in HCC onset and development. HCC often develops from a state of liver cirrhosis. In this context the secreted protein acidic and rich in cysteine (SPARC) and the epidermal growth factor (EGF) protein could be involved in hepatocellular carcinogenesis. The aim of this study was to evaluate the association between the rs2304052 and the rs4444903 single nucleotide polymorphisms (SNP), located respectively on the SPARC and EGF genes and HCC susceptibility.
Methods: 75 HCC cases and 170 healthy controls were collected from a Southern Italian population. For each sample the DNA concentration was evaluated. Every sample was genotyped for the rs2304052 and the rs4444903 SNP through an amplification followed by a restriction fragments length polymorphism reaction (PCR–RFLP). A statistical analysis was performed; p values and ORs were determined.
Results: For both the SNPs we did not obtain any statistically significant p values. For the rs2304052 SNP we obtained ORs that are pointer of no association. For the rs4444903 SNP we obtained an OR of 1.12 (95 %CI = 0.72–1.74) and an OR of 0.99 (95 %CI = 0.43–2.33) for the dominant model. A result of weak association was obtained with the recessive model (OR: 1.41, 95 %CI = 0.65–3.05) and with the recessive model for HCV positive and male subjects (OR: 1.72, 95 %CI = 09.62–4.66). A moderate association was obtained with the male and HCV positive C/C versus A/A carriers (OR:2.57 95 %CI = 0.53–13.89).
Conclusions: The rs2304052 SNP is not associated with the risk of HCC in a Southern Italian population. Male and HCV positive rs4444903 SNP C/C carriers have an increased risk of developing HCC compared with that of the A/A carriers in a Southern Italian population.

Cancer cells reprogramming: stem cell differentiation stage factors and their epigenetic influence on tumor growth

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On the basis of evidence that tumor development is suppressed by the embryonic microenvironment, we carried out experiments on a series

of in vitro human tumor cell lines, using stem cell differentiation stage factors (SCDSFs) from Zebrafish embryos; a significant slow-down in tumor growth was confirmed. Further experiments showed the observed mechanism of tumor growth inhibition to be connected with the key-role cell cycle regulator molecules, such as p53 and pRb, which are modified by transcriptional or post-translational processes. Research on apoptosis and differentiation revealed that treatment with SCDSFs induces caspase-3 with a p73 apoptotic-dependent pathway activation and a concurrent significant normalization of E-cadherin and beta-catenin ratio. Other experiments found a synergistic effect on the colon cancer proliferation curve after concurrent treatment with SCDSFs and 5-fluorouracil. A significantly slowed tumor growth was also obtained in C57BL/6 mice injected with Lewis lung carcinoma after treatment with these factors. Finally, a product prepared for human therapy containing SCDSFs demonstrated 19.8 % regression and 16 % stable disease in an open randomized clinical trial on intermediate-advanced hepatocellular carcinoma. In addition a cohort study on patients with advanced stage hepatocellular carcinoma demonstrated a sustained complete response in 13.1 % of them.
Research on SCDSFs and others approaches to cancer treatment lead to a more complex and integrate comprehension of the biological processes which sustain tumor growth. Although not fully developed, these researches are proceeding worldwide and the scientific community is now ready to accept new systemic views to cancer treatment, as some authors witness.

Breast cancer in older patients: clinical objectives are different according to the patients age

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Introduction: The aging process brings along changes amongst these the epidemiological ones. These are characterized by the increase of chronic-degenerative diseases (hypertension, diabetes mellitus, stroke, impaired cognitive functions, cancer) which are long-lasting conditions and whose appropriate care demands high amounts of human and material resources.
These alterations shown by older patients make them consume a high amount of medications. Often their lack of understanding, forgetfulness, reduced visual acuity and manual dexterity, could trigger serious complications when drugs are misused.
Older oncology patients with multiple co-morbidities are at risk of adverse drug events associated with polypharmacy and drug interactions due to patients' altered pharmacokinetic/pharmacodynamic status.
Objective: To evaluate and describe characteristics of polypharmacy in the outpatient after diagnosis of breast cancer and identify some specific clinical goals related to this population.
Materials and Methods: A retrospective cohort study on 145 consecutive breast cancer patients in the adjuvant setting with multiple co-morbidities, attending oncological ambulatory care at the Parodi Delfino Hospital was performed.
Results: 145 patients (142 female age 67.9 ± 11.4 years; 3 male 75.66 ± 4.5 years), socio-demographic characteristics: education, (illiterate or incomplete elementary school 20 %; elementary school 37 %; secondary school 21 %; high school 17 %; graduate 5 %); marital status (lived with partner 61 %; lived without partner 49 %). Clinical features: Body Mass Index (BMI) distribution, normal weight 25 %, overweight 32 %, obese 43 %; medication, 60 % of patients used no medication—up to 4, while the other 40 % used from 5 up to 15 medication; co-morbidity was present in 36 % of population (two or more disease in addition to breast cancer).
Drugs daily intake increases with the patients age $p < 0.001$; this difference is maintained when evaluated for age group: young-old (Y–O) (65–74 years) and old–old (O–O) (75 years and over) $p = 0.001$. A difference is present even when drugs daily intake was evaluated regarding BMI group $p = 0.03$.
Conclusion: Our older population is fast growing and cancer management is becoming an increasingly common problem. Therefore it is important to know this population characteristics and healthcare needs. This will help to improve elderly patients classification respect to the various medications so to have a more personalized and thus more effective medical treatment.
Based on these evidences we identified two groups related to age, presence of co-morbidity and medication intake. Y–O in which the main clinical objective is prevent a relapse of breast cancer and the control of adjuvant hormonal therapy, involving changing in lifestyle related to it (obesity, physical activity).
O–O people, using multiple drugs are prone to a higher vulnerability due to their health conditions, where co-morbidity has a significant impact on mortality. Low literacy and live alone may cause a major risk of adverse drug events for both groups. The correct use of medications and procedures within this population are a pressing necessity to prevent any adverse drug events and to improve patients' life conditions.
Our results suggest for both groups some practical targets for intervention. These include improved information concerning drugs administration both in hospital and at home, and the monitoring of prescribed medications to avoid preventable harmful drug events.

Malignant peritoneal mesothelioma as a rare cause of ascites

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On march 2012 a 53 years old man was admitted to our department with a 1 year history of asthenia, abdominal pain and ascites. He was a non smoker and denied drinking alcohol. His medical history was negative for asbestos exposure. His laboratory tests were normal except for elevated inflammatory markers. Before admission he was given through medical examinations including abdominal ultrasonography (US) and computed tomography at several hospitals and clinics that showed a moderate ascites; a diagnostic paracentesis documented the presence of a neuthrophil rich exudate. A chest X ray film was normal. His echocardiogram revealed minimal pericardial effusion. Broad-spectrum antibiotics and analgesics were given. However, the imaging studies after administration of antibiotics for 1 week showed increased ascites. A diagnosis of polyserositis was hypothesised and the patient was treated with short courses of oral steroid without any benefit. On admission, clinical examination revealed abdominal discomfort and moderate ascites but no signs of chronic liver disease. Examination of cardiovascular and respiratory system was normal. Laboratory test including full blood count, electrolytes, liver and kidney functions, serum albumin were normal. Prothrombin time and international normalized ratio were normal too. Negative for viral hepatitis markers for current and previous infections. The C- reactive protein level was 6 mg/dl (normal value <0.5 mg/dl), ESR was >83 mm/h and fibrinogen 862 mg/dl (normal value 220–500 mg/dl). The serum levels of CEA, CA19.9 and AFP were normal. CT of the abdomen showed a swelling of the greater

omentum, suggestive of peritoneal carcinomatosis of unknown origin. Histology of a CT-guided biopsy of mesenterial tissue revealed actived mesothelial cells, while immunohistochemistry of a laparoscopic biopsy of the omentum allowed the diagnosis of mesothelioma. So he was sent to a Surgical Department, where he was submitted to peritonectomy and cytoreductive surgery of all affected tissue with hyperthermic intraperitoneal chemotherapy. Malignant peritoneal mesothelioma is a rare primary tumor of serous membranes, and its prognosis is poor. Symptomatology is insidious and poses difficult problems in diagnosis and treatment. A precise diagnosis based on imaging findings alone is not possible. Therefore, the definitive diagnosis of peritoneal mesothelioma depends on histologic and immunohistochemical examination obtained by laparoscopy or open surgery with biopsy. This case report points out that when more frequent causes are excluded in patients presenting with ascites, asthenia, abdominal pain and elevated levels of inflammatory markers, rare diseases such as peritoneal mesothelioma have to be considered as a possible diagnosis.

A spike at tumor onset earmarks low level instability in peripheral blood cells from lynch syndrome patients

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Microsatellite instability (MSI) is described as length alterations of repetitive sequences (also known as microsatellite), in a small cluster of tumor tissue. MSI is associated with 10–15 % of sporadic tumors (colorectal, endometrial, gastric) and is considered the hallmark of hereditary non-polyposis colorectal cancer (HNPCC or Lynch syndrome) related-tumors. It is universally accepted that MSI is the consequence of slippage errors of the DNA polymerase during DNA replication. These errors are usually corrected by the post-replication mismatch repair (MMR) system. Subjects affected by Lynch Syndrome carry a germline heterozygous mutation in a MMR gene, usually either in MSH2 (MIM# 120436) or MLH1 (MIM# 609309), less frequently in MSH6 (MIM + 600678) and PMS2 (MIM + 600259). The non-neoplastic cells of these individuals are phenotypically normal, since the protein encoded by the wild-type allele of the MMR gene is enough to warrant repair proficiency.
The loss or inactivation of the normal allele inherited from unaffected parent, due to point mutations, deletions, methylation or gene conversion, is responsible for the so-called "mutator phenotype" of HNPCC tumors. The MMR deficiency in a somatic cells lead to a progressive accumulation in a stepwise model of hundreds of mutations in target genes, characterized by the presence of repetitive sequences in the coding region. These sequential events can be considered the trigger of carcinogenesis process.
Due to the recessive nature of MMR deficiency, in the non-neoplastic cells of HNPCC patients a functional MMR system should maintain microsatellite stability. However, also normal cells of HNPCC subjects may have low level of microsatellite changes, before tumor diagnosis. In fact, it has been reported that a number of oncogenic mutations may precede MMR loss, in normal appearing colon cells, although the identities of these mutations remain unknown. Recent studies, performed on peripheral blood cells (PBL) of carrier and non-carrier members of HNPCC families, demonstrated that heterozygosity for MMR gene mutations causes the presence of BAT26 shorter alleles in non-neoplastic cells and a higher frequency of mutant microsatellite fragments analyzed in six loci in carriers when compared to normal controls.
Surprisingly, MSI identified in non-neoplastic cells, was not limited to HNPCC patients, but also present in normal individuals and appears to increase with age. More recently, MSI in PBL DNA of 7 HNPCC patients has been compared with normal age-matched controls and with patients with sporadic colorectal cancers (CRCs), showing that the level of microsatellite instability in DNA from HNPCC patients was always higher when compared with controls of the same age ($p > 0.01$).
In the present study, we aimed to evaluate the level of microsatellite instability in DNA isolated from peripheral blood leukocytes (PBLs) and normal tissue cells from 17 different MMR-gene mutations carriers, split into two subgroups, cancer-free and cancer-affected, using a PCR-cloning approach. The present study reports data concerning the level of microsatellite instability in circulating cells in the largest cohort of LS patients thus far analyzed. Our analysis, carried out on both cancer-free and cancer-affected mutation carriers, demonstrated that the frequency of mutant alleles in circulating cells correlates significantly with the presence/absence of LS-spectrum cancer at the time of blood sampling, rather than with age. By contrast, age is the most relevant factor responsible for MSI level augmentation in non-LS healthy controls. Based on our results, the dramatically high MSI levels found in the mutation carriers diagnosed with LS-related tumor at time of blood sampling are effects likely due to circulating neoplastic cells. Therefore, we investigate the possibility of the presence of CK20 positive cells in blood samples of our LS patients.

Prevalence of pre-cachexia and cachexia, body composition and muscle function in surgical cancer patients

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Rationale: Cachexia is a complex metabolic condition negatively affecting morbidity and mortality.
Recent definitions and classifications of cancer pre-cachexia and cachexia point to early detection and to timely appropriate preventative and therapeutic interventions. The present study aimed at evaluating the prevalence of pre-cachexia and cachexia in cancer patients as well as at studying the relation between anthropometric measures and body composition.
Methods: Immediately before operation, thirty-six consecutive surgical cancer patients (21 M, 15 F) were assessed for weight loss, anorexia and serum biochemistry. Based on the recent classifications of pre-cachexia and cachexia, patients were classified into pre-cachectic, cachectic or no pre-cachectic/cachectic. In 19 patients, body composition via bioimpedance spectroscopy (BIS) (BCM–Fresenius) and handgrip muscle strength (HGS) (JAMAR Dynamometer) were assessed. Statistical analysis was performed using ANOVA, two-way Dunnett post hoc analysis, Kruskal–Wallis test, Spearman test.
Results: According to the available criteria, pre-cachexia was present in 6 patients (16.7 %), cachexia in 13 patients (36.1 %), while 17 (47.2 %) patients did not match both criteria.
Body mass index (BMI) was decreased in cachectic patients with respect to no pre-cachectic/cachectic ($p = 0.01$). In the subset of 19 patients, 4 (21 %) were pre-cachectic, 7 (37 %) were cachectic, 8

(42 %) were no pre-cachectic/cachectic. Fat-free mass (FFM) was decreased in cachectic versus pre-cachectic and no pre-cachectic/cachectic patients ($p = 0.009$ and $p = 0.035$, respectively).
HGS negatively correlated with CRP ($r = -0.478$, $p = 0.039$), and increased with FFM ($r = 0.577$, $p = 0.01$).
Conclusions: The study suggests that pre-cachexia and cachexia are present in >50 % of pre-surgery cancer patients. Pre-cachexia and cachexia are associated with decreased FFM and functional impairment and might predict surgical outcome. Preoperative screening for pre-cachexia and cachexia should be considered in cancer patients.

Non-organ specific and organ-related autoantibodies in patients with colorectal cancer and in patients with cancer at other sites

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Aim: The role and significance of increased autoimmunity in cancer patients is yet a matter of debate[1]. We aimed at investigating the presence and distribution of autoimmunity hallmarks in colorectal cancer patients and in other cancer patients in different stages of disease.
Materials and Methods: 131 consecutive cancer patients sent to our ward from the Emergency Department were enrolled in a period ranging from June 2009 to January 2011. Criteria of exclusion: severe kidney impairment (GFR < 10 ml/min or hemodialysis), ongoing sepsis, severe prognosis (exitus within 48 h), recent infusions of blood, or blood derivatives (within 2 weeks). A blood sample for serum extraction was collected from each patient and stored frozen at −20 °C until test execution. Indirect immunofluorescence (IIF) essays were performed on rat tissues as described below:

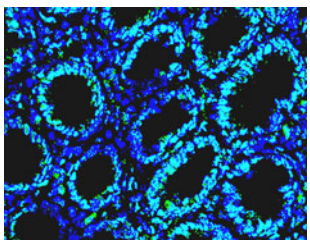

Fig. 1 Confocal microscopy

(A) non-organ specific autoantibodies (NOSAs), using gastric, kidney, and liver tissue substrates;
(B) colonic-related autoantibodies (CAAs), using colon tissue substrates;
(C) antinuclear antibodies (ANAs), using HEp-2 cell line commercial slides (Bio-Rad srl, Kallestad HEp-2 Slides #26104).
Tissue slides described in (A) and (B) were processed and prepared *in house* in accordance with literature recommendations[2]. All slides were observed in blind by two experienced examinators with fluorescence microscopy. A titer of 1/40 or above was considered positive. Statistical analysis between the colorectal cancer group and the other cancer group has been performed using z-Test Analysis to compare proportions (SigmaPlot for Windows, Version 12, Systat Software, Inc.).
$p < 0.05$ was considered significant.

Table 1

Variables	All patients (n = 131)	Colorectal cancer (n = 65)	Other cancers (n = 66)	p
Stage, M(± SD)	2.9(±1.1)	2.7(±1.1)	3.1(±1.1)	0.02
Deceased, n(%)	67(51.1)	21(32.3)	46(69.7)	<0.001
NOSA Pos, n(%)	89(67.9)	38(58.4)	51(77.3)	0.03
CAA Pos, n(%)	91(69.5)	45(69.2)	46(69.7)	0.90
GE-ANA	9(9.9)	8(17.8)	1(2.2)	0.03
OCMAR	14(15.4)	11(24.4)	3(6.5)	0.04
Hep-2 Pos, n(%)	98(74.8)	53(81.5)	45(68.2)	0.12
Cytopl react	24(18.3)	7(10.8)	17(25.8)	0.04

Results: Patients' characteristics and main results are summarized in Table 1. Age, sex, and cancer onset time did not differ between the two groups (data not shown). NOSAs resulted significantly increased in the other cancer group. CAAs did not differ significantly between the two groups. However, analyzing the subsets of patterns of CAA reactivity, a statistically significant colonic reactivity of mucosal epithelial nuclei (GE-ANA and **Table 1**. Abbreviations: GE-ANA: glandular epithelial cell associated OCMAR) emerged in the colon ANA; OCMAR: overall colonic mucosal ANA reactivity cancer group (Figure 1).
Discussion and Conclusions: Increased non-specific autoimmunity may be related to a more advanced stage of disease in the other cancer group. Of interest is that a subset of autoimmune reactivity localized to colonic mucosal epithelial and glandular nuclei characterizes the colon cancer group. This may indicate the production of antibodies towards colonic mucosal nuclear antigens in colon cancer patients.

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Ischemic lesions during therapy with Ipilimubab in patient with metastatic melanoma

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Introduction: We present a 69 year old woman who received a diagnosis of cutaneous melanoma under the right breast in 1989.
Clinic History: In December 2009 a right axillary lymph node biopsy was performed with histologic diagnosis of melanoma metastasis. A TC scan showed metastatic right axillary/clavicular and abdominal lymph nodes. For this reason the patient performed dacarbazine chemotherapy with stabilization of disease. In January 2011 for progression disease, the patient was treated with fotemustine till June 2011. In February 2012 a TC scan showed a metastatic progression lymphnodes and the patient started therapy with Ipilimumab at the dose of 3 mg/kg i.v. About one week after infusion she developed ischemic lesion with painfull ulcer on the tip of the third finger of the right hand. The lesion was similar to vasculitis ulcers. The second dose of Ipilimumab was delaided without improvement and steroide

therapy with prednisone 1 mg/kg was administered. The situation worsened because also the second finger of her left hand, developed an ulcer. For this reason the patient performed high dose steroid therapy without clinical benefit. In accord to the oncologists the patient was admitted to our hospital.

Clinical Laboratory and Instrumental Results: Laboratory investigations showed only small increase of ESR and CRP. Liver and renal function tests, glucose, Rheumatoid Factor, cryoglobulins, Hcv antibodies, C3, C4, Antinuclear, Anticitrulline, AntiNeutrophil Cytoplasmic, Antib2 glycoprotein and Anticardiolipid Antibodies were normal. Color-coded duplex ultrasound neck vessels, arms and legs venous and arterial color-coded duplex ultrasound, nailfold capillaroscopy and transthoracic echocardiogram: were normal.

Clinical Course: We started local medication of the fingers 'ulcers and daily intravenous infusion of Epoprostenol from 0.7 to 1.2 ng/kg/min for 8 h daily for 12 days. We observed a complete healing of the ulcer on the third finger of the right hand and a progressive improvement of the last ulcer on the left hand. The patient was dismissed from the hospital, she received acidoacetilsalycil therapy (100 mg daily) and Epoprostenol infusion once a week for 4 weeks and now once a month.

Discussion and Conclusion: Ipilimumab belongs to a class of immunomodulatory agents which alters the inherent balance of the immune system. It is a monoclonal antibody targeting the immune protein cytotoxic T-lymphocyte antigen (CTLA-4) and it has demonstrated improvement in overall survival of metastatic melanoma patients (1).I-pilimumab induces autoimmune-like adverse events in treated patients. Across early studies, the most commonly encountered immune-mediate effects were dermatitis (Stevens–Johnson syndrome, toxic epidermal necrolysis, necrotic, bullous, or hemorrhagic desquamation, or full-thickness ulceration), hepatitis, enterocolitis, hypophysitis, Guillain Barré syndrome and uveitis.(2-3-4).These effects (26 up to 80 % of patients on clinical studies) are termed immune-related adverse events (irAEs).The median time to resolution of immune-related adverse events was evaluated in one study and determined to be 6.3 weeks.

Guidelines have been developed to treat immune-mediated adverse reactions (5).In gastrointestinal toxicity, ipilimumab should be withheld and antidiarrheal medications utilized. If severe or life-threatening symptoms are present, ipilimumab should be permanently discontinued and corticosteroids initiated at 1–2 mg/kg/day and prednisone tapered slowly over 1 month.

For severe dermatological effects (Stevens–Johnson syndrome, toxic epidermal necrolysis, necrotic, bullous, or hemorrhagic desquamation, or full-thickness ulceration) ipilimumab should be permanently discontinued and systemic corticosteroids administered at 1–2 mg/kg/day of prednisone equivalent.(5).This case report is interesting for the unusual development of ischemic ulcers after infusion with Ipilimubab, for poor response to systemic corticosteroids and for progressive improvement after vasodilator therapy with Epoprostenol infusion.

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Alpha-fetoprotein predicts clinical outcome of patients with hepatocellular carcinoma

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Objective: Alpha-fetoprotein (AFP) is currently the only marker widely used in clinical practice for the surveillance of patients at high risk for developing HCC, but little is known about the significance of AFP as a prognostic factor. Goal of this study is to test the hypothesis that AFP is predictive of the clinical outcome of patients with Hepatocellular carcinoma (HCC).

Methods: From January 2007 to April 2012, an analytical study of 102 patients with known chronic liver disease complicated by the development of HCC was made at the Clinical Unit "C. Frugoni" Polyclinic of Bari. Patients were divided into 3 groups according to the Barcelona Cancer Liver Center (BCLC) staging system: stage A (22 pts: group 1), B (52 pts: group 2) and C + D (29 pts: group 3). Quantitative variables had no Gaussian distribution and were analyzed by non parametric methods. Results are expressed as median and interquartile ranges. Correlations among quantitative variables were assessed by Spearman's correlation coefficient, and differences between independent groups by Kruskal–Wallis test. Qualitative variables were summarized as counts and percentages and associations were studied by Chi-square test. Significance was set at a value of $p < 0.055$. Statistical analyses were done with software SAS 9.2 for personal computer.

Results: AFP levels were not statistically different among the different Child-Pugh classes ($p = 0.85$). The interquartile median AFP value was 15.4 IU/mL (8.16–1826) in class A; 69.35 IU/mL (9.4–751) in class B; and 25 IU/mL (16.4–116.0) in class C (Fig. 1). Moreover, no correlation was observed between AFP values and size of nodules, nor were AFP values statistically different according to the number of nodules (1 vs. 2 vs. multifocal, $p = 0.22$). A statistically significant difference was found in HCC patients stratified according to the BCLC classification: the interquartile median AFP value was 9.8 IU/mL (2.42–52.2) in group A; 23.2 IU/mL (9.2–741.0) in group B; and 98.45 IU/mL (17.4–3557.0) in group C. There was a significant correlation of serum AFP levels with progression of the BCLC stage in hepatocellular carcinoma ($p = 0.0069$), (Fig. 2).

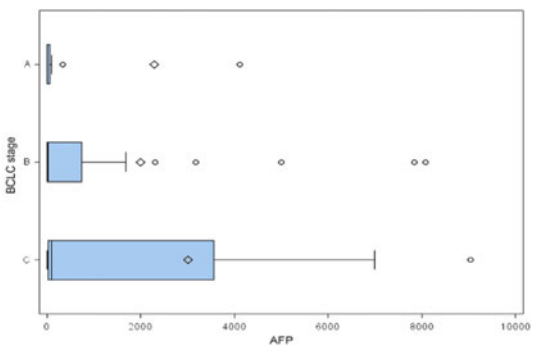

Figure 1

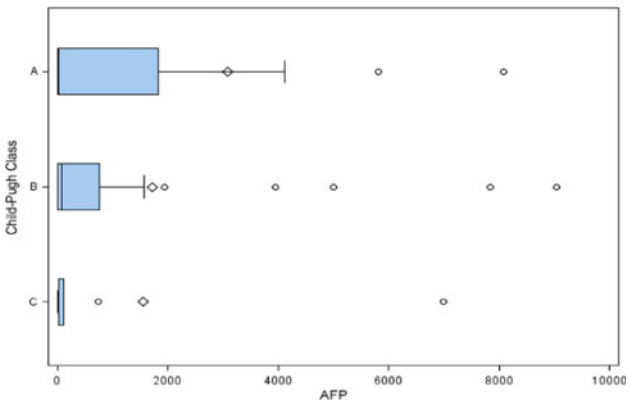

Figure 2

Conclusion: Our study suggests that serum AFP values are significantly correlated with the liver disease stage according to the BCLC classification. AFP has a predictive value and can be used to plan therapeutic strategies. Further studies are needed to shed light on the role of AFP as a prognostic biomarker.

A diagnosis in a … Chest-X-ray

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Introduction: Clinicians should get used to examine personally the radiograms and to work directly with radiologists; if not, they could make mistakes, as in the case described below.
Case Report: EE, male, 63, smoker (over 60 p/y), reaches our observation with a diagnosis of "pneumonia". Ex-rally driver, up 8 flights of stairs without problems with a lit cigarette, and he boasts. Examination of the chest: no obvious bruits; SpO2 98 %. The report of a recent chest-X-ray (CXR), practiced because of cough, describes generic parenchymal thickening, that must be re-evaluated after therapy. Looking at the radiogram we see *the right lung reduced in size, and denser*. Clinical history and direct "vision" of radiogram determine "alarm"; therefore further investigations are practiced:

- CT chest extended to Total Body, reveals the presence, on the right, of solid mass in soft edges, starting from the main bronchus, compressing the right pulmonary artery; there are also multiple hepatic metastatic lesions.
- FBS: macroscopic confirmation of the cancer.
- LDH > 2000 and NSE > 200 are sign of small cell lung cancer, subsequently confirmed by
- Cytology on FNAB.

The patient then undergoes chemotherapy and radiotherapy.
Discussion: Smoking is the leading cause of lung Ca. Very often, especially in the absence of suggestive symptoms (hemoptysis), we arrive late at diagnosis. The nonspecific symptoms (cough, phlegm, and dyspnea), and their possible changes, should be well researched and evaluated every time a smoker comes to our attention
Conclusions: The case shows that CXR, frequently practiced in smokers, should never be underestimated. The simple reading of the reporting can mislead; detailed request, with a description of symptoms and diagnostic doubt, it's useful for the collaboration of radiologist. The "holistic" approach, with direct evaluation of the radiograms, is an important "added value" to clinical activity.

The putative DNA/RNA helicase SLFN11 is causative in determining human cancer cell sensitivity to DNA damaging agents

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DNA damaging agents (DDAs) are the mainstay of treatment in human cancer. We analyzed the NCI-60 panel to identify new potential biomarkers of sensitivity to topoisomerase I (Top1) inhibitors, a broadly employed category of DDAs. We studied the NCI-60 transcriptome with Affymetrix Human Exon 1.0 ST microarrays and correlated the in vitro activity of four Top1 inhibitors in the NCI-60 with more than 17,000 transcripts. We discovered a single gene, Schlafen-11 (SLFN11) showing an extremely significant positive correlation with the response not only to Top1 inhibitors, but also to Top2 inhibitors, alkylating agents and DNA synthesis inhibitors (see Table). We show that SLFN11 is causally associated with cell survival upon camptothecin, etoposide and cisplatin administration in cancer lines from different tissues of origin, after siRNA-mediated silencing of SLFN11 expression. We also explored SLFN11 expression in ovarian and colorectal cancers and healthy related tissues from The Cancer Genome Atlas (TCGA) database, and observed that SLFN11 has a wide expression range in those tumors. We also observed that high SLFN11 transcript is an independent predictor of overall survival in a group of ovarian cancer patients treated with cisplatin-containing regimens. We conclude that SLFN11 expression is causally associated with the activity of DDAs in human cancer cells, has a wide expression range in colon and ovarian carcinomas, and should be further studied as a new biomarker for prediction of response to DDAs in the clinical setting.

NSC*	Chemical Name†	Category‡	r§	*P* value
609699	Topotecan	Topoisomerase I inhibitors	0.714	2.2×10^{-10}
616348	Irinotecan	Topoisomerase I inhibitors	0.613	2.5×10^{-7}
301739	Mitoxantrone	Topoisomerase IIinhibitors	0.624	1.3×10^{-7}
141540	Etoposide	Topoisomerase II inhibitors	0.533	1.4×10^{-5}
82151	Daunorubicin	Topoisomerase II inhibitors	0.399	0.002
123127	Doxorubicin	Topoisomerase II inhibitors	0.387	0.002
3088	Chlorambucil	Alkylating agents at N7 guaine	0.750	8.1×10^{-12}
8806	Melphalan	Alkylating agents at N7 guanine	0.680	3.2×10^{-9}
119875	Cisplatin	Alkylating agents at N7 guanine	0.619	1.7×10^{-7}
241240	Carboplatin	Alkylating agents at N7 guanine	0.488	8.9×10^{-5}
409962	Carmustine	Alkylating agentsat O6 guanine	0.439	0.001
79037	Lomustine	Alkylating agents at O6 guanine	0.343	0.008
613327	Gemcitabine	DNA synthesis inhibitors	0.669	7.0×10^{-9}
63878	Cytarabine	DNA synthesis inhibitors	0.644	3.8×10^{-8}

Table: Clinically used DNA damaging anti-cancer agents and their correlations with SLFN11 transcript. This table represents the correlation between the in vitro activities of commonly used FDA-approved anticancer drugs and SLFN11 transcript across the NCI-60.

For correlation analysis, the negative Log_{10} of the GI_{50} (the concentration of a compound that slows cell growth by 50 % compared to untreated control, measured by Sulforhodamine assay) of drugs tested in the 60 cell lines was correlated with SLFN11 transcript, obtained by micro-array analysis conducted in triplicate with the Affymetrix Human Exon 1.0 ST chips, and expressed as Log_2 intensity. * National Service Center number assigned by the Developmental Therapeutics Program to compounds tested in the NCI-60. † Commonly used chemical name. ‡ Main category of action - if known. § Pearson's correlation coefficient. Two-sided P value.

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Cardiovascular Diseases

Arterial stiffness in intracerebral hemorrhage

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Introduction: Intracerebral hemorrhage (ICH) accounts for approximately 10 % of all strokes. Hypertension may play a role in the pathogenesis of ICH that occurs in the basal ganglia, thalamus, pons, and cerebellum, but not in that of lobar ICH. Hypertension contributes to decreasing the elasticity of arteries, thereby increasing the likelihood of rupture in response to acute elevation in intravascular pressure. Aim of this study is to evaluate arterial stiffness (by means of ambulatory arterial stiffness index, AASI) in patients with deep (putaminal, thalamic) ICH in comparison with patients with lobar ICH.
Methods: 64 patients (mean age: 74 ± 10.7 years; 47 males, 17 females) referred consecutively to our department for intraparenchymal hemorrhage were enrolled in the study. All the subjects were submitted to brain CT scan and cerebral angio-CT scan. 24-h heart rate and blood pressure monitoring were measured in all subjects. The linear regression slope of diastolic BP on systolic BP was assumed as a global measure of arterial compliance, and its complement (1 minus the slope), named AASI, has been taken as a measure of arterial stiffness. Statistical analysis included comparison of AASI in patients with deep (putaminal, thalamic) and lobar ICH, by means of non-parametric Mann–Whitney test for unpaired data.
Results: In patients with deep ICH, AASI was significantly higher in comparison with patients with lobar ICH (0.64 ± 0.19 vs. 0.53 ± 0.17; p = 0.04).
Discussion: Our results suggest that, in deep ICH, arterial stiffness represents a possible pathogenetic factor modifying arterial wall properties and contributing to vascular rupture in response to acute elevations in intravascular pressure.

Cardiac power output accurately reflects external cardiac work over a wide range of inotropic states

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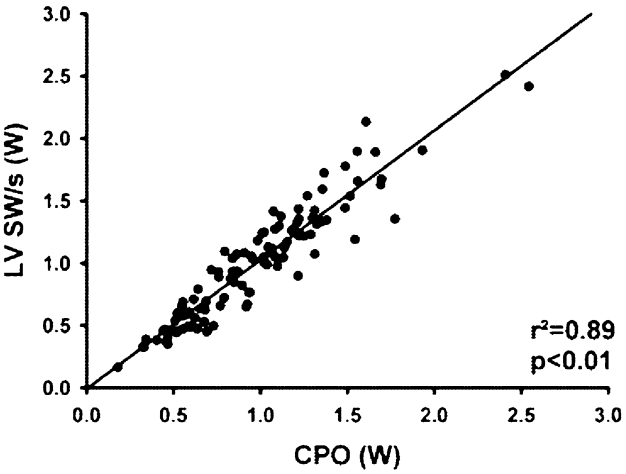
Introduction: Cardiac power output (CPO) is assessed as the product of cardiac output and mean aortic pressure, and it is the best predictor of intra-hospital mortality in cardiogenic shock. In classic hemodynamics, LV external work is assessed as stroke work (LV SW) and stroke work per second (LV SW/s). LV SW is represented by the LV pressure–volume loop area, and LV SW/s is measured in the same physical unit as CPO (Watt). Whether CPO is correlated to LV SW/s has not been tested yet.
Methods: We retrospectively analysed experimental data from studies in anaesthetized landrace pigs (n = 30) including protocols of septic shock, ventricular fibrillation/resuscitation, myocardial infarction, and hypertensive cardiomyopathy. CPO was derived from a Swan-Ganz catheter and an aortic pressure line during different stages of the respective protocols. Simultaneously, LV SW was calculated from LV pressures and volumes assessed by a LV conductance catheter.
Results: Heart rate ranged from 68 to 202 bpm, maximum LV pressure from 57 to 167 mmHg, mean aortic pressure from 41 to 151 mmHg, cardiac output from 2.0 to 10.1 l/min, and systemic vascular resistance from 4.3 to 26.2 mmHg*min/l. There was a strong correlation between LV SW and CPO (graph).
Conclusions: We conclude that under a wide range of inotropic states, CPO is an excellent measure of LV external work. These data further recommend the use of CPO to monitor the success of inotropic therapy in patients with depressed cardiac function.



GH/IGF-1 axis abnormalities are a common finding in mild-to-moderate Chronic Heart Failure

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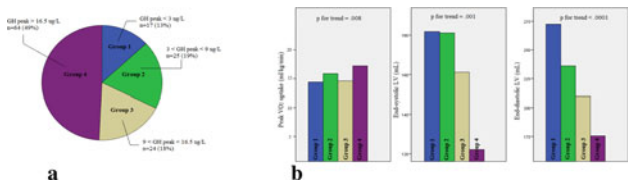
Introduction: Several studies have reported abnormalities of the GH/IGF-1 axis in chronic heart failure. Specifically, some investigators found normal IGF-1 values, some decreased, and some even increased. Very little information is available as to GH stimulatory test in a population of CHF patients, which appears of the utmost importance in view of the remarkable influence of several external variables on IGF-1 circulating levels including BMI, age, sex. No study have so far systematically investigated pituitary function in

large population of CHF patients, nor have addressed its impact on clinical status, exercise performance, and LV architecture and function.

Populations and Methods: 130 consecutive patients with CHF, NYHA class I to III, underwent a GHRH + Arginine stimulation test and a comprehensive basal hormonal evaluation. We diagnosed GH deficiency (GHD) if GH peak with stimulatory test was below 9 μg/L. GH status in CHF was also categorized in four different classes of GHD severity: very severe GHD (GH peak < 3 μg/L), severe GHD (GH peak 3 to 9 μg/L), partial GHD (GH peak 9 to 16.5 μg/L), and normal (GH peak > 16.5 μg/L). All patients underwent extensive cardiovascular study with complete echocardiography, cardiopulmonary exercise testing, NT-proBNP levels measurement. We also studied basal hormonal pattern in 135 age- sex- and BMI-matched controls.

Results: IGF-1 values in Controls and CHF were similar (137.7 ± 5.2 vs. 135.4 ± 4.6, $p = .78$). IGF-1 activity estimated by IGF-1/IGFBP-3 molar ratio was significantly higher in CHF then in Controls (138.1 ± 3.8 vs. 154.8 ± 3.9, $p = .003$). Prevalence of GHD in our CHF population was 34 %. Total IGF-1 and IGF-1/IGFBP-3 ratio did not differ in GHD and no-GHD, no correlation were found between GH peak and GH-related hormones (IGF-1, IGFBP-3, IGF-1/IGFBP-3 molar ratio). GHD population showed a higher prevalence of diabetes, a worse exercise capacity, higher LV volumes. Most alterations were also related to GHD severity (Fig. 1).

Conclusion: One third of our CHF population was GH deficient. Presence of GHD, and consistently its severity class, is associated to a pattern of worse clinical status including higher LV volumes and lower peak oxygen uptake and it is more.



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TIA or not TIA! Is it a problem?

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A 48-year old normal weight man and a low cardiovascular risk (according to The Cardiovascular Risk Chart) who he denied a drug abuse, he had been in his usual state of health despite transient episodes of dizziness after prolonged orthostatism attributed to orthostatic hypotension. About five months earlier hyposthenia of right arm appeared lasting about 10 min; none further investigation was made. The day of admission, just awaked, at 7 a.m. hyposthenia of right arm appeared together with numbness, difficult to make coordinated both gross movements and fine movements like write, but the patient was able to drive to work. At about 12 a.m. suddenly blurred vision and phosphenes take place in half the left visual field, thus the patient autonomously presented to Emergency Department. After 7 h, at 13 p.m., the symptoms have completely resolved. Whereas the duration of symptoms and a negative CT cranial scan a study was performed with a brain RMN. It showed multiple subacute ischemic lesions on left precentral gyrus, right temporal superior gyrus in cortical-subcortical areas and an ischemic lesion in left occipital cortex with it characteristics suggestive of cardioembolic stroke. Therefore we look for possible mechanism of recurrent atheroembolism in a young patient that could also explain stroke. The ECG showed a sinus rhythm, P pulmonary wave and a right conduction delay while a two dimensional transthoracic echocardiography normal cardiac findings. A Doppler ultrasound of epiaortic arteries was negative; then a complete haemostasis profile and autoantibodies screening were performed to rule out possible less common causes of ischemic stroke, negative for genetic or acquired prothrombotic state (in particular antiphospholipid autoantibody syndrome). Nevertheless the embolic origin was confirmed. A transesophageal echocardiogram showed nor thrombosis neither slowly flow in left auricle, instead disclosing a small aneurysm of interatrial sept with patent foramen ovale (PFO) of 2 mm leading to a right to left shunt of moderate entity. Before assign a pathogenetic role to patent foramen ovale it is mandatory to prove a source of thrombosis unrecognized, in particular performing a venous Doppler ultrasound of inferior extremity (upper extremities thrombosis is rare, in absence of trauma) and looking for cardioembolism in particular due to atrial fibrillation by performing Holter ECG, even if a single negative result could not rule out arrhythmia. In our patient we couldn't find a source of cardioembolism or thrombosis but patent foramen ovale account for a strong role in cryptogenic stroke, in particular in cerebral lesions of embolic pattern.

The presence of PFO in a patient with cryptogenic stroke increases the risk of relapse if in association with aneurysm of the septum and inter atrial shunt.

The clinical case described is a further confirmation of the most recent definition of TIA that is a brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than hour and without evidence of acute infarction at RM.

A therapeutic strategy concerning secondary prevention of stroke in our patient is not well defined, however our choice has been directed toward the use of ASA 300 mg/die considering brain lesion occurred in the absence of therapy.

Impaired ischemia-induced angiogenesis in diabetic mice depends on glycemic variability

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Background and Objectives: To investigate the role of glycemic variability (GV) on diabetic vascular complications and to explore the molecular pathways modulated by glycemic "swings".

Methods: 30 diabetic mice received once daily basal insulin administration plus 2 oral bolus of glucose solution (GV group, V) and 30 diabetic mice received once daily basal insulin plus 2 oral bolus of saline solution (stable hyperglycemia group, S) for a period of 30 days. Glycemia was measured 8 times daily to detect GV. Finally, post-ischemic neovascularization, induced by hindlimb ischemia 30 days after diabetes onset, was evaluated.

Results: GV was significantly different between S and V groups, whereas no significant difference of the mean glycemic values was detected. Laser Doppler perfusion imaging and histological analysis revealed that the ischemia-induced angiogenesis was significantly impaired in V mice compared to S group, after ischemic injury. In addition, immunostaining and western blot analyses revealed that impaired angiogenic response in V mice occurred in association with reduced VEGF production and decreased eNOS and Akt phosphorylation.

Conclusions: This is the first murine model of GV. GV causes an impairment of ischemia-induced angiogenesis in diabetes, regardless of average blood glucose levels, and this impaired collateral vessels formation depends on altered VEGF pathway.

Usefulness of lung ultrasound and bioelectrical impedance vector analysis (BIVA) in differential diagnosis of dyspnea in patients with comorbidity

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Background: Acute dyspnea is a common cause of emergency department (ED) admission. In 2010, patients presenting for dyspnea at the ED of Padua University Hospital were 5 % of the total accesses (3975 cases) and 13 % of hospitalizations. Despite new technologies, the diagnosis of dyspnea represents a relevant problem, particularly in elderly patients with comorbidity.
Aim: To evaluate the usefulness of lung ultrasound and of bioelectrical impedance vector analysis (BIVA) in the differential diagnosis of dyspnea.
Patients and Methods: We included 37 patients (12 female and 25 male) with a mean age of 78.7 ± 11.4 year hospitalized in the Medicine Department of Padua University Hospital. The ED admission diagnosis was cardiac (according to the European Society of Cardiology criteria) in 19 patients, infective in 10 (pneumonia or decompensated COPD), mixed (cardiac and infective) in 1 and only descriptive in 7 (respiratory distress or dyspnea). Patients were excluded if they had pulmonary embolism or cancer. All patients underwent lung ultrasound and BIVA on day first, third and before discharge. Lung ultrasound examinations were performed by a single operator, bilaterally scanning the anterior and lateral chest wall, with the patient in supine position. Each scan was considered to be positive when ≥ 3 close B-lines were visualized (maximum distance between adjacent B-lines of 7 mm). BIVA measurements were obtained with standard tetrapolar bioelectrical impedance electrodes at a frequency of 50 kHz using a phase-sensitive analyzer (Akern 101 Anniversary). The 2 vector components R and Xc were recorded and divided by the subject's height. All BIVA measurements were performed by one operator.
Results: Lung ultrasound modified admission diagnosis in 24 patients (65 %; $p < 0.01$), with an increase of mixed dyspnea (from 1 to 13), a decrease in cardiac (from 19 to 17) and infective (from 10 to 7) dyspnea; no patients had a descriptive diagnosis. The number of positive lung scans at admission was not different between patients with heart failure and patients with mixed dyspnea, but was significantly higher in these two groups compared with patients with infective dyspnea (5.0 ± 2.52 and 4.62 ± 2.72 vs. 0.57 ± 1.13 $p < 0.01$). Patients with heart failure had a significant reduction in number of positive lung scans at discharge (5 ± 2.52 vs. 2.24 ± 2.36 $p < 0.01$) and the reduction was already present three days after admission (5 ± 2.52 vs. 2.42 ± 2.71 $p < 0.01$). Also patients with mixed dyspnea had a decrease in positive scans at discharge (4.62 ± 2.72 vs. 2.46 ± 1.71 $p < 0.05$), but without any significant difference the third day (4.62 ± 2.72 vs. 3.78 ± 2.28 NS). All patients with infective dyspnea had negative lung sonography (less than 3 B-lines for each scan). Regarding BIVA evaluation, R value was not different between subgroups (heart failure 295.13 ± 76 vs. mixed dyspnea 290.48 vs. 106.07 vs. infective 355.3 ± 94.7). Xc value was not different between the three subgroups (heart failure 27.96 ± 17.15 vs. mixed 21.15 ± 7.26 vs. infective 24.14 ± 6.5). There were no significant differences at discharge.
Conclusions: Lung sonography is a useful tool in differential diagnosis of dyspnea in patients with comorbidity, as it can identify and quantify pulmonary stasis. BIVA is not useful in differential diagnosis of dyspnea and is not suitable to identify pulmonary congestion.

Exercise-induced endothelial dysfunction predicts cardiovascular events in patients with intermittent claudication

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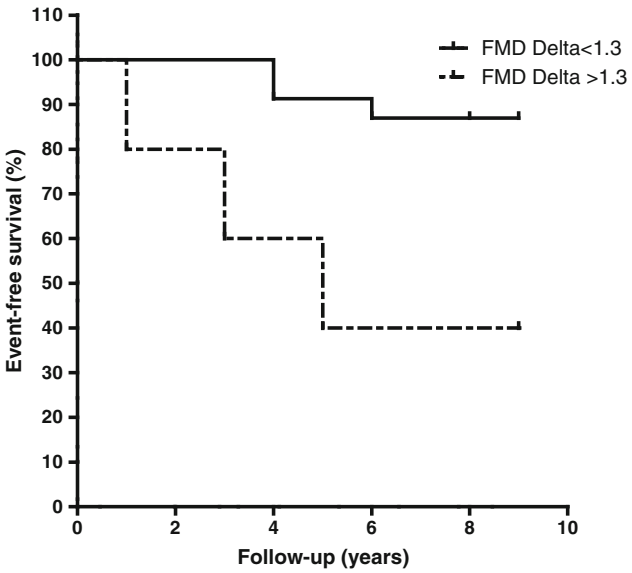
Background: Flow-Mediated Dilation (FMD), represents an established measure of the endothelial vasodilatory function of conduit arteries. An impaired FMD predicts adverse cardiovascular events in various categories of patients at risk, including peripheral arterial disease (PAD). Among the mechanisms leading to impaired FMD, ischemia/reperfusion injury plays a pre-eminent role. Intermittent claudication (IC) is an example of repeated ischemia/reperfusion injury that may contribute to the progression of vascular disease by worsening endothelial function, a trigger for acute cardiovascular events.
The predictive value of effort-induced endothelial dysfunction for cardiovascular events in patients with IC has not been studied previously.
Objective: To assess whether exercised-induced endothelial dysfunction is predictive of adverse cardiovascular outcome in IC.
Methods and Results: In 44 patients with IC we measured brachial artery FMD by B-Mode ultrasonography (according to current guidelines) at rest and 10 min after a maximal treadmill exercise (3 km/h, 10 % incline). Basal FMD was lower (3.5 ± 0.6 %) as compared with age- and sex-matched controls (5.7 ± 0.6 %), in agreement with previous results. Treadmill exercise halved the FMD (from 3.5 ± 0.6 to 1.45 ± 0.7 %, $p < 0.0372$). Upon a mean follow-up period of 108 months a total of 9 cardiovascular events occurred (2 vascular death, 1 STEMI, 2 critical limb ischemia, 4 peripheral arterial revascularization). In a multivariate analysis, a post exercise reduction on brachial FMD > 1.3 % was predictive for cardiovascular events (Fig 1).



Conclusions: Maximal exercise-induced systemic endothelial dysfunction, assessed by a drop of brachial artery FMD, is predictive of cardiovascular events in patients with IC. Ischemia/reperfusion injury may be a target for therapeutic intervention in IC.

Different behavior of NOX2 activation in patients with paroxysmal/persistent or permanent atrial fibrillation

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Background: NOX2, the catalytic sub-unit of NADPH oxidase, is suggested to play a role in favoring the occurrence of atrial fibrillation (AF) after cardiac surgery via formation of reactive oxidant species. However its role in spontaneous FA is still unclear.
Objective: The aim of this study was to define the role of NOX2, the catalytic sub-unit of NADPH oxidase, and isoprostanes, a marker of oxidative stress, in the different settings of AF.
Patients and Main Outcome Measures: The study was performed on 174 patients with AF (82 with paroxysmal/persistent and 92 with permanent AF) and 90 controls matched for sex and age and atherosclerotic risk factors. Urinary isoprostanes and soluble serum NOX2 (sNOX2-dp) were measured in each patient.
Results: Urinary isoprostanes and sNOX2-dp concentrations were significantly higher in patients with paroxysmal/persistent AF than in permanent AF and controls. Compared to controls, patients with permanent AF showed a weak increase of sNOX2-dp and no difference in isoprostanes. Multivariable analyses demonstrated that baseline values of sNOX2-dp, and urinary isoprostanes were independently associated with the type (paroxysmal/persistent vs. permanent) of AF ($\beta = -224$, $p = 0.007$ and $\beta = -231$; $p = 0.005$, respectively). A significant correlation between sNOX2-dp levels and urinary excretion of isoprostanes was also detected ($R = 0.707$; $p < 0.001$).
Conclusions: The study provides evidence that NOX2 is up-regulated only in patients with paroxysmal/persistent AF and is responsible for isoprostanes over-production. This finding warrants study to see if inhibition of NOX2 may reduce the risk of paroxysmal/persistent AF.

Effectiveness of integration hospital/territory in management of oral anticoagulant therapy of patients undergoing to Electric Countershock: an internal medicine department experience

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Background: The intensive proliferation of guidelines and stratification scores for thromboembolic and hemorrhagic risk, such as CHA_2DS_2-VASC and HAS-BLED, focuses its interest on the proper management of oral anticoagulant therapy (OAT). In clinical practice, narrow therapeutic index of warfarin can be achieved through three cornerstones: (1) reliable laboratory (2) good medical expertise in OAT (3) Patients Compliance. In our Internal Medicine Department (IMD) atrial fibrillation (AF) is among the top 5 DRG by frequency. Driven by this reality, we prepared specific evidence-based protocols and pathways for AF management. Optimal OAT for 4 weeks is required before attempting sinus rhythm restoration, in order to reduce cardioembolic risk related to cardioversion (CV). Current guidelines confirm inverse relationship between time taken to proceed with CV and success of SR restoration. Many procedures still delay because at time of CV, patients (pts) were not in range. We can improve outcomes aiming at stable INR in the 5 weeks before the CV. A strict follow-up of these pts may reduce variations which lead to significant delays in CV. Our department routinely follows pts requiring OAT in preparation for CV.

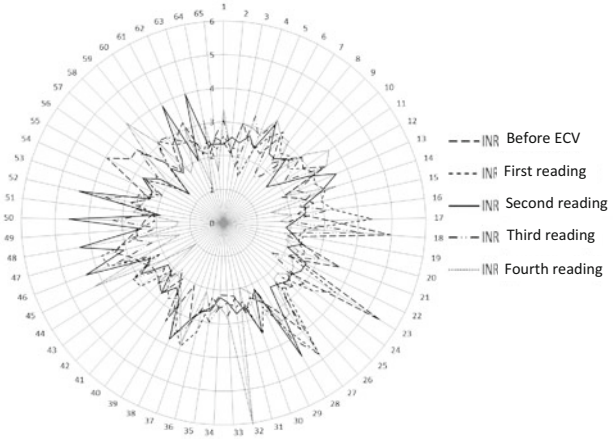

Figure 1

Aims: evaluate the effect of Patient Care Management by our IMD, from diagnosis to CV, especially on the stability of INR values in the 5 weeks preliminary to Electric Countershock (ECV), as indicator of a better outcome, in pts followed by our unit for AF.
Methods: We followed 121 pts affected by persistent AF, who underwent ECV. 52 were excluded for AF recurrence, the other 60 were referred to our surveillance center for OAT before ECV. All pts were treated with the same pharmacologic protocol, including 4 weeks of therapy with oral anticoagulants, class III antiarrhythmic, angiotensin receptor blocker (irbesartan) and statin. After 4 weeks, pts underwent to ECV with standard protocol (first shock: 150 J, second shock: 200 J, third shock: 200 J). INR variations in this population of pts were evaluated. Multivariate GLM for repeated measures and Cronbach's reliability analysis were performed with SPSS 13.0 for Windows systems.
Results: The mean value of PT/INR in the 5 reading performed before ECV remained between 2.5 and 3.0 with a 95 %CI between 2.4 and 3.0 in each of the 5 measurements. The multivariate evaluation of intra-subject variation was not significant in the 5 measurements ($p > 0.05$). This observation remained statistically non-significant also in direct comparison of the mean of single measurements, demonstrating a substantial homogeneity of the mean values of PT/INR. The internal reliability of the data was assessed using Cronbach's test (alpha: 0.72), which confirmed the high intra-survey validity of the INR in pts followed in our center (Figure 1).
Conclusions: OAT management resulted highly reliable in our center: PT/INR controls remained substantially stable in the controls prior to ECV. We observed no major thrombotic nor hemorrhagic adverse events nor major complications in the selected sample. Most of pts are in range the day of ECV after 4 weeks of anticoagulation. With an efficient laboratory and a reliable center, as an IMD, it is possible to keep the dose of warfarin within the therapeutic range, optimizing resources. Undertaking this office, our IMD increases success chances of the procedure. However, the dark horse of pts, who must be reliable. It seems reasonable to argue that attending a reference center, compliance to OAT could be increase.

Normalization of portopulmonary hypertension after treatment with sildenafil and successful treatment of chronic hepatitis C

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Introduction: Patients with chronic liver disease are at risk for the development of portopulmonary hypertension. Data from epidemiological studies reveals that about 2–6 % of patients with portal hypertension develop pulmonary hypertension. Of note, about 10 % of these patients do not present with liver cirrhosis. In patients with portopulmonary hypertension the same treatment algorithm as in patients with idiopathic pulmonary hypertension should be considered, taking into consideration comorbidities (e.g. anticoagulant therapy may not be recommended for patients at increased bleeding risk).

We present the case of portopulmonary hypertension successfully treated with sildenafil.

Case Report: A 39-years-old man came to the Emergency Room complaining of worsening fatigue, dyspnea and leg edema. He was a current smoker and had a previous history of addiction to diacetylmorphine. He underwent appendicectomy when he was 13 years old. The physical examination was significant for the presence of jugular veins distension, a holosystolic murmur best heard over the tricuspid area, moderate hepatomegaly, leg edema to the thighs. The ECG showed signs of right ventricular strain. During the hospital stay he was treated with intravenous furosemide and oral spironolactone with modest improvement of the overt right heart failure. Ace inhibitor therapy was considered not indicated because of his arterial pressure (90/50 mmHg). Thromboembolic pulmonary disease was excluded by contrast CT angiography and ventilation/perfusion scintigraphy. Other extensive clinical and laboratory examination were not significant but for the echocardiographic findings of severe pulmonary hypertension (severe right chambers dilation, hypokinesia of the right ventricle with tricuspid annular plane systolic excursion of 12 mm, short pulmonary acceleration time, severe tricuspid regurgitation with atrio-ventricular pressure equalization) and chronic liver disease due to hepatitis C infection with signs of portal hypertension.

Then he underwent right heart catheterization with demonstration of pre-capillary pulmonary hypertension (mean pulmonary arterial pressure 35 mmHg, cardiac index 1.9 L/min). Treatment with sildenafil 20 mg TID was promptly started. Afterwards, the patient presented a progressive and dramatic improvement of functional capacity, and of the electrocardiographic and echocardiographic findings.

Considering the significant clinical improvement we decided to treat the HCV infection (genotype 3, low viral load) with pegylated interferon and ribavirin, obtaining sustained virological response.

Nowadays the patient is in functional capacity NYHA I, with 604 m at the 6 min walking test. The electrocardiographic, echocardiographic and laboratory findings are all normalized.

Considerations: The case presented: confirms that portopulmonary hypertension can occur even in patients with chronic liver disease who do not have liver cirrhosis, and that sildenafil is effective in the treatment of pulmonary hypertension associated with portal hypertension.

It's likely that with normalization of liver disease (and of pulmonary pressures) the specific treatment of pulmonary arterial hypertension may be withdrawn, even if there are still no data in literature on this topic.

BNP levels are related to days of hospitalization independently to the pathology in critical care settings

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Background: Increased brain natriuretic peptide (BNP) levels have been related to several conditions, such as acute heart failure (AHF), pulmonary embolism (PE) and acute coronary syndromes (ACS). Particularly among elderly patients, a longer hospitalization is related to higher morbidity and mortality. The usefulness of BNP as a prognostic factor is amply demonstrated in different subpopulations of both medical and surgical patients.

Aims: To evaluate the relationship between BNP levels and length of in-hospital stay in patients with PE, ACS, AHF, septic and cardiogenic shock admitted to our internal medicine department (IMD).

Methods: We retrospectively evaluated 500 consecutive patients admitted to our IMD. BNP was evaluated at the admission in all the patients. Each patient underwent a complete diagnostic workup. We evaluated the curve-fit correlation between BNP levels and days of hospitalization using SPSS 13.0 for windows systems.

Results: Mean age was 80 $\pm$ 9.85 years, males representing 58 % of the sample. AHF represented 74.9 %, ACS 13.5 %, PE 11.6 % of the sample. We found that BNP levels and days of hospitalization were better described by a logarithmic regression model (R^2: 0.674, $p < 0.0001$) (Figure 1).

Conclusions: Among elderly patients admitted in an IMDs, higher BNP levels are associated to longer hospitalizations independently to the pathology. This relationship is better described by a logarithmic regression model. However, larger cohorts are required to validate this observation.

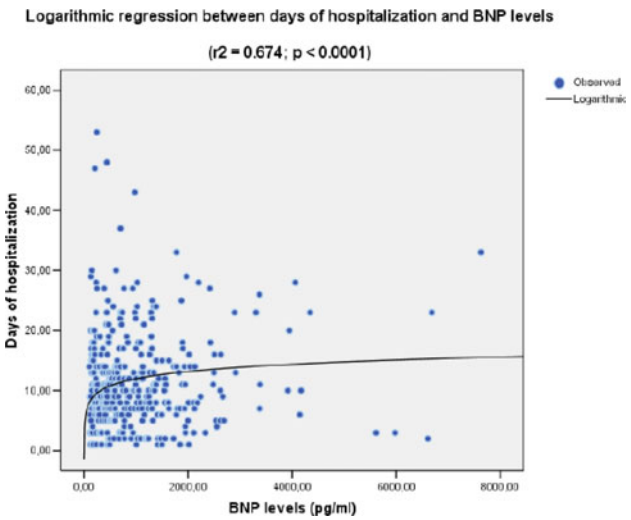

Figure 1 Logarithmic regression between days of hospitalization (any cause) and BNP levels, as taken at the admission. The correlation among the two variable is highly significant ($p < 0.0001$).

Venous thromboembolism and Hughes syndrome: case report

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Introduction: This case concerns a 33 year-old man suffering from dyspnea and chest pain, with a turgid limb since a few days, turgidity in the left inferior limb since 20 days after sport trauma.
Purpose of the Experiment: We have the following goals: to show the case report of Hughes syndrome, connected with deep venous thromboembolism; to check the relationship between the syndrome and deep venous thromboembolism.
Case Report: At the beginning the anamnesis showed breathing difficulty (arterial blood gas analysis value pO2 < 60 mmHg) associated with chest pain, confused state of mind, hemodynamic instability (PAS < 90 mmHg). The patient was submitted to: chest, abdomen and pelvic TC with mcm, which revealed thrombosis in the lower lobar region of the left pulmonary artery as well as of the segmental parts of the right pulmonary artery, many ground glass areas bilaterally, perviety of inferior vena cava; thrombosis occlusion of the left iliac femoral artery; a pre discharge from hospital echography (within the limits) with pulmonary arterial pressure measurement within the limits; venous and lower limb echo color Doppler (thrombosis occlusion of the left popliteal femoral iliac artery) and elastic compression bandage; spirometry (ventilatory deficiency with DLCO within the limits); neoplastic markers research (negative); thrombophilic markers research (positive):

- Anticardiolipin antibodies IgG 150.00 U/mL (VN 0–10)
- Anticardiolipin antibodies IgM 47.00 U/mL (VN 0–10)
- Basal aPTT (repeated) always > 85 s.
- Positive MTHFR C677T with different homozygous genotype
- Homocysteine 28 micromol. (VN < 15)
- LAC (lupus anticoagulant) is present: viper poison Russell 3.10 (ratio < 1.21); silica clotting time 2.62 (ratio < 1.31)
- Antibetaglycoprotein antibodies IgG 100.99 SGU (VN < 20)
- Antibetaglycoprotein antibodies IgM 8.93 SMU (VN < 20)

The patient was treated with LMWH together with oral anticoagulants previous check INR daily, until optimizing the therapeutic range.
Discussion: This case of venous thromboembolism is chronologically correlated with sport trauma, positive LAC, anticardiolipin antibodies, antibetaglycoprotein antibodies, peculiar to Hughes syndrome. LAC test studies the capacity of antiphospholipid antibodies to extend the coagulation time in the phospholipid-addicted tests. The anticardiolipin antibodies are specific autoantibodies for negatively-charged phospholipids or for complex phospholipid proteins. The antiphospholipid antibodies' syndrome is characterized by the combination of thrombotic events and/or obstetric complications due to positivity for at least one test for aPL (LAC, aCL and anti-β2GPI). The thrombotic events with APS are variable, since each organ and tissue may be concerned about thrombus formation. The pulmonary ground glass aspect means there is an alveolar-capillary damage, due to hemodynamic alterations in the course of embolism. It is reversible with the remission of vascular pathology, as shown in angio TC test the patient was submitted to some weeks afterwards.
Conclusions: The authors showed a case report of Hughes syndrome (LAC positivity, anticardiolipin antibodies and anti-β2GPI) correlated with deep venous thromboembolism and basal aPTT values, constantly greater than 85 s. That is why he was submitted to LMWH treatment, as aPTT could not be controlled in case of sodic heparin.

Venous thromboembolism and reconstruction of femoral epiphysis for cephalic necrosis: case report

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Introduction: We present a case of a 30 year-old man suffering from dyspnea and chest pain, with a turgid limb since a few days, turgidity in the left inferior limb since 20 days. The results obtained from the case history showed bilateral necrosis of femoral epiphysis. That is why he had an operation approximately 1 month before for cephalic necrosis stadium III-IV with autolog engineering cartilage, bioceramic cylinders, freeze-dried bone chips in association with piastrinic gel and a concentration of medullary cells.
Purpose of the Experiment: We have the following goals: to show a case report concerning the reconstruction of femoral epiphysis for cephalic necrosis, in order to check the relationship between the operation and venous thromboembolism. Moreover, to report any similar cases in literature.
Case Report: At the beginning the anamnesis showed breathing difficulty (arterial blood gas analysis value pO2 < 60 mmHg) associated with chest pain, confused state of mind, hemodynamic instability (PAS < 90 mmHg) according to American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition).
The patient was submitted to: chest, abdomen and pelvic TC with mcm; pulmonary angiography with loco-regional fibrinolysis in association with sodic heparin, in peripheral vein; a pre discharge from hospital echocardiography with pulmonary arterial pressure measurement; implant of removal caval filter OPTEASE; phlebography of the left inferior limb with loco-regional fibrinolysis; venous and lower limb echo color Doppler and elastic compression bandage; negative identification of thrombophilic and neoplastic markers; pelvic RM carried out before the operation and 6 months after the operation.
Discussion: This case of venous thromboembolism is chronologically correlated with the operation the patient was submitted to, despite the anticoagulant prophylaxis monitored carefully after the operation. Anyway the research for primary and secondary thrombophilia was negative. The patient belongs to a very restricted group of people (20) enrolled with the same pathology (Stadium III-IV with cephalic necrosis), who were recruited in order to find the reconstruction of femoral epiphysis with autolog engineering cartilage, bioceramic cylinders, freeze-dried bone chips in association with piastrinic gel and a concentration of medullary cells. This was the only patient suffering from thromboembolism among the 20 patients enrolled. We report the experiences of Karatoprak, Hattori, Doi, Wang, Chang, Liang. There are no other case reports correlated with venous thromboembolism.
Conclusions: We showed a case report concerning the necrosis of the femoral head, according to a research project enrolling 20 patients with cephalic femoral necrosis (Stadium III-IV), with the reconstruction of femoral epiphysis with autolog engineering cartilage, bioceramic cylinders, freeze-dried bone chips in association with piastrinic gel and a concentration of medullary cells, complicated by venous thromboembolism.

Thoracic outlet syndrome: case report

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Introduction: We illustrate the case report of a 26 year-old woman suffering from turgidity in the left superior limb after weight lifting at the gym without chest pain or dyspnea that looks to be a Thoracic Outlet Syndrome (TOS).
Case Report: There are no pathologies at all emerging from the case history. She took estro-progestinic oral contraceptives in the last few years. From the check-up we observed turgidity in the left superior limb as well as in the upper left clavicle region. The patient was chilly. PA was 110/60 mmHg, FC 80/m rhythmic. The oxygen saturation at 99 % with FiO2 21 %. During the short stay in hospital we carried out the following examinations: several ECG revealing a sinus rhythm; hematochemical exams: within the limits. Markers of primary and secondary thrombophilia: within the limits; chest x-rays with no pleuroparenchymal alterations in action; TT echocardiography with kinesis was normal, (FE 70 %), right region in the limits, absence of pericardial effusion; venous echo-color Doppler of the inferior limbs demonstrated perviety of superficial and deep venous circulation; venous echo-color Doppler of the upper limbs delineated a thrombosis occlusion of the left homer-subclavian region; chest CTA + superior chest showing absence of filling defects of pulmonary arteries and thrombosis in the left subclavian artery; superior chest angioRM with hyperabduction test, assessing thrombosis of the left subclavian region and compression during hyperabduction test. The patient was submitted to LMWH treatment and warfarin therapy until INR assessment. At her discharge we observed detumescence in the upper limb.
Discussion: Upper extremity symptoms due to compression of the neurovascular bundle by various structures in the area just above the first rib and behind the clavicle. Etiologies include congenital bony structures, fibromuscular abnormalities, posture, certain movements, trauma. Epidemiology: 3 to 80 cases per 1000, ages 20–40, women > men (4:1), neurogenic TOS (90 %) > Venous TOS > Arterial TOS (<1 %), cervical ribs occur in <1 % of population 70 % women. Cervical disc disease. Differential diagnosis with: cervical facet disease, malignancies (Pancoast/local tumors), peripheral nerve entrapments (ulnar or median nerve), Brachial plexitis, rotator cuff injuries, fibromyalgia, muscle spasm, neurologic disorders, chest pain, angina, vasculitis, vasospastic disorder (Raynaud's), neuropathic syndromes of upper extremity. This case report depicts TOS clinical trial, due to hyperabduction test during angioRM, and compression mainly venous. As a matter of fact, the patient has never suffered from paraesthesia or any signs of arterial ischemia of the limb. Gym (weight lifting) associated with the compression behind the clavicle in hyperabduction of the left subclavian region and taking estro-progestinic oral contraceptives are the very primum movens. As far as the therapeutic strategy is concerned, we had a standby behaviour. This means: (a) this was the first case we presented; (b) the result we succeeded in was a venous rehabilitation of the obstructed region during a Doppler ambulatory monitoring 30 days after the episode; (c) the patient has never suffered from neurogenic or arterial compression. Therefore, we agreed with vascular surgeon on a constant clinical monitoring as time goes by. We also thought about the surgical decompression just in case of relapse symptoms. Our conservative approach reflects Benhamou experience: the aim of his controlled studies is to test the therapeutic validity of recent alternatives such as thrombolysis, angioplasty procedure, venous stents. Another significant surgical decompression is Vogelin study, which revealed the success in supraclavicular region associated with the absence of symptoms after 12-year follow-up. TOS treatment has to deal with a multidisciplinary approach with specific algorithm according to the compressed case report, as it clearly emerges from Brooke's work.
Conclusions: The Authors showed a TOS case report with venous thrombosis of the left homer-subclavian region after physical activity associated with costo-clavicular compression during hyperabduction test in a young patient who took estro-progestinic oral contraceptives.

Indirect central echocardiographic criteria in pulmonary embolism. Cochran's Q test and "since" study. Comparative analysis for nominal variables with venous thromboembolism in 20 patients during the two-year period 2010–2011

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Introduction: "SINCE" study, acrostic of "Signs echocardIographic iNdirect Central of pulmonary Embolism" enrolled 20 patients, between 48 and 82 years old, with venous thromboembolism (central pulmonary embolism) hospitalized in the two-year period 2010–2011. The results obtained from the case history showed a severe respiratory failure in all patients (arterial blood gas analysis value $pO2 < 60$ mmHg), associated with chest pain, confused state of mind, hemodynamic instability ($PAS < 90$ mmHg). In the 20 patients, we examined echocardiographic values at the entrance, both direct and indirect, of the overload of the right ventricle according to Kurzyna criteria. As a consequence we carried out a comparative analysis for nominal variables with the Cochrna's Q test to check if there is a significant relationship between A conditions (RV overload criteria), B (60-60 SIGN), C (Mc Connell Sign).
Purpose of the Experiment: "SINCE" study has the following goals: to test any association with A conditions (RV overload criteria), B (60-60 SIGN), C (Mc Connell Sign) in 20 patients enrolled in SINCE study. Moreover, to check its statistical importance by applying the Cochran's Q test in order to determine if the differences are due to chance.
Procedures Used: To calculate χ^2 we apply the following formula: $\chi^2 = (k\text{-}1)[(k\ x)\text{-}y^2]/(k\ y)\text{-}z = 28.9$. "K" refers to 3 variables, "X" refers to the total sum of squares of the 3 variables. "Y" stands for the total of the chosen scores. "Y^2" is the square of the total chosen scores. "Z" means the sum of the squares of the chosen scores. The χ^2 relative value (VR) is 28.9 with Degree of Freedom (GL) = 2. The χ^2 critical value (VC) per $p = 0.001$ is 13.816.
Observation/Data/Results: By applying the Cochran's Q test, the results demonstrate how A, B, C conditions are not at all due to chance. They have indeed a significant importance because the χ^2 obtained relative value (VR) is 20.95 with Degrees of Freedom (GL) = 2, and the χ^2 critical value (VC) per $p = 0.001$ is 13.816. The differences in choice are consequently strongly significant with $p < 0.001$.
Discussion: The results obtained show how the significant association in SINCE study, reveals the coexistence, according to Kurzyna criteria, of A conditions (RV overload criteria) + B conditions (60-60 SIGN) + C conditions (Mc Connell Sign). This means that the case report begins with right ventricular distress. From the literature we survey the following experiences that come out. Pech connects PEI with the survival of patients with pulmonary embolism. Miller focused on a scoring system based on the number of obstructive vascular segment during pulmonary angiography. Fava explains the effectiveness of mechanical fragmentation linked to pulmonary intra

arterial thrombolysis with urochinasi. Nakazawa looked into the risk of distal embolization with pulmonary hypertension after loco-regional lysis combination with thromboembolism fragmentation. Kursyna and Toosi considered indirect central echocardiographic criteria in order to assess the ventricular overload in those patients affected with severe pulmonary embolism. Casazza studied Mc Conell's signs, concerning those patients with acute right ventricular failure, a particular marker for pulmonary embolism.

Conclusions: "SINCE" study showed how in 20 patients affected with venous thromboembolism (central pulmonary embolism), the most significant association is linked to the coexistence of A conditions (RV overloaded criteria) + B conditions (60-60 SIGN) + C conditions (Mc Connell Sign). This correlation is very significant according to the Cochran's Q test, in 20 patients with central pulmonary embolism. Among all the similar case reports in literature, "SINCE" study reveals data that complete those provided from Kurzyna, Toosi, Casazza.

Influence of systolic and diastolic blood pressure on nail-fold capillary rarefaction

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Hypertension represents one of the most important atherosclerotic risk factors, since it causes vascular damage both to macro and microcirculation. Capillaroscopy is very useful to examine in vivo the small vessels of naifold, **The aim of the study** was to evaluate capillaroscopic characteristics in a consecutive and non selected series of elderly hypertensive patients with ISH and SDH and to compare the findings of nail fold of the hands to those observed on feet.

Eighty hospitalized patients aged 65 years or over (mean age 74.36 ± 8.40, range 65–96), with essential hypertension, 52 M and 28 F were studied. Forty-four were affected with ISH and thirty-six with SDH with a time period of disease between 4 and 30 years (mean 11.70 ± 6.06 years). Mean values of blood pressure were 162.08 ± 12.02 and 92.88 ± 6.06 mmHg in patients with SDH and 166.12 ± 82.04 ± 8.22 mmHg in patients with ISH. All the patients were under hypertensive treatment. The patients with diabetes mellitus and secondary arterial hypertensive were excluded. Eighteen patients were obese and thirty-one had a history of tobaccos. All the subjects enrolled in the study underwent a nail fold capillaroscopy at 2nd, 3rd, 4th, and 5th finger or both hands and 1st, 2nd, 3rd, finger of both of feet and Eco-Color Doppler on leg.

Results: Nail fold capillaroscopic analysis revealed that the decrease in number of capillary loops was more marked in the patients with SDH. The most frequent capillaroscopic abnormalities were lengthened capillaries (80 %), Thinner capillaries 38 %), ectasias (62 %), dystrophic capillary loops (72 %), oedema (80 %) and microhemorrhages (42 %). Dilated and tortuous capillaries, arteriovenous sludge, and fleabite juxtacapillary microhemorrhages, were found especially in the patients with ISH. Those findings were statistical significant on the feet comparing with hands in ISH: Lengthened Capillaries 76 % (Hand) versus 82 % (Feet) pNs; thinner capillaries 38 % (H) versus 44 % (F) pNS; ectasias 55 % (H) versus 85 %(F) $p < 0.005$; oedema 61 %(H) versus 93 %(F) $p < 0.005$; microhemorrhages 38 %(H) vs80 %(F) $p < 0.005$; sludge A.V 49 % (H) versus 39 % (F) pNS; number of capillaries < 9/mm: 90 %(H) versus 100 % (F) pNS. We revealed coronary heart disease in 16.2 % (ISH) versus 4.4 % (SDH patients) $p < 0.1$; cerebrovascular disease in 21 % versus 85 (SDH patients) $p < 0.1$. Our study revealed a decrease of the number of capillary loops, the loops appear thinner and lengthened in the hypertensive people without any significant difference between ISH group and SDH group. Such changes are due to a decrease in blood flow to micro vessels because of arteriolar diameter constriction.

Conclusion: About the evaluation of fingernail fold of hands and feet we found dilated and tortuous capillaries, edema and fleabite juxtacapillary microhemorrhages more frequently in the feet of the patients with ISH. These results confirm the strong and continuous relationship between ISH and the risk of stroke, coronary heart disease and end-stage renal disease. As compared with SDH, traditionally considered as main target of hypertension treatment, ISH represents a stronger predictor of the risk of cerebro- and cardiovascular events and the prevalence of ISH results markedly elevated among elderly people.

Variation of plasma γ-MSH levels after extracellular body fluid manipulation in salt-sensitive and salt-resistant hypertensive patients

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The γ-melanocyte stimulating hormone (γ-MSH) derives from the neurointermediate lobe of the pituitary gland and its inhibition induces salt-sensitive hypertension in rat fed a high-salt diet. To date and to our knowledge, a role for γ-MSH in salt-sensitive hypertension has been showed only in rodents and not in humans. The aim of this study was to verify whether γ-MSH responds to variations of sodium-load in hypertensive patients and whether these variations are different between patients with salt-sensitive (SS) or salt-resistant (SR) hypertension. Fourteen essential hypertensive patients (age 48 ± 13 years, sex M/F = 9/5) were classified as SS or SR analyzing blood pressure response to an acute sodium-load (2L of normal saline in 4 h) and sodium-depletion (furosemide 125 mg/d) according to Weinberger's protocol. Then, the same patients were orally supplemented with 15 g/d NaCl for 3 days. Body fluids distribution was evaluated at each manipulation of sodium-load by bioimpedance analysis. SS were older (54 ± 13 vs. 41 ± 10 years, P = 0.05) and had higher brain natriuretic peptide (BNP) levels (26 ± 21 vs. 9 ± 8 pg/mL, P = 0.02) than SR. After the acute sodium-load, mean arterial blood pressure (MAP) and extra- to intra-body water ratio (E/I) increased only in SS, whereas γ-MSH increased only in SR. Plasma active renin (PAR) and aldosterone (PA) levels increased and BNP decreased in both groups of patients. After sodium-depletion, MAP and E/I ratio decreased and γ-MSH increased only in SS. PAR and PA increased and BNP decreased in both groups of patients. After supplementation with NaCl, MAP increased only in SS, whereas PAR and PA decreased and urinary sodium and BNP increased in both groups of patients. Neither body fluids distribution nor γ-MSH change after chronic NaCl supplementation. In conclusion, γ-MSH responds to acute sodium variations and in a different manner in SS and SR. γ-MSH might have a role in blood pressure response to body fluid volume manipulations in hypertensive patients.

Pon1 activity and coagulation biomarkers: no association with thrombin generation parameters, but an inverse correlation with d-dimer plasma concentration

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Background: High-density lipoproteins (HDLs) have been recently demonstrated to attenuate coagulation response, prompting the hypothesis of a potential influence on hemostasis. Serum paraoxonase (PON1) is a HDL-associated pleotropic enzyme, whose interest in cardiovascular disease grew progressively during the last two decades, with low PON1 activity related with an increased cardiovascular risk in several studies. The possible relationship between PON1 and coagulation markers has not been investigated so far.
Materials and Methods: We selected within the Verona Heart Study (VHS) population 236 subjects (males 54.7 %; mean age 60.4±9.4 years; 70.3 % with coronary artery disease (CAD)), who were not taking anticoagulants and for whom both PON1 activities versus different substrates (i.e. paraoxonase, arylesterase, TBBLase, and DEPCyMCase activity) and coagulation data were available.
Results: There was no significant association of PON1 activities with either prothrombin time or activated partial thromboplastin time. Similarly, no significant correlation was found for any parameter of thrombin generation (i.e. lag-time, time-to-peak, peak of thrombin, and endogenous thrombin potential). On the other hand, significant inverse correlations were found between D-dimer and arylesterase, TBBLase, and DEPCyMCase activity, but not with paraoxonase activity. After including all PON1 activities in a linear regression model, only DEPCyMCase activity, that is considered a surrogate marker of PON1 concentration, maintained a statistically significant correlation (standardized beta-coefficient $= -0.247$; $P < 0.001$). Such correlation remained significant also after adjustment for age, sex, CAD diagnosis, HDL concentration, renal function, hs-CRP, and fibrinogen levels (standardized beta-coefficient $= -0.312$; $P = 0.002$).
Conclusions: Our results show an inverse correlation of PON1 activity with D-dimer plasma concentration, that is a reliable and sensitive index of fibrin deposition and stabilization, thus suggesting a link of PON1 with thrombosis pathway. On the other hand, the lack of association with thrombin generation parameters warns that PON1 is not involved in mechanisms regulating the individual's plasma potential to generate thrombin.

Risk of constrictive pericarditis after acute pericarditis

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Background: Constrictive pericarditis (CP) is a rare, dreaded complication of pericarditis. There is a lack of prospective studies evaluating the specific risk according to different etiologies. This risk is evident in particular after tuberculous pericarditis, whereas it is not well established after idiopathic and viral acute pericarditis, the most common causes of acute pericarditis (AP).
Objective: The aim of this study is to prospectively evaluate the incidence of constrictive pericarditis after a first episode of AP in a cohort study with a long-term follow-up (range, 24 to 120 months). To the best of our knowledge, this is the first prospective study in contemporary patients with AP.
Methods and Results: From January 2000 to December 2008, all consecutive cases with a first episode of AP (n. 500; age 51 ± 16 years; 270 men) were recorded and prospectively studied for outcomes. Etiologies were viral/idiopathic in 416/500 cases (83.2 %; age 50 ± 17 years; 233 men), connective tissue disease/pericardial injury syndromes in 36/500 cases (7.2 %), neoplastic pericarditis in 25/500 cases (5.0 %), tuberculosis in 20/500 cases (4.0 %) and purulent in 3/500 cases (0.6 %). Serology data supported the diagnosis of viral infection in 166/416 patients (39.9 %; Coxsackie in 66 patients, Ebstein-Barr virus in 25 patients, cytomegalovirus in 24 patients, parvovirus in 24 patients, influenza/parainfluenza viruses in 15 patients, and adenovirus in 12 patients). During a median follow-up of 72 months, CP developed in 9 patients (1.8 %): 2/416 patients with idiopathic/viral pericarditis (0.48 %) versus 7/84 patients with a non viral/non idiopathic etiology (8.3 %). The incidence of CP was 0.76 cases per 1000 person-years for idiopathic/viral pericarditis, 4.4 for connective tissue disease/pericardial injury syndrome, 6.33 for neoplastic pericarditis, 31.65 for tuberculous pericarditis and 52.74 for purulent pericarditis. All patients with chronic constriction had a surgically confirmed diagnosis of constrictive pericarditis. On histopathological examination of pericardiec- tomy specimens, 1 patient (11.1 % of all cases of CP) had normal pericardial thickness. Furthermore, patients who developed CP showed a higher frequency of specific features compared with those without such evolution: fever > 38 °C (66.7 % versus 14.5 %, respectively; $P < 0.001$), incessant course (55.6 % versus 6.9 %, respectively; $P < 0.001$), large pericardial effusion (66.7 % versus 8.6 %, respectively; $P < 0.001$), cardiac tamponade (44.4 % versus 3.7 %, respectively; $P = 0.002$), and aspirin/nonsteroidal anti-inflammatory drug failure at 1 week (66.7 % versus 18.7 %, respectively; $P = 0.002$). Over the same years we observed other 11 patients with CP; they presented directly with typical signs of congestion (2 for tuberculosis, 1 for radiotherapy).
Conclusions: CP is a very rare complication of a first episode of viral/idiopathic AP (<0.5 %) but in contrast is relatively frequent after AP of specific etiologies, especially bacterial. In all, the more common presentation of CP is congestion, without previous history of pericarditis. Specific features, such as incessant course, large pericardial effusions, and failure of empirical anti-inflammatory therapy, may represent potential risk factors for the evolution toward constrictive pericarditis. In contrast, a true idiopathic recurrent course has a lower risk of constriction.

T helper 17/1 in atherosclerosis

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A pathogenetic role for infections in atherosclerosis has been suggested by the detection of pathogens in the arterial vessels and by the association between atherosclerosis and serological responses to different pathogens, such as *Chlamydophila pneumoniae*, *Helicobacter pylori*, cytomegalovirus, herpes simplex virus, Haemophilus influenzae, or between the extent of atherosclerosis and the infectious burden.

Phospholipases are produced from bacterial pathogens causing very different diseases. One of the most intriguing aspects of phospholipases is their potential to interfere with cellular signaling cascades and to modulate the host-immune response.
We investigated the role of the innate and acquired immune responses elicited by *Chlamydophila pneumoniae* phospholipase D (CpPLD) in the pathogenesis of atherosclerosis. We evaluated the cytokine and chemokine production induced by CpPLD in healthy donors' monocytes and in vivo activated T cells specific for CpPLD that infiltrate atherosclerotic lesions of patients with *C. pneumoniae* antibodies (12 males and 12 females; mean age 68.9 years) with or without anti-*C. pneumoniae* antibodies. We also examined the helper function of CpPLD-specific T cells for monocyte matrix metalloproteinase (MMP)-9 and tissue factor (TF) production as well as the CpPLD-induced chemokine expression by human venular endothelial cells (HUVECs).
We found that CpPLD is a TLR4 agonist able to induce the expression of interleukin (IL)-23, IL-6, IL-1β, TGF-β, and CCL-20 in monocytes, as well as CXCL-9, CCL-20, CCL-4, CCL-2, ICAM-1, and VCAM-1 in HUVECs. In the lymphocytic infiltrates of human atherosclerotic lesions, we showed a significant ($p < 0.001$) predominance of T cells producing interleukin-17, gamma-interferon and other cytokines. Plaque-derived T cells produce IL-17 in response to CpPLD. Moreover, CpPLD-specific T lymphocytes display helper function for monocyte MMP-9 and TF production. CpPLD promotes Th17/Th1 cell migration through the induction of chemokine secretion and adhesion molecule expression on endothelial cells.
CpPLD is able to drive the expression of IL-23, IL-6, IL-1β, TGF-β, and CCL-20 by monocytes and to elicit a Th17/Th1 immune responses that play a key role in the genesis of atherosclerosis, thus suggesting that Th17/Th1 cell pathways and CpPLD may represent novel therapeutic targets for the prevention and treatment of the disease.

Effect of cPAP on blood pressure in patients with obstructive sleep apnea/hypopnea. A systematic review and meta-analysis

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Background: Obstructive sleep apnoea (OSA), characterized by periodic reduction or cessation of breath during sleep, represent a risk factor for hypertension and other cardiovascular disease. When frequent apnoeic episodes are accompanied by symptoms of daytime somnolence or unrefreshing sleep they connote the OSA syndrome. Continuous positive airway pressure (cPAP) is considered the therapy of choice for OSA, but the extent to which it can reduce blood pressure (BP) is still under debate. We conducted a systematic review and meta-analysis to quantify the effect size of the reduction of BP, by cPAP therapy as compared to other "passive" (sham cPAP, tablets of placebo, non-structured counselling on weight reduction, conservative measures) or "active" (oral appliance, antihypertensive drugs) treatments, in randomized controlled trials (RCTs).
Methods: We conducted our search following the general guidelines of the "Cochrane Handbook for Systematic Reviews of Interventions" collecting RCTs retrieved from four different databases (Medline, Embase, Web of Science and the Cochrane Library form inception to the 31st of March 2012)using specific inclusion criteria. We included only studies published as "full article", without language restrictions. We included both cross-over and parallel design studies, in which BP was measured either by "office" or 24-h ambulatory blood pressure monitoring (ABPM), after at least 2 weeks of treatment by cPAP/other treatments. No restriction for associated comorbidities was applied and studies recruiting normotensive as well as hypertensive subjects were included. Only studies in which the diagnosis of OSA was verified by polysomnography (Apnoea/hypopnoea index of at least 5/h) were considered eligible. All the analyses were performed using the software "Comprehensive Meta Analysis V2."
Results: From 1235 articles we selected 31 RCTs (1987 patients), which compared the addition of CPAP to another "passive" treatment (30 studies), or to an anti-hypertensive drug (1 trial) or to oral appliance (2 studies). In a "random effect" meta-analysis vs. passive treatment we found a mean net difference in systolic BP (mean ± SEM) of 2.6 ± 0.5 and in diastolic BP of 2.0 ± 0.4 mmHg favouring treatment with cPAP ($p < 0.001$ for both). Among studies using ABPM presenting data on daytime and night-time periods ($n = 14$), the mean difference in systolic and diastolic BP was respectively 2.2 ± 0.7 mmHg and 1.9 ± 0.7 mmHg during daytime 3.9 ± 1.0 mmHg and 1.9 ± 0.6 mmHg ($p < 0.001$) during night-time. In meta-regression a higher baseline AHI was associated with a greater mean net decrease in systolic BP. There was no evidence of publication bias and heterogeneity resulted mild to moderate ($I^2 = 31–34$ %).
Discussion: Therapy with CPAP reduces BP in patients with OSAs. The effect size of BP reduction is mild, but it becomes greater when baseline AHI is higher.

Low-grade inflammation modulates t-lymphocyte renin-angiotensin system activation in hypertensives and obeses

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Purpose: In these last years human T-lymphocytes were shown to be endowed with a functional active renin-angiotensin system (RAS), independent to the circulating system, and to have a role in the development of hypertensive target organ damage. T-lymphocyte RAS seems to be more activated in hypertensive patients with low-grade inflammation. Low-grade inflammation is reported to mediate cardiovascular risk also in obeses. The aim of this study is to assess the activation of T-lymphocytes RAS in hypertensives and/or obeses and the possible correlation with low-grade inflammation.
Methods: T-lymphocytes were obtained from peripheral blood samples of 8 obeses (BMI > 29) (7 M, 1 F, 47 ± 11 years), 9 hypertensives with BMI < 29 (7 M, 2 F, 63 ± 11 years) and 7 hypertensives and obeses (7 M, 52 ± 10 years). No patients was affected by diabetes mellitus or glucose intolerance. No patients was in therapy with ACE-inhibitors and/or Angiotensin receptor blockers. Seven healthy subjects formed the age and sex-matched control group. After isolation, T-lymphocytes were put in culture and at 6 h mRNA for ACE was quantified by RT-PCR. Presence of low-grade inflammation was defined by serum levels of high sensitive C-reactive protein (hsCRP) > 2 mg/L.
Results: hsCRP showed large distribution in groups, with mean values significantly higher than controls. All hypertensive with BMI > 29 patients presented hsCRP levels > 2 mg/L. ACE mRNA levels showed a large distribution inside the three groups as well, with mean values significantly higher than controls. ACE mRNA levels were linearly related to hsCRP levels ($R = 0.79$; $p < 0.0001$). There was a positive correlation between hsCRP levels and BMI. No significant correlation was found between ACE mRNA levels and BMI. In the three groups, ACE mRNA levels were significantly higher than controls only in patients with low-grade inflammation.
Conclusion: Circulating T-cells ACE gene expression is modulated in presence of low-grade inflammation. In hypertensive and/or obese

patient, a selective T-lymphocytes RAS activation can occur. If these results will be confirmed, T-cells RAS activation could be considered as a new marker for the optimization of both cardiovascular risk definition and antihypertensive therapy.

Relationship between stability of sinus rhythm and number of DC shock in a series of patients with AF undergoing to electrical cardioversion

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Background: Electric cardioversion (ECV) is a common procedure to restore a sinus rhythm (SR) from an abnormal cardiac pulse. It is widely used as elective procedure to treat atrial fibrillation (AF) or flutter without signs of haemodynamic impairment, while its use in emergency is indicated in all the ventricular or supraventricular tachyarrhythmias with signs of severe haemodynamic impairment or cardiogenic shock. In our Internal Medicine Department (IMD), AF represents the fifth DRG in order of frequency. For this reason, we currently follow patients affected by AF waiting for an ECV with well-defined, evidence-based protocols. However, despite optimal medical therapy, we still frequently observe a failure to maintain SR in a high percentage of patients. For this reason, we retrospectively analyzed 121 patients admitted to our IMD for elective ECV, analyzing SR stability at 30 days after DC shock as our main outcome.
Aims: To evaluate retrospectively an association between the number of shocks and the SR stability at 30 days after a successful ECV procedure. To our knowledge, there are no studies that enlightened the relationship between the number of DC shocks required to restore SR at the first electric cardioversion and SR maintenance at 30 days.
Methods: We enrolled 121 consecutive patients admitted in our ED in the year 2010–2011 for an AF episode. We excluded 9 patients who underwent to ECV (all with SR restoration) within 48 h from the event. We excluded 52 patients who underwent to ECV for an AF relapse. 60 patients were suitable for analysis and were treated with the same pharmacologic protocol including 4 weeks of therapy with oral anticoagulants, a class III antiarrhythmic, an angiotensin-receptor blocker (irbesartan) and statins. After 4 weeks, patients underwent to ECV with standard protocol (first shock: 150J, second shock: 200J, third shock: 200J). We evaluated age, sex and comorbidities (cardiopathy, hypertension, diabetes mellitus, cerebrovascular or vascular pathology), drug therapy, the number of shocks required to restore SR and SR maintenance at 30 days. Statistical analysis, accounting for sex, age, therapies and comorbidities, was performed with a multinomial logistic regression model with SPSS 13.0 for Windows systems.
Results: SR remained stable at 30 days in 48 patients; 12 patients had an AF relapse at 30 days. Adjusting for age, sex and comorbidities, we found that the number of shocks given during the ECV procedure was independently correlated with maintenance of SR at 30 days: subjects achieving SR restoration after the first shock had an OR of 14.083 (95 %IC: 3.708–53.496, $p < 0.05$) of SR maintenance at 30 days in respect to patients who achieved SR after 2 or more shocks (Figure 1).

Discussion: AF is the most common malignant arrhythmia observed in an IMD. Its mortality and morbidity is mainly related to internistic pathologies, such as cardioembolic stroke. In a recent work, our group observed how internistic comorbidities (hypertension, diabetes mellitus, chronic heart failure and stroke, coronaric and peripheral atherosclerotic pathology), age and sex, synthesized in the CHA_2DS_2-VASc variable, can predict the success of ECV at 24 h, probably indicating an electrical and mechanical remodeling of the atrium. This current work adds another piece to the puzzle of clinical prediction of ECV success in AF, enlightening the concept that refractoriness to DC shock could represent itself a marker of atrial electrical/mechanical remodeling and warn the clinician on the high likelihood of short-term treatment failure in this subset of patients. Larger cohorts and multi-centric studies are required to validate this observation.

Parameter Estimates

ESITO_CA[a]		B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
								Lower Bound	Upper Bound
1,00	Intercept	-,368	,434	,719	1	,396			
	[N_SCARICHE=1,00]	2,645	,681	15,088	1	,000	14,083	3,708	53,496
	[N_SCARICHE=2,00]	0[b]	.	.	0	.	.	.	.

a. The reference category is: ,00.
b. This parameter is set to zero because it is redundant.

Fig. 1 Main results of multinomial logistic regression model. The "N_SCARICHE" variable is a dichotomous variable (value 1: 1 shock, value 2: 2 or more shocks).

Cerebral vascular reactivity and cognitive performance in patients with extracranial asymptomatic carotid stenosis

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Background: Preliminary studies have reported cognitive dysfunction in unilateral asymptomatic carotid stenosis (ACS). Impaired cerebral hemodynamic status measured by cerebrovascular reactivity has been associated with cognitive dysfunction in unilateral ACS.
Aims: (1) To evaluate cognitive performance in bilateral ACS compared to unilateral ACS and healthy subjects and (2) to explore the relationship between cognitive performance and cerebral hemodynamic status in bilateral ACS.
Methods: Asymptomatic patients with ultrasound evidence of bilateral or unilateral ACS (60 %-99 % diameter reduction) were prospectively collected. Healthy subjects (HS) comparable for demographics and vascular risk profile served as controls. A neuropsychological investigation included phonemic and categorical Verbal Fluency (VF) tests to explore the left hemisphere and Colored Progressive Matrices (CPM), and Complex Figure Test Copy (CFTC) tests to explore the right hemisphere. Cerebrovascular reactivity (CVR) to hypercapnia using the transcranial Doppler (TCD) based breath-holding index (BHI) test was performed in each subject. Impaired CVR was defined as a BHI < 0.69. Generalized linear multivariate and univariate models were employed to evaluate the mean difference on left and right cognitive test abilities in bilateral ACS patients with left and right preserved or impaired CVR. Vascular risk factors, education years, mini-mental status examination (MMSE), and current medications were included as covariates.
Results: 333 consecutive subjects were included: 126 bilateral ACS; 73/75 left/right unilateral ACS; 56 HS; mean age: 70 ± 3.78

years; males: 65 %; education years: 10.3 ± 3.7; MMSE score: 26.7 ± 1.27. Bilateral and unilateral ACS patients showed significantly lower scores in all cognitive tests compared to HS ($p < 0.05$). In the multivariate analysis, among bilateral ACS an impaired CVR in the right side was associated with a significantly reduced CPM score: from an estimated mean of 32.6 [95 % Confidence Interval (CI): 29.8–35.4) to 23.0 (95 % CI: 20.2–25.8) and the CFTC score from 34.7 (95 % CI: 32.0–37.4) to 26.0 (95 % CI: 23.3–28.7). Similarly, an impaired CVR on the left side was associated with a reduced phonemic VF score: 13.5 (95 % CI: 11.2–15.8) to 7.5 (95 % CI: 5.4–9.7) and categorical VF score from 21.1 (95 % CI: 18.1–24.1) to 12.3 (95 % CI: 9.5–15.1). All comparisons were statistically significant ($p < 0.05$).

Conclusions: Patients with unilateral or bilateral ACS are more likely to suffer cognitive dysfunction compared to healthy controls. Impaired CVR predicts the development of cognitive dysfunction in bilateral ACS. A non-invasive assessment of CVR using the TCD-based BHI test may contribute to a more comprehensive risk stratification in these patients.

Association between the RS1333040 polymorphism on the chromosomal 9P21 locus and sporadic brain arteriovenous malformations

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Introduction: Single nucleotide polymorphisms on chromosome 9p21 have been recently associated with intracranial aneurysms and stroke. In this study, we tested the association between the rs1333040C>T polymorphism on the 9p21 locus and sporadic brain arteriovenous malformations (BAVM).

Methods: We studied 78 patients with BAVM and 103 unaffected controls. Genomics DNA was isolated from peripheral blood and the rs1333040C > T polymorphism was assessed by PCR–RFLP using the BsmI restriction endonuclease. SNP association with gender, age of clinical onset, cortical or deep localization, supra- or infra-tentorial localization, bleeding, nidus size, presence of deep venous drainage, perforator feeders, and epilepsy was also verified. Chi-square test established significant difference ($p < 0.05$).

Results: We first compared the frequency of the 3 possible genotypes of the rs1333040 polymorphism (CC, CT and TT) between cases and controls and found that the TT genotype was significantly more frequent among individuals with sporadic BAVM than controls (43/78 vs. 36/103; $p = 0.006$). Similarly, the T allele was significantly more common among patients than controls (73.1 vs. 60.2 %; $p = 0.01$). Next, we evaluated the possible association with prototypical angioarchitectural (such as Spetzler-Martin grading, nidus localization, size, feeder arteries and venous drainage pattern) and clinical features (such as bleeding and epilepsy) of the disease and found a significantly higher frequency of the TT genotype ($p = 0.003$) and the T allele ($p = 0.008$) among subjects with nidus larger than 4 cm in diameter compared to those with nidus < 4 cm. Also, we found that the T allele was significantly associated with BAVM of Spetzer-Martin grade IV and V ($p = 0.04$).

Conclusions: This is the first study demonstrating an association between a single nucleotide polymorphism (rs1333040C>T) on chromosome 9p21 and sporadic BAVM. Our results emphasize the relevance of this chromosomal locus as a common risk factor for various forms of cerebrovascular diseases.

Meta-analysis of single nucleotide polymorphisms in sporadic brain arteriovenous malformations

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Introduction: Brain arteriovenous malformations (BAVM) are characterized by a tangle of abnormal vessels directly shunting blood from the arterial to venous circulation. Although sporadic forms do not recognize a specific genetic cause, in recent years several single nucleotide polymorphisms (SNPs) in two main families of genes have been associated with disease susceptibly and increased hemorrhagic risk. These genes are mainly involved in the inflammatory cascade and in the regulation of angiogenesis. In this study we have reviewed the polymorphisms so far investigated in association with sporadic BAVM in the medical literature and performed a meta-analysis on SNPs and BAVM susceptibility and risk of bleeding.

Methods: We analyzed the SNPs associated of BAVM in 21 papers identified on PubMed using the key words "polymorphism" and "arteriovenous". All these studies were published between 2004 and 2012. Selected SNPs were identified and divided based on their pathophysiological role. For the meta-analysis, the Mantel–Haenszel method was used to compare case–control studies with dichotomous outcomes. The DerSimonian-Laird method was used when the preliminary test of heterogeneity yielded different results for the 2 studies.

Results: All SNPs displaying significant association with BAVM susceptibility and risk of bleeding belong to genes related to angiogenesis and inflammation. In particular, SNPs involved in BAVM susceptibility were: a) IL6-174G>C, IL1α-889C>T, IL1β-511C>T, IL1β-31T>C, IL1β+3953C>T, TGFRβ2-875A>G, IL1RN 10908A>G, MMP3-707A>G (inflammatory cascade); (b) ALK1 IVS3-35A>G, ENG+207G>A, ANGPTL4+9511G>A, VEGF-A IVS5-892T>C, VEGF-A-634C>G, VEGF-A+3596A>G, VEGF-A-8339A>T (angiogenesis). Regarding the SNPs involved in risk of bleeding: (a) IL6-174G>C, TNFα-238G>A, IL1β-511C>T, IL1β-31T>C, IL17A-197G>A, TGFRβ2-875A>G, ApoE ε2 Cys112Arg T>C (inflammatory cascade); (b) EPHB4 rs314308C>T and rs314313T>C, VEGF-A-8339A>T (angiogenesis pathway). From our analysis of the medical literature, we found that 5 SNPs (ApoE ε2, TNF-α –238G>A, IL6-174G>C, TNF-α-308G>A, and IL-6-572G>C) were studied in more than one manuscript for their association with risk of bleeding and two (IL-1β-511C>T and ALK1 IVS3-35A>G) for their association with BAVM susceptibility. These studies were included in our meta-analysis, which showed that the IL6-174G>C and TNF-α-238G>A gene polymorphisms were associated with increased risk of bleeding with odd ratio OR of 1.97 (95 % CI: 1.15–3.38) and 2.19 (95 % CI: 1.25–3.83), respectively. Likewise, the ALK1 (ACVRL1) IVS3-35A>G was associated with disease susceptibility, with an OR of 2.42 (95 % CI: 1.54–3.8).

Conclusions: This study strengthens the hypothesis of a crucial role of ALK1 gene in the susceptibility of sporadic BAVM development. It also supports the concept that the inflammatory genes IL-6 and TNF-α play a role in the mechanisms underlying risk of bleeding in individuals with BAVM.

Endocarditis in internal medicine departments: a case series

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Background: Infective endocarditis (IE) is a rare pathology, with an incidence of 3–10 cases/100.000 person-year (1). The incidence didn't significatively change in the last century: the decrease of post-rheumatic valvular heart disease at population level is compensated by an increase in degenerative valvular heart disease as predisposing factor. Moreover, the share of patients with intravascular foreign material is increasing. IE is often diagnosed late. The clinical features are usually atypical. Since the introduction of the Duke criteria, clinical, bacteriological and echocardiographic findings (transthoracic and transoesophageal echocardiography) are being integrated, allowing an earlier definite diagnosis (1). Normochromic normocytic anemia, elevated ESR, neutrophilia, increased immunoglobulins, circulating immune complexes and rheumatoid factor are often present in IE. Many factors affect the outcome of this serious disease, including virulence of the species, patient's characteristics, comorbidities, delays in diagnosis and treatment, surgical indications, and timing of surgery (2). Endocarditis is frequently characterized by a complicated course. About 50 % of the patients develop heart failure. One third of the patients present with cerebral or peripheral embolization. Embolization predominantly occurs at the beginning, in the first two weeks of antibiotic treatment. Abscess formation occurs more frequently than suspected if diagnosis is lead by ultrasonographic methods. Staphylococcus aureus infection is particularly aggressive in the presence of an artificial valve, often leading to extravalvular extension with abscess formation around the artificial valve. Despite improvements in medical and surgical therapies, IE is associated with poor prognosis and remains a diagnostic and therapeutic challenge. For its systemic involvement, endocarditis is typically an internistic pathology, and must be managed in an Internal Medicine Department (IMD) with critical care competence.
Aims: To evaluate incidence, prevalence and clinical manifestations of endocarditis in our IMD.
Methods: We retrospectively evaluated all the patients admitted in the critical area of our IMD in the year 2011–2012. We selected all the patients dismissed with a diagnosis of IE and reviewed the clinical, laboratoristic and echocardiographic data.
Results: Seven patients were discharged with a definite diagnosis of native-valve IE. The most frequent clinical manifestations were dyspnea (57 %) and fever (43 %); our ED admitted the patients in our IMD with the diagnosis of AHF in 57 % of the cases, fever of unknown origin in 14.3 %, other diagnoses in 28.3 %. Mean ESR at diagnosis was 70 mm/h (SD ± 41 mm/h), CRP was 7.57 ng/ml (SD ± 6.16 ng/ml). Many patients (86 %) presents anemia, neutrophilia and increased hypergammaglobulinaemia. New ECG alterations were observed in 28.6 % of the sample. Only two cases resulted positive for rheumatoid factor. 71 % of the performed coltures resulted negative. Among the positive specimens, the most prevalent species found were Enterococcus spp and Staphylococcus spp (14.3 % of the cases each). Transthoracic echocardiography (TTE) resulted positive in 57 % of the cases, while transesophageal study confirmed the diagnosis in all the cases. No one of the described patients had recent hospitalization, carried a CVC or urinary catheter. In only one case IE was related with colon cancer, in another case the way of infection was related to drug addiction. No patient who was found to be diabetic or seriously immunocompromised.
Discussion: IE still represents a complex diagnosis. In our series of patients is not possible to identify a common denominator, which could simplify the diagnostic process. The most frequent data (anemia, neutrophilia, hypergammaglobulinemia) is also the most unspecific. Although current guidelines clearly express how to the diagnose and manage IE, this pathology still remains very hard to diagnose without a correct clinical method and proven experience in cardiac ultrasound. IMD with competence both in echocardiography and critical care can carry the right methodological approach, diagnosing and managing most of the cases.

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The relationship between SHBG, sex hormones and endothelial function in older subjects: data from the PIVUS STUDY

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Background: Endothelial dysfunction is an early predictor of cardiovascular diseases. The role of sex hormones has been advocated to explain the different prevalence in men and women before menopause. Sex hormone binding globulin has been recently considered a novel independent risk factor for diabetes and cardiovascular diseases even in older individuals. However, the relationship between SHBG, sex hormones and endothelial function has never been addressed in older population.
Methods: We evaluated 1016 participants aged 70 years of Prospective Study of the Vasculature in Uppsala Seniors study (52 % women), with complete data on measurements of endothelial function. These tests included Endothelium-dependent vasodilation (EDV) assessed by invasive forearm technique with acetylcholine given in the brachial artery, flow-mediated dilatation (FMD) and the pulse wave analysis (reflection index, RI). Information was also available on endothelium-independent vasodilation (EIDV). Our analysis was restricted to 854 subjects (430 men and 424 women) having complete data on SHBG, testosterone (T), estradiol (E2) whose levels were assessed by access test chemiluminescence provided by Beckman Coulter. Generalized linear models adjusted for multiple confounders were used to test the relationship between T, E2, SHBG (predictors) and endothelial function (outcome).
Results: In men, we found a positive relationship between SHBG and EDV ($\beta \pm SE = 3.60 \pm 0.83$, $p < 0.0001$) that was unaffected by the adjustment for confounders including T, E2 ($\beta \pm SE$ 3.02 ± 1.16, $p = 0.009$). No relationship was found between T, E2 and EDV, FMD, RI and EIDV in both men and women. In men ($\beta \pm SE$ 1.51 ± 0.82 $p = 0.06$) and more significantly in women ($\beta \pm SE$

1.41 ± 0.58, p = 0.02) SHBG levels were also positively associated with EIDV.
Conclusions: In older men SHBG, but not T and E2, was positively and independently associated with endothelium-dependent vasodilation. In both sexes, SHBG was positively and independently associated with endothelium-independent vasodilation.

Clinical manifestation in large cohort of pediatric patients with HHT1 and HHT2

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Background: Hereditary Haemorrhagic Telangiectasia (HHT) is a genetic disorder, inherited as an autosomal dominant trait and is determined by mutations in either ENG (HHT1) or ACVRL1 (HHT2) gene. The disease manifests itself with numerous angiodysplasias, diffuse in different organs. HHT entails a marked clinical relevance, due to sudden vascular complications, secondary to visceral arteriovenous malformations (AVMs). Such AVMs and their complications can also occur in childhood. However, the risk associated to AVMs can be considerably reduced by means of an early preventive screening. To date, there are still insufficient data regarding the clinical features of pediatric HHT patients, in terms of prevalence, symptoms, onset, and morbidity of AVMs.
Objective: The goal of the present study consists in an evaluation of the clinical features in a large cohort of pediatric patients with genetically confirmed HHT.
Methods: The children were enrolled in this study by genetic testing, through confirmation/exclusion of the disease-causing mutation previously identified in the family. Genetic testing excluded the familial mutation in 35 children, while 48 children resulted carriers of the familial mutation. Carriers of ENG mutations and of ACVRL1 mutations were thus defined as HHT1 and HHT2 patients, respectively. Out of the 48 mutation carriers, 38 children accepted to be subjected to instrumental screening. Screening for brain AVM was carried out by MRI and MRA, pulmonary AVMs were detected by Multi-Slice CT, liver involvement was investigated through Eco-Color-Doppler and Abdominal Dynamic MRA. Endonasal and cutaneous telangiectases were visualized by rhinoscopy and capillaroscopy, respectively.
Results: Thirty-eight children (mean age: 9.65; range 1–18 years) were subjected to instrumental screening, of which 20/38 were HHT1 and 18/38 were HHT2. Cerebral screening disclosed a large AVM in 3/38 cases, all HHT1, and a dubious micro-AVM in two cases. Pulmonary AVMs were detected in 21/38 pazienti (14 of which being HHT1) and six of them had lung AVMs amenable to treatment. Two children had cerebral lesions secondary to lung AVMs. Hepatic screening showed signs of liver involvement in 18/38 children (13 of which being HHT2), without association to clinical risk in any case. Endonasal telangiectases were found in 26/38 patients, with associated epistaxis in all but 3 cases. Fifteen children had cutaneous telangiectases at capillaroscopy.
Conclusions: Children with HHT have a high prevalence of AVMs, so an appropriate clinical and instrumental screening is advisable.

Integration between hospital and community services in providing care for patients affected by chronic heart failure: our experience in the province of Lecco

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Heart failure is a disease of epidemic proportions, characterized by poor prognosis and quality of life for patients and their family. Chronic heart failure is the first discharge diagnosis in departments of internal medicine and contributes to 2–2.5 % of all health spending in our country, 60–70 % of the cost of heart failure is due to hospitalization. Among chronic diseases this accounts for the highest prevalence (1.5–2 %) and absorption of resources. Since 2003 Heart Failure (DRG 127) is the leading cause of hospitalization after birth in Italy and at least 5 % of hospital beds are occupied by patients with this disease. The treatment of heart failure has nowadays considerably improved, but integration between hospital and community is crucial for improving the management of this type of patients.
The purpose of this work is to promote an integrated approach in managing the patient with advanced heart failure through the sharing of a path between hospital and community, leaving the overall care of the patient to a multi-professional team (General Practitioner, hospital cardiologist/internist, nurse).
The main strengths of our protocol are: (1) Recognition and early treatment of acute exacerbations of illness at home (2) reduction of new episodes of hospitalization resorting to it only in selected cases based on clinical judgment of GPs supported by the "indications and priorities to hospitalization" in the protocol itself. (3) maintaining the best quality of life and independence as possible for the patient.
Materials and Methods: Our pathway is provided for heart failure patients discharged from acute care hospital with these features: Frail patients with chronic heart failure in NYHA class 3^/4^ at admission, who need additional support and advice after being discharged.
The nurses of our Home Care Service provide specialist advice, support and monitoring of patients' condition in their own homes always in close cooperation with the GP and the possibility of a phone consultation with the hospital cardiologist. Education and advice play a vital role in the patient's quality of life and in the prevention of readmission to hospital.
The path: a few days before hospital discharge the patient is reported to the Continuity of Care Service of our Department, and the care manager nurse will assess the eligibility of the patient to home care. A joint evaluation of the patient (GP and the nurse of home care service) is performed within the first week after being discharged. During the period of assistance the patients will receive 10 nursing visits and two visits by GP for the first month, 8 nursing visits and two visits by GP during the 2nd and 3rd month. In any evaluation the patients' clinical stability by determining the body weight and fluid balance, treatment compliance, side effects of drugs, availability of drugs at home, self-analysis of some parameters such as urine output, heart rate and blood pressure, are checked.
The main outcome will be: (1) Hospital admissions at 30 and 90 days after discharge (2) Access to ER at 30 and 90 days after discharge (3) Mortality at 30 days after discharge.
Conclusions: We believe that this path is structurally solid but flexible in its articulation, of adequate duration to maintain tight control of a variety of patients with high complexity and high rates of re-hospitalization. It allows to achieve economic sustainability when compared with the average cost of hospitalization.

The therapeutic care pathways if designed and shared between hospital and community and adequately relate to the epidemiological situation and the potential of the local service network, will ensure sustainable management of chronic diseases combining a balanced absorption of resources with the centrality of patient and family.

An early increase in renal resistive index is shown in hypertensive patients with diabetes mellitus and normal arterial stiffness

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Background: Renal resistive index (RRI) detected by Doppler ultrasound is influenced by intra- and extra-renal factors. Increased RRI in patients with normal renal function detects tubulo-interstitial damage, which may be present before glomerular damage. Arterial wall stiffness evaluated by estimation of pulse wave velocity (PWV) is one of the most significant extra-renal factors. Both RRI and PWV are significantly higher in patients with hypertension and diabetes mellitus (DM) than in age-matched control subjects. However the role of intra- and extra-renal factors in determining the RRI increase is still under debate. This study was aimed to evaluate whether high RRI values of patients with hypertension and DM reflect tubulo-interstitial damage or increased arterial stiffness.
Methods: We studied hypertensive patients between 28 and 75 years, in chronic antihypertensive therapy, with or without DM, with conserved renal function (creatinine clearance > 60 mL/min). RRI [(peak systolic velocity – end-diastolic velocity)/peak systolic velocity] was calculated by the analysis of the Doppler flow wave obtained at renal interlobar arteries and considered pathologic when ≥ 0.70.
Results: We evaluated 51 patients (59 ± 10 years, 29 M/22F). Patients with DM ($n = 25$) were older (63 ± 8 vs. 54 ± 10 years, $p = 0.001$) and had significantly higher RRI values (0.71 ± 0.05 vs. 0.65 ± 0.06, $p = 0.001$) and higher prevalence of pathologic RRI (64 vs. 19 %, $p = 0.001$) compared with patients without DM. There was no significant difference in PWV values between hypertensive patients with or without DM (8.27 ± 1.70 vs. 7.97 ± 1.47 m/sec; $p = 0.503$). DM resulted a significant independent predictor of pathologic RRI even after adjustment for age (O.R. 5.05; IC. 95 % 1.30–19.67; $p = 0.019$) and PWV (O.R. 7.34; I.C. 95 % 2.03–36.51; $p = 0.002$).
Conclusions: In our hypertensive patients with DM, increased RRI values may reflect a reduction in intra-renal compliance due tubulo-interstitial damage, rather than an increase in systemic arterial stiffness.

A strange mandibular pain

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A 75-years-old female patient was admitted to our Internal Medicine department for severe oppressive chest pain radiating to the neck, breathlessness and cold sweating. These symptoms started few hours before admission, precipitated by moderate exertion (the patients was climbing the stairs) and did not show any regression with resting. The patients have history of hypertension, ischemic stroke, ascending aorta ectasia, chronic kidney disease and a previously treated vulvar cancer. Complete physical examination reveals no significant differences between peripheral arterial pulses (right arm Blood pressure [BP] = 150/110 mmHg; left arm BP = 160/110 mmHg); Heart Rate (HR) was 84 bpm (rhythmic). Chest X-ray confirmed thoracic aorta ectasia, laboratory showed a slight increase of troponin I (up to 154 ng/mL), increased D-dimer values (up to 1189 ng/mL) and reduced eGFR. ECG and transthoracic echocardiography did not show any signs suggesting cardiac ischemia.
Five days after admission the patient experienced severe and progressive worsening mandibular pain, without chest pain. No neurovegetative signs and dyspnea were present. Physical examination revealed high BP values on the right arm (BP = 180/110 mmHg) despite undetectable BP values on left one. ECG, Troponin I, CK-MB and myoglobin did not show any significant abnormality, thus excluding the diagnosis of Acute Coronary Syndrome. An urgent transesophageal echocardiography revealed a severe enlargement of ascending aorta with high suspicion of intramural hematoma and mild pericardial effusion. The patients underwent CT-angiography that showed a progression of pericardial effusion and confirmed the presence of intramural hematoma. Thus, considering the clinical scenario and the progression of pericardial effusion, a diagnosis of evolving type A (Stanford) Aortic Dissection was formulated and the patient was immediately transferred to Cardiac Surgery Unit for an immediate surgical treatment.

Endogenous thrombin potential, but not D-dimer concentration, is associated with coronary artery disease independently of traditional risk factors, including inflammatory markers

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Background: Coagulation pathways are thought to play a pivotal role in cardiovascular disease, even beyond thrombosis superimposed on ruptured or unstable atherosclerotic plaques. Several coagulation biomarkers have been associated with an increased risk of either coronary artery disease (CAD) or myocardial infarction (MI), but such results remain still controversial. The aim of the present study was to investigate D-dimer plasma concentration and thrombin generation parameters in a subset of patients from the angiography-based Verona Heart Study (VHS), with or without objectively proven CAD.
Materials and Methods: A total number of 775 subjects (170 CAD-free and 605 CAD, of whom 355 with MI history), not assuming anticoagulants at enrolment in the VHS and with available data about thrombin generation and D-dimer, were included in the present study.
Results: CAD patients had significantly higher lag-time, time-to-peak and endogenous thrombin potential (ETP) levels, as well as a higher D-dimer concentration, as compared to CAD-free. However, after including all these variables in a multiple logistic regression model adjusted for the traditional CAD risk factors (sex, age, smoke, diabetes, hypertension, renal function, BMI, cholesterol, triglycerides, fibrinogen, and high-sensitivity C-reactive protein (hs-CRP)), only ETP levels remained significantly associated with CAD. As regards D-dimer, subsequent analysis showed that the statistical significance of association with CAD vanished after adjustment for hs-CRP. The prevalence of CAD subjects increased progressively across ETP tertiles ($P < 0.001$ by Chi-square for linear trend). In the adjusted model, ETP in the highest tertile conferred a two-fold increased risk of CAD as compared to the lowest tertile (OR 2.11 with 95 %CI 1.01–4.42). On the other hand, no association with MI history was found.
Conclusions: Our results suggest that elevated ETP levels are associated with angiographically confirmed CAD independently of traditional cardiovascular risk factors, while the association of D-dimer appears to be substantially influenced by inflammatory status.

Uric acid, atrial volume and diastolic function in essential hypertension

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Several evidences suggest that left atrial enlargement is a significant predictor of cardiovascular (CV) outcomes. Moreover, high levels of uric acid (UA) are associated with hypertension, diabetes mellitus, metabolic syndrome, vascular disease, kidney disease and CV events. In this study we addressed the question if UA is associated with the left atrial volume (LAV).

We enrolled 755 (388 males and 367 females, age mean 54.0 ± 13.6 years) never-treated hypertensive patients. All subjects underwent standard M-Mode and B-mode echocardiography, in accordance to the American Society of Echocardiography. LAV was measured by biplane area-length method and indexed for body surface area (LAVI). The left ventricular mass (LVM) was calculated using the formula of Devereux and indexed for body surface area (LVMI). We also performed the measurements of transmitral flow and mitral annulus tissue Doppler (TDI) by using the pulsed Doppler, obtaining thus the peak of early diastolic filling (E), the atrial diastolic filling (A), the E/A and E/e' ratio. In all patients, we have measured the following laboratory parameters: fasting glucose and insulin, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, UA, fibrinogen, hs-CRP, creatinine. The glomerular filtration rate was calculated by CKD-Epi equation, while insulin sensitivity was assessed by HOMA-index.

There was a direct correlation between UA levels with LAVI ($r = 0.559$; $P < 0.0001$) and LVMI ($r = 0.402$; $P < 0.0001$). By contrast, UA was inversely related with E/A ($r = -0.354$; $P < 0.0001$) and E/e′ ($r = -0.181$; $P < 0.0001$). At multiple regression analysis, UA resulted the most important predictor of LAVI, E/A and E/e′, explaining the 31.2, 11.9 and 3 % of their variation, respectively.

In conclusion we demonstrate that there is a direct and significant correlation between UA levels and LAV in hypertensive patients. In addition UA is inversely associated with the diastolic function parameters. These data allows to extend the actual knowledge about the role of UA in the development of cardiac damage. Therefore it is important to measure UA levels in all hypertensive subjects, for a better stratification of the CV profile risk.

Usefulness of electrocardiography to predict left ventricular diastolic dysfunction

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The left ventricular (LV) diastolic dysfunction can help to diagnose the heart failure and is associated with mortality. The aim of this study was to evaluate the ability of electrocardiography to predict left ventricular dysfunction.

Forty-two consecutive patients, affected by systemic hypertension (defined as systolic blood pressure >140/90 mmHg or treatment with antihypertensive drugs), underwent 12-lead elettrocardiography (ESAOTE P8000 resting ECG system, Florence, Italy) and echocardiography (Toshiba Aplio CV, Tokyo, Japan). We documented the sinus rhythm and measured the P wave duration, PR interval, QRS duration and QT interval. The lead with the longest QT duration was used for the QT interval. The corrected QT interval (QTc) was calculated using Bazett's formula. The Romilht-Estes criteria were used in the ECG diagnosis of left ventricular hypertrophy. The LV diastolic function was analyzed using pulse wave tissue Doppler echocardiography of the septal mitral anulus. Diastolic dysfunction was diagnosed when tissue Doppler early velocity of the septal mitral anulus (e') was <8 cm/s. We compared the electrocardiographic and echocardiographic parameters between patients with normal (≥8 cm/s) and reduced (<8 cm/s) septal e' using t tests for continuous variables and chi-square (or Fisher's exact) tests for categorical variables. Data were considered significant at p-value <0.05.

Characteristics and parameters	All subjects (n = 42)	Septal e' <8 cm/s (n = 20)	Septal e' ≥8 cm/s (n = 22)	p-value
Age (years)	61 ± 13	65 ± 13	57 ± 13	0.053
Men (n)	31 (73.8 %)	14 (70 %)	17 (77.3 %)	0.592
Echocardiographic parameters				
LV end-diastolic diameter (mm)	46 ± 6.5	45.7 ± 7.8	46.3 ± 5.3	0.770
Ejection fraction (%)	58.8 ± 6.6	58 ± 7	59 ± 6	0.620
Septal thickness (mm)	11.3 ± 2.3	11.9 ± 2.4	10.7 ± 2.2	0.106
Posterior wall thickness (mm)	9.7 ± 1.7	9.9 ± 1.9	9.5 ± 1.5	0.970
Left atrial diameter (mm)	37.2 ± 5.8	37.2 ± 6.2	37.2 ± 5.6	0.987
Electrocardiographic parameters				
P wave duration (ms)	105 ± 12	110 ± 11	100 ± 11	0.005
PR interval (ms)	180 ± 28	181 ± 29	180 ± 28	0.940
QRS interval (ms)	94 ± 21	101 ± 27	88 ± 9	0.039
QT interval (ms)	395 ± 43	410 ± 40	381 ± 40	0.024
QTc interval (ms)	428 ± 33	441 ± 40	415 ± 18	0.009
P wave duration ≥110 ms (n)	20 (47.6 %)	15 (75.0 %)	5 (22.7 %)	<0.001
QTc interval >440 ms (n)	11 (26.2 %)	9 (45 %)	2 (9.1 %)	0.008
Left ventricular hypertrophy (n)	8 (19.0 %)	6 (30.0 %)	2 (9,1 %)	0.085
Left fascicular block (n)	5 (11.9 %)	0	5 (22.7 %)	0.023
Left bundle branch block (n)	1 (2.4 %)	1 (5.0 %)	0	0.288
Right bundle branch block (n)	4 (9.5 %)	3 (15.0 %)	1 (4.5 %)	0.249

In conclusion, using a cutoff >440 ms for the QTc interval and ≥110 ms for the P wave duration, a significant association was found between QTc or P wave prolongation and LV diastolic dysfunction. These two electrocardiography findings seem to be able to predict LV diastolic dysfunction.

Inhibition of nicotinamide phosphoribosyltransferase reduces neutrophil-mediated injury in myocardial infarction

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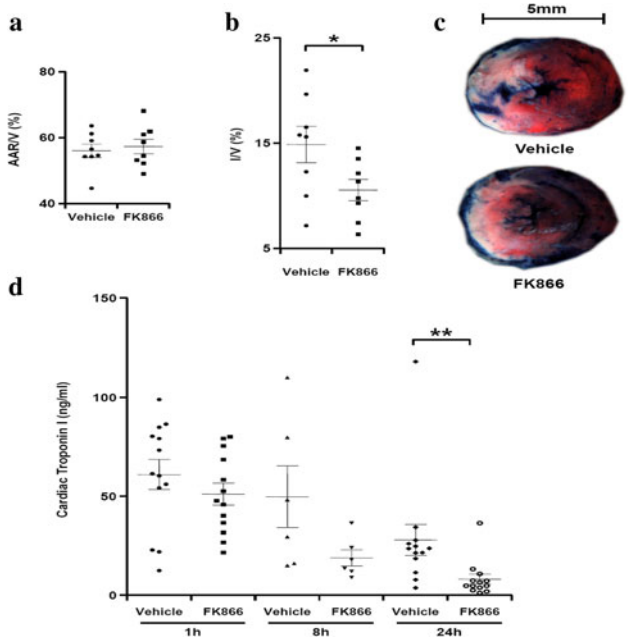
Nicotinamide phosphoribosyltransferase (Nampt) is a key enzyme for nicotinamide adenine dinucleotide (NAD^+) biosynthesis, and recent

evidence indicates its role in inflammatory processes. Here, we investigated the potential effects of pharmacological Nampt inhibition with FK866 in a mouse myocardial ischemia/reperfusion model. In vivo and ex vivo mouse myocardial ischemia/reperfusion procedures were performed. Results: Treatment with FK866 reduced myocardial infarct size, neutrophil infiltration, and reactive oxygen species (ROS) generation within infarcted hearts in vivo in a mouse model of ischemia and reperfusion. The benefit of FK866 was not shown in the Langendorff model (ex vivo model of working heart without circulating leukocytes), suggesting a direct involvement of these cells in cardiac injury. Sera from FK866-treated mice showed reduced circulating levels of the neutrophil chemoattractant CXCL2 and impaired capacity to prime migration of these cells in vitro. The release of CXCL8 (human homolog of murine chemokine CXCL2) by human peripheral blood mononuclear cells (PBMCs) and Jurkat cells was also reduced by FK866, as well as by sirtuin inhibitors and SIRT6 silencing, implying a pivotal role for this NAD^+-dependent deacetylase in the production of this chemokine. Conclusions: Nampt inhibition appears as a new strategy to dampen CXCL2-induced neutrophil recruitment and thereby reduce neutrophil-mediated tissue injury in mice.



Difficulties in diagnostic and therapeutic management of myocardial bridging

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Introduction: Myocardial bridging is a frequent anatomical variant that often covers part of a major sub-epicardial coronary arterial segment (tunneled artery). Myocardial bridge frequency is around 50 % by autopsy, and nowadays with improved cardiovascular imaging it is more and more often detected in vivo (3–58 % by CT, 0.4–15.8 % by angiography).

It is generally a benign condition but may be associated with sudden cardiac death, myocardial ischemia and infarction, coronary spasm, brady- and tachy-arrhythmias, transient ventricular dysfunction. In sport medicine, myocardial bridge is one of main causes of sudden cardiac death among young athletes, but symptoms may occur more frequently after the third decade of life.

Therapeutic strategies for symptomatic patients include medical therapy, stent placement, and surgical treatment. However the best therapeutic strategies is still debated and should be individualized considering the anatomical properties of the myocardial bridge.

Herein we describe the case of myocardial ischemia due to myocardial bridge in a 62-years-old man, treated with medications and coronary stent placement.

Case Report: A 62-years-old amateur cyclist (13,000 km annually), undergoing every year a sport medicine evaluation and with a recent diagnosis of arterial hypertension treated with olmesartan/hydrochlorothiazide 20/12.5 mg daily, presented a first transient episode of effort angina during physical training. The subsequent day he presented syncope preceded by palpitations, fatigue and diaphoresis. One day later, in the evening, he complained chest pain at rest lasting 5 min, that recurred some hours later. The ECG performed at home by the Emergency Staff (118) showed mild ST-elevation with negative T wave in V1–V3. Upon arrival at the Emergency Room the patient was asymptomatic while ECG alterations were still present. Troponin-HS and the isoform MB of creatine kinase resulted slightly elevated, 31 pg/mL and 5.92 ng/mL respectively (normal values 0–14 and 0–4.94), with normal echocardiographic findings. The patient was admitted to the Coronary Care Unit and treatment with clopidogrel 600 mg, ASA 300 mg and atorvastatin 80 mg was started. Coronary angiography resulted as totally normal except for a long myocardial bridge with milking effect in the mid portion of the left anterior descending artery, that sub-occluded during systole and deep inspiration. Four days later the patient complained chest pain with ST elevation in V2–V4. The continuous ECG monitoring showed episodes of sinus bradycardia and sino-atrial block with emergence of junctional escape beats, ventricular bigeminy and one non-sustained ventricular tachycardia. Then it was decided to perform a percutaneous coronary intervention (PCI) guided by intravascular ultrasound (IVUS). A stent Promus Element 3 × 38 mm was directly placed to cover completely the coronary segment under the myocardial bridge (i.e. with the edges of the stent beyond the myocardial bridge), and post-dilated with non-compliant balloon 3.5 mm. The cross-sectional area of the left anterior descending artery was reduced by 60 % in systole before the procedure, and resolved with PCI. The patient was discharged with the following drug regimen: prasugrel 10 mg, ASA 100 mg, olmesartan 20 mg, atorvastatin 40 mg, pantoprazole 20 mg OD; 5-mononitrate 40 mg BID (withdrawn on a subsequent outpatient clinical visit). Three months later the patient presented recurrence of angina, with ST-depression in V4–V6. The coronary angiography showed coronary artery spasm of the left anterior descendent, just proximally and distally to stent previously placed, resolved by intracoronary nitroglycerin infusion. The patient was discharged adding to treatment regimen 5-monitrate 40 mg TID and verapamil 40 mg BID. Nine months later the patient was well and he had started again his sport practice. Both a maximal ECG stress test while on treatment and a dipyridamole stress echocardiography were negative and coronary flow reserve was estimated as normal by echocardiography.

Conclusions: Our case illustrate the existing difficulties in the diagnostic and therapeutic management of myocardial bridging; medical therapy resulted insufficient so that stenting placement was added. The pathophysiological mechanism of the coronary spasm occurred proximally and distally to the stent in our patient remains to be clarified; however, after the reintroduction of nitrate the patient has become symptoms free. Further studies are needed to explore the pathophysiology and the diagnostic and therapeutic management of myocardial bridge.

Synergistic effects of sonic hedgehog gene transfer and bone marrow-derived endothelial progenitor cells therapy on angiogenesis and muscle regeneration in mouse hindlimb ischemia model

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Background: We have previously demonstrated that sonic hedgehog (Shh) gene transfer improves angiogenesis in the setting of ischemia by upregulating the expression of multiple growth factors and enhancing the incorporation of endogenous bone marrow (BM)-derived endothelial progenitor cells (EPCs). In this study, we hypothesized that combined therapy with Shh gene transfer and BM-derived EPCs is more effective than Shh gene therapy alone in an experimental model of peripheral limb ischemia.
Methods and Results: We used old mice, which have a significantly reduced angiogenic response to ischemia, and compared the ability of Shh gene transfer, exogenous EPCs, or both to improve regeneration after ischemia. We found a significantly higher capillary density in the Shh + EPC-treated muscles compared to the other experimental groups. We also found that Shh gene transfer increases the incorporation and survival of transplanted EPCs. Finally, we found a significantly higher number of regenerating myofibers in the ischemic muscles of mice receiving combined treatment with Shh and BM-derived EPCs.
Conclusions: In summary, the combination of Shh gene transfer and BM-derived EPCs more effectively promotes angiogenesis and muscle regeneration than each treatment individually and merits further investigation for its potential beneficial effects in ischemic diseases.

Vascular endothelial dysfunction in duchenne muscular dystrophy: a new role and a potential novel target for treatment

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Background: Dystrophin, the missing or defective protein in Duchenne muscular dystrophy (DMD), is expressed not only in muscle cells, but also in vascular endothelial cells (ECs). In this study, we assessed the effects of dystrophin deficiency on the angiogenic capacities of ECs.
Methods and Results: We isolated vascular ECs from *mdx* mice, the murine equivalent of DMD in humans, and wild-type controls and found that *mdx*-derived ECs have impaired angiogenic properties, in terms of migration, proliferation, and tube formation. They also have reduced ability to support myoblast proliferation when co-cultured with satellite cell-derived primary myoblasts. These endothelial defects are mirrored by systemic impairment of angiogenesis in vivo, both upon induction of ischemia, stimulation with growth factors in the corneal model and matrigel plug assays, and tumor growth. We also found that cGMP formation and NO production are compromised in ECs isolated from *mdx* mice and that treatment with aspirin enhances production of both cGMP and NO in dystrophic ECs. Aspirin also improves the dystrophic phenotype of *mdx* mice in vivo, in terms of resistance to physical exercise, muscle fiber permeability, and development of fibrosis.
Conclusions: These findings demonstrate that impaired angiogenesis is a novel player and potential therapeutic target in DMD.

Coexistence of obesity and hypercholesterolemia is associated with NOX-2 generated oxidative stress and arterial dysfunction in children

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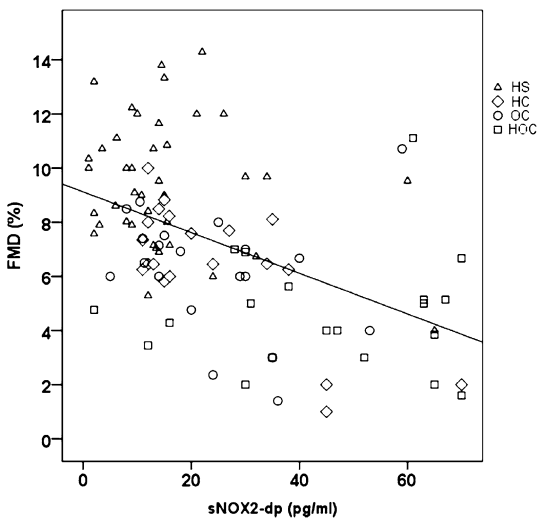
Background: Coexistence of multiple cardiovascular risk factors (CVRF) in children is associated with a greater severity of asymptomatic atherosclerosis but the mechanism underlying is still unclear. Oxidative stress is believed to play a pivotal role in the atherosclerotic process. NADPH oxidase, one of the most important cellular sources of reactive oxygen species (ROS) in humans, is implicated in arterial dysfunction.
Objective: Aim of the study was to analyze the interplay among oxidative stress, NOX2, the catalytic core of NADPH oxidase, endothelial dysfunction in children with obesity and/or hypercholesterolemia.
Methods: We performed a cross-sectional study comparing flow-mediated dilation (FMD), ox-LDL and urinary excretion of isoprostanes (8-iso-PGF2α), as markers of oxidative stress, and NOX2 activity, as assessed by blood levels of soluble NOX2-dp (sNOX2-dp), in a population of 100 children, matched for age and gender, including 40 healthy subjects (HS), 20 hypercholesterolemic children (HC), 20 obese children (OC) and 20 children with coexistence of hypercholesterolemia and obesity (HOC).
Results: HOC had higher sNOX2-dp and OX-LDL levels compared to HS, HC and OC. HC, OC and HOC had lower FMD values compared to HS. Urinary 8-iso-PGF2α excretion was higher in HOC compared to HS. FMD was inversely correlated with sNOX2-dp levels ($r = -0.483$; $p < 0.001$) (figure) and with the number of CVRF ($r = -0.617$; $p < 0.001$). Multiple linear regression analysis showed that the number of CVRF was the only independent predictive variable associated with FMD (β:-0.585; $p < 0.001$; $R2 = 35$ %) and sNOX2-dp (β:0.587; $p < 0.001$; $R2 = 34$ %).
Conclusion: The study suggests that NOX2-generating oxidative stress may have a pathogenic role in the functional changes of the arterial wall occurring in children with coexistence of obesity and hypercholesterolemia.



Figure

Linear and non-linear indexes as markers of cardiovascular risk in moderate psoriasis

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Psoriasis vulgaris is a chronic, inflammatory, immune-mediated skin disease and clinically characterized by chronic erythematous plaques, generally at the elbows, knees, scalp, and lumber area. Recent studies have reported that psoriasis is associated with metabolic syndrome and other disorders, including obesity, dyslipidemia, and diabetes. Other studies suggest that psoriasis is an independent risk factor for myocardial infarction, greatest in young patients with severe psoriasis, and is attenuated with age.

However, the relationship between cardiovascular risk factors and psoriasis has not been sufficiently clarified. In particular the effects of psoriasis on autonomic nervous system are not defined.

The aim of our study has been to evaluate whether in young patients with moderate psoriasis in absence of the metabolic syndrome or other comorbidity the autonomic function, analyzed by means linear and nonlinear methods of hearth rate variability, is affected.

Materials and Methods: 19 young subjects, aged between 18 and 35 years, of both sexes affected by moderate Psoriasis (PASI Index 7.1 ± 1.7) have been enrolled and compared with a control group of 22 normal subjects sex and age matched. We recorded 10-min ECG (XAI-MEDICA) in rest condition. We analyzed recorded data with XAI-MEDICA software for HRV linear analysis and also with KUBIOS-HRV software for the HRV non linear analysis.

Linear Methods: These methods are used for direct amounting of estimation of HRV at investigated period of time. Statistic characteristic of dynamic row of cardiointervals include: SDNN, RMSSD, Analysis of the HRV by means the frequency domain describes the periodic oscillations of the heart rate signal decomposed at different frequencies and amplitudes, and provides information on the amount of their relative intensity in the heart's sinus rhythm. The power spectrum can be classified into two principal bands: the low frequency band (LF) and the high frequency band (HF). The HF component is generally defined as a marker of vagal modulation. The LF component is modulated by both the sympathetic and parasympathetic nervous systems. The LF/HF Ratio is considered an index of sympato-vagal balance.

Nonlinear Methods: Poincarè Plots: Two-dimensional vector analysis was used to quantify the shape of the plots. In this quantitative method, short-term (SD1) and long-term R–R interval variability (SD2) and the ellipse area of the plot are separately quantified. SD2 is generally considered expression of the vagal modulation of sinus node.

Detrended fluctuation analysis (DFA). This technique was used to quantify the fractal scaling properties of short- and intermediate-term R–R interval time series. The HR correlations were defined separately for short-term (<11 beats, 1) and longer-term (>11 beats, 2) R–R interval data. Thus, fractal analysis can be considered as an improvement of spectral analysis, without any interference of environmental and physiological changes, such as respiration and physical activity. Statistics: to compare the two groups we used non paired t-test with a p value of 0.05 considered significant. Data are expressed as mean ± ESM.

Results: RMSDD showed a significant difference between the two groups (Normal 57.0 ± 6.3 vs. Psoriasis 35.7 ± 4.4 ms). Concerning Power spectral analysis: Total power was significant less in psoriasis group (4202.1 ± 675.5 vs. 2915.5 ± 473.7 ms^2), and in HF component (49.9 ± 3.1 vs. 37.6 ± 4.1 nu), while the LF component and LF/HF ratio showed a significant increase in the psoriasis group (50.1 ± 3.1 vs. 62.4 ± 4.1 nu, and 1.1 ± 0.1 vs. 2.8 ± 0.8 respectively). Using the Poincarè plot the SD1 index was significantly more less in the psoriasis group (250.8 ± 21.6 vs. 176.9 ± 20.8 ms). Finally the DFA 1 index was significant more high in the psoriasis group (0.95 ± 0.05 vs. 1.21 ± 0.06).

Conclusion: Our data suggest that in the moderate psoriasis there is a balanced reduction in the parasympathetic modulation associated with an increase sympathetic modulation of sinus node.

Because the increase in sympathetic activity may be associated with an increase in cardiovascular risk (ventricular arrhythmias, sudden cardiac death, etc.) we can conclude that moderate psoriasis might represent a possible independent cardiovascular risk.

Increased serum concentrations of soluble adhesion molecules in "non-dipper" hypertensives

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Blood pressure (BP) normally declines at night. Individual who fail to dip their night-time BP relative to their average day-time BP are termed as 'non-dippers'. A non-dipping pattern is found more frequently in hypertensive individuals.

The underlying pathogenetic mechanism potentially linking non-dipping with cardiovascular disease are largely unclear. In particular, the relationship between nocturnal blood pressure (BP), dipping and inflammatory alterations has not been investigated.

Proinflammatory alterations play a crucial role in atherosclerosis initiation and progression and acute coronary events.

Similarly, the proinflammatory state observed in hypertension might contribute to adverse cardiovascular outcome in patients with essential hypertension. The atherosclerotic risk associated with non-dipping may essentially relate to relatively greater blood pressure load throughout the day and night on endothelial cells of non-dipping individuals.-Atherosclerosis is accompanied by impaired endothelial function giving rise to upregulation of cellular adhesion processes.

Hence, we investigated whether plasma levels of Intercellular Adhesion Molecule-1 (ICAM-1) Vascular Cell Adhesion Molecule-1 (VCAM-1) and E-Selectin would be relatively higher in non-dippers.

We examined 208 never treated patients with mild hypertension and 110 healthy subjects matched for age and sex.

Blood sample for the measurements of soluble ICAM-1, VCAM-1 and E- Selectin were collected overnight fast. Measurements were performed in duplicate by commercially available enzyme-linked immunosorbent assay kits (R&D System).

Outpatient ambulatory monitoring was performed for a 24 h period using the SpaceLabs model 90207.

We defined non-dippers as those subjects whose average BP dipped at night <10 % as compared with their average daytime BP.

Plasma levels of ICAM-1, VCAM-1, and E- Selectin all were higher in hypertensive patients as compared with the normotensives ($p < 0.01$).

Soluble cell adhesion molecules levels were all higher in non-dipper than in dipper subjects ($p < 0.05$).

In conclusion, our study provides evidence that subjects who fail to dip their BP at night experience elevated levels of molecules related to endothelial dysfunction and atherosclerosis.

This finding provides one possible mechanism linking non-dipping with cardiovascular disease.

Is Growth Hormone replacement therapy in Chronic Heart Failure safe and effective in a long-term administration trial?

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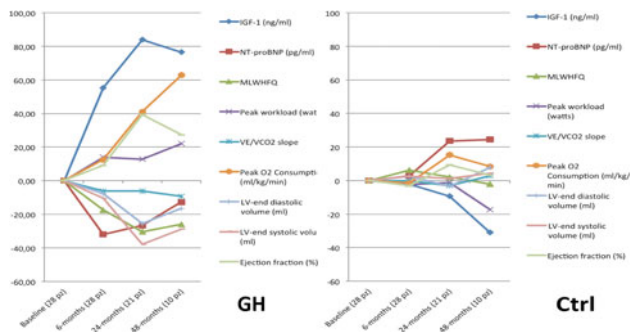
Context: Recent evidence suggests that GH replacement has a beneficial effect in Chronic Heart Failure. However only short duration studies are currently available although data on long-term efficacy and safety of GH replacement therapy in Chronic Heart Failure would be of great importance
Objective: To evaluate the effect and the safety of GH replacement therapy after a 2 and 4-year of follow-up
Design and Setting: A randomized, single-blind, and controlled trial.
Participants: 56 patients with coexisting Chronic Heart Failure and GH Deficiency were enrolled in the trial. Twenty-eight of them were treated with GH replacement therapy on top of standard medical therapy. Twenty-one of them reached the 24-months of follow-up, and 17 of them the 48-months of follow-up.
Intervention: The treated group received GH, at a replacement dose of 0.012 mg/kg every second day (~2.5 IU).
Main Outcomes Measures: Clinical Status, Neurohormonal activity, Exercise capacity, Left Ventricular Architecture and Function.
Results: GH replacement had a constant beneficial effect on exercise capacity during the all administration period as shown by the increasing value of Peak Oxygen Consumption (from 14.1 ± 1.2 to 18.2 ± 1 after 24-months, and to 21 ± 1 after 48-months; both $p < .001$ vs. baseline). The remarkable improvement of Left Ventricular (LV) function observed after 24-months (Ejection Fraction from 31.4 ± 4.1 to 45.9 ± 4.2; $p < .001$) was followed by a stability when re-analyzed after 48-months. No remarkable changes were observed in the control group.
Conclusions: In a selected group of patients with coexisting CHF and GHD, long-term replacement therapy appears to be safe and effective.



Circulating MRP 8/14 is associated with thromboxane-dependent platelet activation in NSTEMI patients: effect of aspirin treatment

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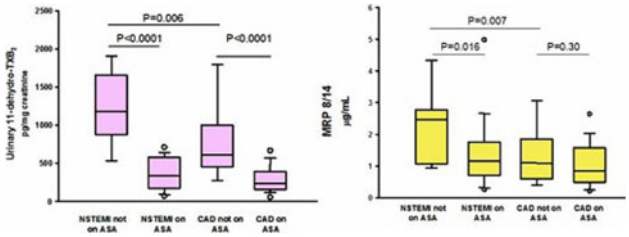
Myeloid related protein (MRP)-8/14 is an heterodimer formed and secreted on activation of platelets, monocytes and neutrophils and regulating vascular inflammation by promoting leukocyte recruitment. A transcriptional platelet profiling approach in ACS patients identified MRP-14 as a novel predictor of MI. Plasma levels of MRP-8/14 are elevated in STEMI patients and predict increased risk of first and recurrent CV events.
We aimed to evaluate whether: (1) NSTEMI patients also exhibit higher MRP 8/14 levels as compared to stable CAD patients; (2) MRP 8/14 release in the circulation is related to thromboxane (TX)-dependent platelet activation; (3) MRP 8/14 may be associated with residual TX biosynthesis in low-dose aspirin-treated NSTEMI patients.
We enrolled stable CAD and NSTEMI (for reperfusion with primary PCI) patients, undergoing coronary angiography.
Plasma levels of MRP 8/14 were significantly higher in NSTEMI ($n = 38$) as compared to stable CAD patients ($n = 58$) [median (IQR) 1.43 (0.94–2.51) vs. 0.91 (0.51–1.58) μg/mL, $P = 0.007$]. Patients with NSTEMI not on aspirin treatment had significantly higher plasma MRP 8/14 (2.46 (1.06–2.77) vs. 1.09 (0.59–1.85) μg/mL, $P = 0.007$] and urinary 11-dehydro-TXB_2 [(1180 (878–1654) vs. 607 (449–999) pg/mg cr, $P = 0.006$] as compared to CAD patients not on aspirin. A significant direct correlation was observed between MRP 8/14 and urinary 11-dehydro-TXB_2 in all NSTEMI patients ($n = 38$, Rho $= 0.549$, $P < 0.0001$). In NSTEMI patients, both urinary 11-dehydro-TXB_2 and plasma MRP 8/14 were significantly lower in aspirin-treated subjects (24 out of 38) as compared to those untreated with aspirin at the time of the cross-sectional evaluation. In aspirin-treated NSTEMI patients, residual TX biosynthesis was significantly related with plasma MRP 8/14 (Rho $= 0.62$, $P = 0.001$). At multivariate analysis, elevated plasma MRP 8/14 (Rho $= 0.572$, $P = 0.02$) remained the only significant predictor of residual TX biosynthesis.
In NSTEMI but not in chronic CAD patients, plasma MRP 8/14 levels are increased and associated with TX-dependent platelet activation. Ongoing low-dose aspirin treatment at the time of the acute event is associated with lower plasma MRP 8/14, whose concentration is associated with residual TX biosynthesis in this setting.



High serum uric acid predicts prevalent cardio-renal anaemia syndrome in a cohort of elderly patients

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Purpose: The triad of heart failure, kidney insufficiency and anaemia is known as the cardio-renal anaemia (CRA) syndrome. Interaction of these three conditions generates a vicious circle causing progressive impairment of both cardiac and renal function, also worsening anaemia itself. It has been argued that CRA syndrome contributes to considerable mortality due to heart failure (HF). The three elements of CRA syndrome share an increased activity of critical mechanisms of disease progression such as sympathetic nervous system and renin–angiotensin-aldosterone axis activation, oxidative stress and inflammation. Recent evidences suggest that serum uric acid contributes to systemic inflammation in humans. Hyperuricaemia has long been known to be associated with cardiovascular disease and it is particularly common in patients with kidney disease. Aims of our work was to examine prevalence of CRA syndrome among old patients hospitalized at Cardiology Unit of our research hospital and assess its association with serum uric acid.

Materials and Methods: In a cross-sectional study we enrolled 165 elderly patients (72 male, 93 female; mean age: 80 ± 7 years), consecutively hospitalized at Cardiology Unit of our research hospital. For all subjects at admission we performed clinical examination, blood pressure measurement, ECG and laboratory tests including serum creatinine and haemoglobin, serum albumin, serum uric acid and C-reactive protein (CRP). In all participants glomerular filtration rate (eGFR) was estimated from Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula. HF was defined according Heart Failure Society of America Criteria. Anaemia was defined as an haemoglobin concentration <13.0 g/dL for males and <12.0 g/dL for females according to the WHO criteria. For association analysis moderate chronic kidney disease was defined by eGFR < 60 mL/min/1.73 m^2. All calculations were made with a standard statistical package (SPSS for Windows version 10.0).
Results: Statistical analysis revealed high prevalences of heart failure (67 %), moderate renal impairment (eGFR < 60 mL/min/1.73 m^2: 50.4 %) and anaemia (54 %). Mean serum creatinine and mean eGFR were 1.19 ± 0.55 mg/dL and 56.93 ± 21.31 mL/min/1.73 m^2 respectively. Subjects with cardio-renal anaemia syndrome were 37 (22.4 %). Interestingly Chi-square tests showed significant associations between cardio-renal anaemia syndrome and higher values of serum uric acid (r: 0.191; p: 0.024), higher values of CRP (r: 0.277; p: 0.029), lower values of serum albumin (r: −0.275; p: 0.002) and age > 80 years (r: 0.209; p: 0.007). In binary logistic regression analysis (backward stepwise) serum uric acid was the only predictor of CRA syndrome (B: 0.392; odds ratio: 1.480; 95 % CI: 1.044–2.097).
Conclusions: Our study highlights that CRA syndrome is common among elderly inpatients. In fact it was diagnosed in more than one-fifth of the participants. Moreover our data demonstrate a significant association between CRA syndrome and reduced serum albumin. Hypoalbuminemia is a frequent condition in patients with heart failure and is mainly related to the malnutrition-inflammation complex syndrome. Other causal factors include hemodilution, nephrotic syndrome, liver dysfunction, increased transcapillary escape rate and protein-losing enteropathy. Hypoalbuminemia is also common in patients with end-stage renal disease and it is a strong predictor of an adverse prognosis. In addition we observed that higher CRP levels were associated with CRA syndrome. It is well known that increased plasma CRP concentration is a marker of chronic inflammation. Furthermore high CRP levels have been related to the features of endothelial dysfunction and to insulin resistance. Of note we found that serum uric acid concentration in elderly individuals was associated with CRA syndrome independent of CRP. Recent findings suggest that elevated serum uric acid is related with markers of pro-inflammatory state. In particular previous evidences showed that serum uric acid was associated positively with IL-6, CRP and TNF-α and negatively with IL-1β. Erythropoietin resistance itself is known to be strongly linked with chronic inflammation. Therefore uric acid should be taken into consideration as a link between renal dysfunction and pro-inflammatory state in patients with CRA syndrome. So, in the clinical setting, more attention should be paid to recognizing and diagnosing hyperuricaemia. More efforts should be dedicated in the research setting to better understand the pathophysiology of CRA syndrome and to identify effective management strategies.

Endothelial dysfunction but not increased carotid intima-media thickness in young European women with endometriosis

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Background: Atherosclerosis is a chronic and degenerative disease developing typically in elderly; nonetheless, a condition of accelerated atherosclerosis can be observed precociously in presence of some diseases. Endometriosis, a chronic benign gynaecological disorder, shows some characteristics, as oxidative stress, systemic inflammation and pro-atherogenic lipid profile, that could lead to an increased risk of developing accelerated atherosclerosis.
The aim of our study was to evaluate markers of subclinical atherosclerosis in young European women with endometriosis.
Methods: This cross-sectional study included 37 women with endometriosis and 31 control subjects. Presence of subclinical atherosclerosis was investigated by ultrasound evaluation of common carotid intima-media thickness (ccIMT) and flow-mediated dilation (FMD); in addition, serum levels of lipids, inflammatory and coagulation parameters, as well as markers of endothelial inflammation and activation, were determined.
Results: Women with endometriosis showed significantly lower values of FMD compared to controls (mean difference −4.62, 95 % confidence interval −6.52, −2.73; $p < 0.001$), whereas no significant differences in ccIMT values were found between the two groups. As regards markers of endothelial inflammation and activation, women with endometriosis had significantly higher values of inter-cellular adhesion molecule 1, vascular cell adhesion molecule 1, E-selectin, von Willebrand factor and ristocetin cofactor compared to controls.
Conclusions: Our study suggests that women with endometriosis have more subclinical atherosclerosis, resulting in higher risk to develop future cardiovascular disorders. Moreover, our findings confirm that endothelial dysfunction can occur in absence of structural atherosclerotic changes, and its evaluation might be helpful especially in young people when these last can miss.

Acute ischemic events and polymyalgia rheumatica: which one comes first? Experience of a case and review of the literature

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Introduction: Polymyalgia Rheumatica (PMR) is an inflammatory condition characterised by pain and morning stiffness of the shoulder and pelvic girdle; it can occur in 'isolated' form or be related to giant cell arteritis (GCA). It has been observed that 'isolated' PMR may be complicated by ischemic manifestations, such as stroke, visual loss, myocardial infarction (MI), maybe due to accelerated atherosclerosis or subclinical vasculitis, even without clinical overt GCA.
Case Report: A 71-year-old man was admitted to our Department because of persistent fever, asthenia, pain of both wrists, ankles and elbows, with difficulty to lift up his arms and on walking. Physical examination revealed signs of inflammation (i.e. *rubor*, *dolor*, *calor*) at both wrists, hands and elbows, with swelling and pitting edema.
Laboratory tests showed normocytic anaemia, elevation of erythrocyte sedimentation rate (ESR 80 mm/h), fibrinogen (1080 mg/dL) and C-reactive protein (CRP 118 mg/dL). Rheumatoid factor, antinuclear antibodies, antiphospholipid antibodies were absent, while muscle enzymes levels were normal. The screening for hereditary or acquired thrombotic risk factors was also negative. A careful clinical history revealed that 30 days before his admission an occipital headache occurred, together with cervical spine tenderness, and weakness of shoulder and pelvic girdle, that the patient attributed to osteoarthritis and treated with analgesics. Also, 15 days after the beginning of these symptoms an acute myocardial infarction (NSTEMI) occurred. Coronary angiography showed a segmental stenosis of anterior descending artery in absence of further vessels abnormalities, which was treated with PTCA-stenting. He was discharged from the Cardiology Department some days

later, while low-grade fever and articular manifestations persisted. When he came to our attention, the presence of polymyalgic symptoms, the high levels of inflammatory markers and the rapid improvement after steroid therapy allowed us to confirm the clinical suspicion of PMR, according to the 1984 Healey criteria. Before starting steroid therapy (Methylprednisolone 8 mg/day) temporal artery Doppler US was also performed, to exclude the presence of 'halo' or thickness signs, typically associated with a concomitant GCA. 3 days after the beginning of steroid therapy the patient could walk; pain and signs of synovial inflammation promptly improved. At the discharge CRP was 15 mg/dL, fibrinogen 530 mg/dL.
Discussion and Conclusions: Given the patient's low cardiovascular risk before the appearance of PMR clinical picture, and given the close temporal relationship between the onset of PMR and the MI, an etiopathogenic correlation between the two events can be hypothesised, as a vasculitic process involving the coronary arteries and causing the ischemic event. A systematic literature survey about polymyalgia rheumatica and cardiovascular events showed that PMR is associated with an increase in mortality due an excess of vascular deaths [1]. Furthermore, there is a significant association between PMR and myocardial infarction, peripheral vascular disease, and cerebrovascular events. Recently, we also found a clinical correlation between fever and ischemic events in a population of 106 patients admitted to our Periodic Fever Research Centre in the period 1978–2010: a significant increase of ischemic manifestations (53 vs. 28.5 %) was observed in the group of PMR patients with fever at the exordium [2], suggesting the potential role of chronic inflammation as a key-factor in the pathogenesis of accelerated atherosclerosis, as well as the possibility of a coexistent subclinical extra-cranial vasculitic process. In conclusion, in case of PMR an accurate cardiovascular work-up should be performed. Also, the precocious steroid treatment as well as treatment with antiaggregants could prevent ischemic complications, especially in patients with signs or symptoms of a severe inflammatory state (such as persistent fever) or in presence of prothrombotic risk factors (antiphospholipid antibodies, factor Leiden V, MTHFR mutations, etc.). Nevertheless, further studies are required to quantify the level or cardiovascular risk in inflammatory rheumatic diseases such as PMR, in order to initiate active surveillance programs and to optimise the therapeutic strategies.

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Electrocardiographic abnormalities due to hyperpotassiemia. Diabetic acidosys. Hyperosmolar syndrome. Hypovolemia. Chronic renal failure. Temporary hepatopathy due to hypoperfusion

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M.G. female, 83 years old, under antihypertensive (ACE-I) and insulin therapy for 15 years. Since last year she was treated with digitalis and frusemide because of heart failure episodes. During the last year creatinine levels were a bit higher then maximum values. Since yesterday she suffered from inappetence, nausea, bouts of sickness, epigastralgy and hyperglycemia. Physical examination: the patient was soporous and slightly dyspneic, with dry tongue and acetonemic breath; bibasilar rales in the lungs; bradycardia (30 bpm); arterial blood pressure was 130/50 mmHg. Common laboratory exams: glycemia 648 mg/dl, uremia 114 mgdL, creatinine 3.3 mg/dL, sodium 134 mEq/L, potassium 8.2 mEq/L, GOT 400 U/L, ALT 360 U/L, LDH 3518 U/L, WBC 22000 cmm, PaO_2 102, $PaCO_2$ 19.9, HCO_3 6.2, Ph 7.12, measured $[H^+]$ 76, SaO_2 98, measured osmolarity 340 mOsm. Negative HAV, HBV and HCV markers. Instrumental exams. Admission ECG: bradycardia, large QRS complexes (0.20 s) with atypical right bundle branch block, left axis deviation, no P waves; high, sharp, symmetric T waves. Chest X-ray: thin bilateral pleural effusion. Negative abdomen US. Therapy: insulin, bicarbonate, calcium gluconate, physiological solutions. Discharge ECG: sinus rhythm, normal QRS complexes without RBBB, normal electrical axis and T waves.

Characterization of circulating endotelial cells in hereditary haemorrhagic telangiectasia

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Background: Hereditary Haemorrhagic Telangiectasia (HHT) is a rare vascular dysplasia, with an autosomal-dominant inheritance pattern, affecting 1–2:10,000 individuals. HHT patients suffer from multiple localized arterio-venous shunts, both macro- and microscopic in size, often prone to haemorrhaging, which manifest in several organs (mainly oral and nasal cavity, skin, lung, liver, brain, GI tract). The disorder is caused by heterozygous mutations in the Endoglin or ALK1/ACVRL1 gene, which lead to abnormal angiogenesis and/or endothelial behaviour, ultimately resulting in the characteristic vascular shunts. Although the molecular and cellular mechanism(s) are still far to be elucidated, HHT-typical shunts seem to be associated to an angiogenic unbalance mainly affecting endothelial cells, consisting in increased mobilization, excessive proliferation, and loss of arterio-venous identity. Similarly to what happens to several other cardiovascular diseases, circulating endothelial cells (CECs) might play a relevant role in the pathogenic mechanism(s) and/or disease severity of HHT. Several studies pointed out that CECs represent a biomarker of different pathological conditions affecting vasculature, such as heart ischemia, diabetes, systemic hypertension, atherosclerosis. CECs can have two different sources, since progenitor CECs derive from bone marrow stem cells, whereas mature CECs arise from mobilization of endothelial cells of pre-existing vessels, due to either active angiogenesis or vascular damage. Levels of CECs have been associated to a different effectiveness of vascular repair, as well as to various degree of vascular damage. Despite the undebated evidence of altered vascular remodelling in HHT, no studies have thus far investigated the profile of CECs in HHT patients.
Aims: To characterize the number of CECs in HHT patients, based on immunophenotypic properties, compared to two age-matched control populations (healthy volunteers and patients affected by vascular-damage-involving diseases different from HHT).
Methods: Forty-four consecutive HHT patients were recruited by the HHT Interdepartmental Center of Bari. Twenty age-matched healthy volunteers were enroled to serve as control group. Ninety patients with different vascular disorders other than HHT were also included in the study a second control group, in order to investigate the correlation existing between overt vascular damage and the CEC number. Peripheral blood was obtained and the number of CECs was assessed by flow-cytometry analysis. CECs were defined as CD31+/VEGFR2+/CD34+/CD45−. Furthermore, to better refine the specificity of our results, the number of circulating hematopoietic cells (HSC) was also measured, as number of CD34 +/

CD45low. The number of CECs and HSCs was statistically analyzed by Mann–Whitney U-test and Kruskal–Wallis test. The number of CECs and HSCs was also correlated with age by linear regression analysis and with several humoral factors by bivariate non-parametric correlation analysis.
Results: HHT patients had a significantly higher number of CECs (50.1 ± 80.5) when compared to both healthy controls (10.9 ± 14.5) and non-HHT vascular-disease controls (5.3 ± 11.9) ($p < 0.0005$). Conversely, the number of HSC cells did not differ significantly in the three groups (652 ± 1053 in HHT, 510 ± 355 in healthy controls, 665 ± 1137 in non-HHT vascular-disease controls). The number of CEC and the number of HSC did not correlate with age, sex, and affected gene (Endoglin vs. ALK1/ACVRL1). CECs and HSCs showed no correlation with biohumoral parameters of either cytometric hemochrome assay or plasma lipid values.
Conclusions: Circulating Endothelial Cells are significantly elevated in HHT. These interesting observations might be explained by either an activated proliferation of bone-marrow-derived CECs or a stronger mobilization from pre-existing vessels. Such angiogenic imbalance favouring endothelial proliferation/migration might be mediated by increased VEGF levels previously reported in HHT patients by our group and others. Since CECs are not increased in non-HHT vascular diseases, our observations suggest in fact that high levels of CECs are not associated to mere vessel damage secondary to haemorrhage.

Longitudinal study of natural history of arteriovenous malformations in evolutionary age of hereditary haemorrhagic telangiectasia

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Background: Hereditary Haemorrhagic Telangiectasia (HHT) is an autosomal-dominantly-inherited angiodysplasia, with typical vascular lesions mainly affecting skin and mucosae, as well as liver, lung, and brain. Mutations in ENG and ACVRL1 genes are responsible for HHT, despite the clinical spectrum of this disorder shows a considerable variability. Although HHT is generally characterized by a higher penetrance with increasing age, HHT-related manifestations can also arise in pediatric age. In a few cases, onset is represented by severe complications secondary to otherwise occult visceral arteriovenous malformations (AVMs). Since AVM-related complications involve a marked clinical risk, HHT International Guidelines recommend HHT patients to be enrolled in a periodic radiological survey, and preventive treatment whenever necessary. However, the most appropriate timing of the radiological surveillance of AVM is still a matter of debate, especially in children and young adults. To this purpose, it would be crucial to know the natural history of already existing AVM over time and the eventual occurrence of de novo AVM. Yet, addressing such target requires a prospective longitudinal observation, which has never been carried out in pediatric HHT patient thus far.
Objective: The objective of the present study is to perform a longitudinal observation of HHT-related visceral AVMs during evolutionary age.
Methods: Patients in pediatric age (1–15 years), previously identified as carriers of the familial disease-causing mutation in ENG or ACVRL1, were initially subjected to screening for AVM. After some years, they were fully instrumentally monitored, independent of their AVM status at the first screening.
Results: A total of 16 children (mean age 10.2; DS:4.8 years) were enrolled in the first screening, with 12/16 patients (media: 15.3; DS: 4.5 years) accepting the instrumental monitoring. The mean time of follow-up after the first screening was 6.6 years (DS: 2.3). In the 12 patients subjected to the longitudinal observation, a de novo pulmonary AVM was detected in one case and regression of a pulmonary AVM occurred in one case. In one patient, we observed enlargement of a lung AVM, already detected upon first screening, which reached the threshold recommended for surgical treatment. In two patients, cerebral ischemic lesions secondary to pulmonary AVM were observed at first screening, which evolved towards lacunar and cyst-like regions inside the brain parenchyma. Onset of de novo brain AVM did not occur in any of the 12 patients, including the two patients with cerebral ischemic lesions upon first screening.
Conclusions: Our study shows that a follow-up of 6 years after the first screening represents an adequate timing for monitoring natural history and de novo formation of AVMs in HHT during evolutionary age.

BNP levels at the admission are related with days of hospitalization in patients with acute heart failure and the overall risk of death

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Background: Acute Heart Failure (AHF) is a frequent condition associated to poor prognosis among elderly patients admitted to Internal Medicine departments (IMDs). Length of hospitalization is associated to higher mortality among medical patients. Increased brain natriuretic peptide (BNP) levels have been associated, in this subset, to a raised mortality and morbidity.
Aims: to evaluate whether BNP levels at admission could be associated to longer hospitalizations and survival time in the subset of patients who die of AHF.
Methods: we enrolled 400 consecutive patients admitted to our IMD with a clinical diagnosis of AHF. BNP was evaluated in all patients at the admission. Subjects were stratified in four categories: BNP less than 100 pg/ml (group 1), 101–500 pg/ml (group 2), 501–1500 pg/ml (group 3) and BNP higher than 1501 pg/ml (group 4). Each patient underwent to a complete diagnostic workup. Patients with BNP levels less than 100 pg/ml or a final diagnosis other than AHF were excluded. Kaplan–Meier model with log-rank test was used to assess the differences. Statistical analysis was performed with SPSS 13 package for Windows systems.
Results: 293 patients were suitable for final analysis. Mean age was 80 ± 9.85 years, males representing 58 % of the sample. Among patients who were successfully dismissed, group 4 had a significantly longer hospitalization time (16.6 days, 95 % CI: 13.7–19.5) than patients in group 3 (13.1 days, 95 %CI:11.7–14.6) or group 2 (12.3 days, 95 % CI: 10.6–13.9) ($p < 0.05$, all ties, Figure 1). Among patients who died of AHF, subjects in group 2 had a significantly longer survival time (mean: 46.0 days, SE 3.71) than patients in group 3 (mean: 36.7 days, SE 2.51) or group 4 (mean: 22.9 days, SE 1.88) ($p < 0.05$, all ties, Figure 2).
Conclusions: BNP is useful for diagnosis and prognostic stratification in patients with AHF. If confirmed in larger cohorts, it could also be used to predict longer hospitalizations among specific subsets of patients. Among elderly patients admitted into IMD who

will die of AHF, higher BNP levels are independently associated to a faster progression of the pathology and death. BNP levels at the admission of patients should be considered as a powerful tool that can help the physicians not only in diagnosis but also in the prognostic stratification of elderly, frail patients affected by AHF.

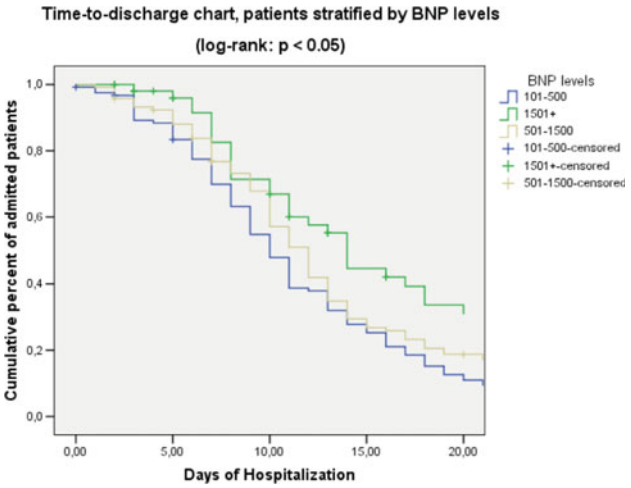

Fig. 1 Kaplan–Meier survival function between BNP levels, organized in three strata, and days of hospitalization. It is noticeable how the median and mean length of in-hospital stay is significantly related to the BNP stratum: patients with a BNP level of 101–500 pg/ml have a median of 10 days (95 % CI: 8.89–11.10), 501–1500 pg/ml have a median of 12 days (95 % CI: 10.80–13.20) while for values more than 1500 pg/ml the median rises to 14 days (95 % CI: 12.56–15.43) ($p < 0.05$, all ties).

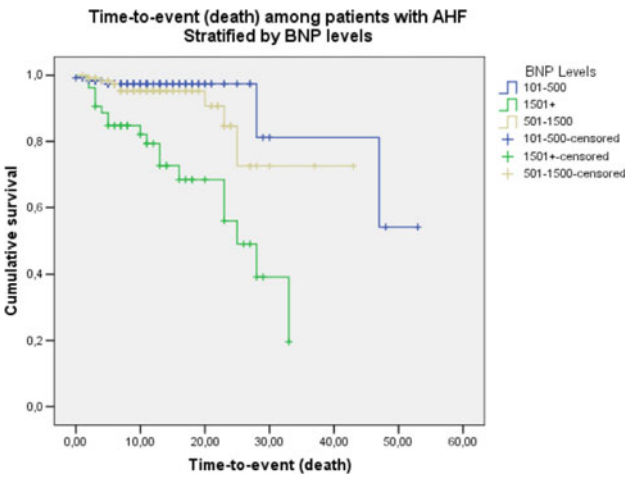

Fig. 2 Kaplan–Meier survival function. The time-to-event (death) is stratified in three groups, depending on BNP levels: group 1 (BNP levels 101–500 pg/ml), group 2 (BNP levels 501–1500 pg/ml) and group 3 (BNP levels > 1501 pg/ml). The difference in the median time-to-event, assessed with log-rank function, is statistically significant ($p < 0.05$, all ties).

Autonomic cardiovascular control during sleep in Brugada syndrome: the impact of comorbid sleep disordered breathing

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Brugada syndrome is a pathological condition characterized by specific electrocardiographic and arrhythmic patterns, such as ventricular arrhythmias and sudden cardiac death. These events seem to be more frequent during the night, when vagal cardiac modulation is likely to be predominant.

Interestingly, recent evidence showed that Brugada patients have a higher likelihood of sleep disordered breathing (SDB) compared to controls. However, the effects of SDB on autonomic regulation during sleep in Brugada patients are still unknown.

We assessed autonomic control in Brugada patients with SDB (BRU-SDB, n = 9), Brugada without SDB (BRU, n = 9) and healthy controls (CON, n = 8) during wake and different sleep stages (Wake, W, NREM 1, NREM 2, NREM 3 and REM). Autonomic regulation was assessed using spectral analysis of heart rate variability (HRV) and entropy-derived indices (regularity index, Ro, and Corrected Conditional Entropy, CCE).

Briefly, spectral analysis of HRV assesses the rhythmical oscillations in the heart period time series; two main components can be identified: the low frequency component (LF), marker of sympathetic modulation, and the high frequency (HF), marker of vagal modulation and synchronous with respiration. Non linear entropy derived indices evaluate the complexity of the cardiac autonomic control. Regularity index (Ro) is derived by dividing Corrected Conditional Entropy by the Shannon entropy and values range from 1 (maximum regularity, lowest complexity) to 0 (lowest regularity, maximum complexity). The CCE, bounded between 0 and Shannon entropy, represents the maximum amount of information derived from the RR series. The CCE decreases to 0 when the new sample is fully predictable, it is of the maximum value when the new sample is unpredictable, and it is of minimum when the knowledge of past values is helpful in reducing the uncertainty associated with future values.

The results showed that BRU-SDB patients were characterized by a reduced total HRV compared to BRU and CON during W (1528 ms^2 vs. 8076 ms^2 and 7993 ms^2 respectively, $p < 0.05$) and sleep and by a significantly smaller LF component, more evident during N2 (47 vs. 66 and 69 nu respectively, $p < 0.05$) and REM (32 vs. 62 and 73 nu respectively, $p < 0.05$). During REM, in BRU-SDB an increased parasympathetic modulation was observed compared to BRU and CON (59 vs. 35 and 24 nu, respectively, $p < 0.05$). Entropy indices were similar in the three groups throughout the sleep stages.

These data suggest that Brugada patients without co-morbid SDB have preserved neural control of HRV during wakefulness and sleep while the presence of SDB is accompanied by altered neural cardiac regulation, namely an increase of vagal modulation more evident during REM sleep; non-linear analysis of HRV revealed that the dynamic changes in the complexity of cardiac neural control are similar in Brugada patients with and without SDB, in comparison with controls.

In conclusion, the results the Brugada syndrome is not associated, per se, with any alterations in autonomic control during wakefulness and sleep. However, the presence of comorbid SDB appears to play a key role in the derangement of autonomic cardiovascular regulation during sleep in Brugada patients.

Outpatient management program for heart failure: results of 40 months of work

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Introduction: Guidelines recommend for patients with heart failure management programs providing follow-up through dedicated outpatient clinic. Limits of these programs are represented by enormous difficulties in getting patients adherence, being still too elevated percentages of abandonments.
Aims of the Study: to evaluate impact of 40 months of work in our dedicated to heart failure outpatient clinic on percentage of rehospitalizations, abandonments and deaths.
Methods: The clinical records of 307 patients admitted to our dedicated to heart failure outpatient clinic from January 2009 to April 2012 we retrospectively evaluated. This is a service led by a cardiologist and a specialized nurse. Patients can easily get a visit or telephone contact.
Results: During 40 months of work in our outpatient clinic 307 patients with heart failure (199 M/108 F; mean age 67.7 aa.) we followed. Of these, 68 % was NHYA I-II; 32 % NHYA III-IV. Mean follow-up was 15.3 months. We performed a visit every 3.2 months of follow-up on average. Rehospitalizations due to heart failure were very infrequent: 0.34 per patient, one every 45 months of follow-up, on average. Most of patients (78.8 %) did not need in hospital admissions for cardiac causes during follow-up. Only remaining 21.2 % needed one or more rehospitalizations for heart failure. Patients who abandoned outpatient clinic were 64: 20 % of followed patients, on average. About one abandonment every 20 days. Total patients dead were 42: a percentage of 13.7 %, equivalent to 4 % of patients per year. A death every 28 days, on average.
Discussion: During 40 months activity of our outpatient clinic, some clinical outcomes were very encouraging: only one fifth of patients needed rehospitalization due to heart failure, while less than one patients every seven is dead during 40 months of outpatient follow-up. Percentage of abandonments was also quite limited: about a patient every 5 has abandoned the follow-up. However, the frequency of visits was too low: each patient came for visit every 96 days, on average.
Conclusions: Results of 40 months activity of our outpatient clinic confirm value of management programs for patients with heart failure, but suggest that there is still to do for improving adherence at this programs.

Thrombotic and hemorrhagic risk scores for patients with atrial fibrillation: use in an emergency department

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Introduction: Thromboembolic events are the most worrying complications in patients with atrial fibrillation (AF). Prophylaxis of this events is based on oral anticoagulant therapy (OAT), use of which is still limited by widespread fear of hemorrhagic complications. This fear is often unjustified. The most recent guidelines suggest adoption of CHA2DS2-VASc, a new score that improve thromboembolic risk stratification rather than traditional CHADS2, because allows to more carefully characterize low risk patients. Moreover, another recommended score, HAS-BLED, allows to determine hemorrhagic risk in patients underwent OAT. Despite of these simple scores, use of OAT in patients with AF is still too limited.
Aims of the Study: (1) to characterize thromboembolic profile risk in a population of patients came to our emergency department (ED) for AF. (2) to characterize hemorrhagic risk in patients using anticoagulant drugs. (3) to determine potential bleeding risk in patients not still using anticoagulant drugs.
Methods: All patients arrived at our ED with AF in a period of six months (oct 2011-mar 2012) were enrolled. Each patient underwent a careful anamnestic and clinical evaluation. Thromboembolic risk stratification we performed by CHADS2 score. For low-risk patients (score 0-1), CHA2DS2-VASc score we employed. To determine hemorrhagic risk we adopted HAS-BLED score, either in patients underwent OAT or in those who were not taking anticoagulant but were at high thrombotic risk.
Results: 154 consecutive patients (88 F/78 M; mean age 69.9 aa.) we enrolled. Most of patients (59 %) had paroxysmal AF; 27 % had a persistent or permanent AF; 13.6 % had an uncertain date onset AF. Patients taking OAT were about a third (54, 35 %), while those without OAT were 100 (64.9 %). High thromboembolic risk patients (CHADS2 $\geq$ 2, or CHADS2 0-1 with CHA2DS2-VASc $\geq$ 2) were 124 (80.5 %), while low risk patients were 30 (19.5 %). About a half (74, 49.4 %) of high risk patients undergone no OAT, in spite of a low hemorrhagic risk (HAS-BLED score 0-2) in most of these patients (56 %). Of patients who took OAT, the majority (30, 55 %) had a low hemorrhagic risk, while the minority of cases (24, 44.4 %) were at high risk (HAS-BLED score $\geq$ 3). Of this last group, a percentage of 27.7 % resulted to have a non therapeutic range (INR $<$ 2.0). Moreover, 27 (17.5 %) low thromboembolic risk patients (CHADS2 0-1 with CHA2DS2-VASc 0-1) were not taking any antithrombotic prophylaxis, in spite of a low hemorrhagic risk (HAS-BLED score 0-2) in the most (67 %) of this patients. The total number of patients do not adequately protected against the risk of thromboembolism were 100 (64.9 %).
Discussion: Most patients arrived at our ED with AF presented a high risk of thromboembolism and a low bleeding risk. Even so this, only a minority of them were subject to OAT. Many patients, even at high thromboembolic risk, didn't take adequate antithrombotic prophylaxis, or even didn't carry out any prophylaxis, despite the fact that the potential bleeding risk was low in most of them. Finally, many patients were receiving OAT without reaching a therapeutic range.
Conclusions: Use in clinical practice of scores recommended by guidelines for thromboembolic and hemorrhagic risk in patients with AF shows that there are considerable margins of improvement in management of antithrombotic prophylaxis.

Coronary CT utility in differential diagnosis of chest pain in three clinical cases

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When a patient is hospitalized for chest pain in an internal medicine department, the first thing is to exclude that it is secondary to coronary ischemia. It must always be remembered that this symptom can be caused by other important diseases or non-specific type. Were are described three cases in which the coronary CT was diriment to define the diagnosis.
(1) A 69 years old woman hospitalized for shortly lasting chest pain, not related to any efforts and radiated to neck and shoulders. History: in a previous hospitalization, all the same for chest pain, stress ECG was

performed: test suspected for coronary stress ischemia and she had been treated with the mere medical therapy; hypertension; arthritis with positive ANA and anti-SSA; chronic cervical disc disease. Routine blood tests: no significant alterations; markers of cardiac necrosis: negative. Physical examination, ECG, echocardiogram and chest x-rays: normal. Coronary CT: intermediate branch of the left coronary artery with a distal intramyocardial course; no significant coronary atherosclerotic lesions.
(2) A 57 years old man hospitalized for shortly lasting chest pain, not related to any efforts and not irradiated. History: gastrectomy for gastric cancer; smoker. Routine blood tests: no significant alterations; markers of cardiac necrosis: negative. Physical examination, ECG, echocardiogram and chest x-rays: normal. Stress ECG: negative for symptoms; mild ST segment depression on high load. Coronary CT: hypodense concentric plaque in the middle section of IVA, that does not cause critical stenosis.
(3) A 54 years old woman hospitalized for shortly lasting chest pain, not related to any efforts and not irradiated. History: hypertension. Routine blood tests: no significant alterations; markers of cardiac necrosis: negative. ECG: negative T waves from V1 to V3 and intermittent left bundle branch block. Physical examination, echocardiogram and chest x-rays: normal. Coronary CT: no significant coronary atherosclerotic lesions; several mediastinal lymph nodes. CT abdomen: expansive formation partially adherent to the small gastric curvature, of diameter approximately 35 mm. Was refused the performance of echo-endoscopy with biopsy of this lesion.
In the first case the coronary CT has documented the intramyocardial course of the distal portion of the intermediate branch of the left coronary artery and the patient was treated for with beta blocker; chest pain may have been due to this anomaly, even if it can not be excluded that rheumatic and chronic cervical disc disease may have contributed. In the second case the coronary CT has determined that, likely, chest pain was of non-specific type for characteristics, negativity of the ECG and cardiac markers of necrosis and has permitted to discover a single-vessel coronary artery disease not critical, that although not responsible for the symptoms, has led to start therapy with acetylsalicylic acid, statin and beta blocker, to prevent its development. In the third case the coronary CT revealed that chest pain was due to a disease of probable neoplastic origin and to exclude that negative T waves and intermittent left bundle branch block documented on ECG were secondary to ischemic origin.

Metabolism, Diabetes and Clinical Nutrition

Enhanced fatty acids intake may affect cell cycle control and energy metabolism through P53 activity modulation

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Background and Aims: Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver injury in the developed world. It's a multifactorial disease and today is worldwide accepted the "two-hit hypothesis" to explain its pathogenesis. This theory indicates liver steatosis, i.e. the simple enhanced intra-hepatic fat accumulation, as the 1st hit responsible of the increased susceptibility of the liver to the 2nd hit, which in turn induces the disease progression to its worst form, namely nonalcoholic steatohepatitis (NASH), which can progress at least to cirrhosis and hepatocarcinoma. At molecular level, lipid and energy metabolisms and mitochondria alterations play a central role in hepatic fatty acid accumulation. Several report speak in support of a deep involvement of mitochondria in NAFLD pathogenesis because are the main cellular power plant, in fact, they are responsible of fatty acids beta oxidation and ATP production. P53 protein, mainly known for its tumor suppressor activity, is also known as major modulator of mitochondrial and cellular metabolism but its involvement in NAFLD pathogenesis is still unclear. Thus our study, performed in an in vitro model of steatosis, was designed in order to investigate the potential role of p53 in NAFLD pathogenesis through the modulation of energy production.
Methods: To study cell response in presence of increased fatty acids uptake, we have treated for 14 and 24 h a hepatocarcinoma cell line Huh 7.5.1 with a solution containing oleic and palmitic acids (in a molar ratio 2:1, final concentration 0.5 mM), two of the most common fatty acids assumed through diet and participating to de novo lipogenesis process. The intracellular raise of lipid content was evaluated through the adipored assay and western blot analysis were performed to highlight p53 protein content and its active phosphorylated status and, moreover, p21 and synthesis of cytochrome c oxidase-2 (SCO-2) proteins, two well known p53 target genes involved in cell cycle and mitochondrial respiration control, respectively. The cytotoxic effects of treatment were evaluated through Alamar blue assay, which is able to reveal the cell metabolic activity and their inclination to proliferate consequently. Furthermore, through spectrophotometric assay mitochondrial complex IV (cytox) activity (a crucial step in mitochondrial respiration process) was analyzed.
Results: Fatty acids treatment produced a progressive increase in intracellular lipid content until 24 h. Western blot analysis highlighted that p53 protein level was not affected by 14 h of treatment but resulted increased its phosphorylated state as well as p21 and SCO-2. At 24 h, instead, p53 content and its phosphorylated form were decreased as well as the above mentioned targets. Alamar blue assay reveals that, in our experimental condition, fatty acids treatment is not cytotoxic and, moreover, indicates an increased proliferation at 24 h. Interestingly, in the same experimental conditions we have appreciated only a slight reduction of mitochondrial complex IV activity after 14 h of treatment but, at 24 h, this mitochondrial respiratory complex displayed a deep dysfunction.
Conclusions: Our data suggest that cells attempt to adapt their energy metabolism to the enhanced fatty acids intake through p53 modulation. In fact, we have appreciated p53 activation together with p21 and SCO-2 up-regulations initially. However, this kind of cell response fails after a prolonged exposure to fatty acids. In conclusion, our data, suggest that high fat intake may produce an impairment of p53 pathway leading to altered energy metabolism and cell cycle control potentially promoting cell transformation.

The association between hypovitaminosis D and metabolic syndrome is not dependent on body fat mass

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Background: Metabolic syndrome (MS) and hypovitaminosis D represent two of the most diffuse conditions worldwide, reaching pandemic proportions in industrialized countries, and are both tightly associated with obesity. Aim of this study was to determine if an independent association exists between low 25(OH) vitamin D_3 levels and MS in obese patients.
Subjects: For this purpose we recruited 107 consecutive obese subjects, 61 with MS (age (mean ± SD): 45.3 ± 13.3, BMI: 43.1 ± 8.3 kg/m^2 and 46 without MS (age: 41.8 ± 11.5, p = n.s., BMI: 41.6 ± 6.5 kg/m^2,

p = n.s.) comparable for sex, BMI, waist circumference and body fat mass, evaluated by bioimpedenziometry. All participants underwent a complete workup including physical examination, blood testing and serum 25(OH) vitamin D_3 measurement. Insulin resistance was estimated by HOMA-IR, ISI and QUICKI indexes.
Results: Serum 25(OH) vitamin D_3 levels were significantly reduced in obese patients with MS compared with obese subjects without MS (14.9 ± 6.2 ng/ml vs. 18.9 ± 8.2 ng/ml, $p < 0.007$). The multivariate regression analysis confirmed that low serum 25(OH) vitamin D_3 levels were associated with the diagnosis of MS in obese patients independently from gender, age serum PTH and body fat mass. After stratifying the study population according to 25(OH)vitamin D_3 levels, patients in the lowest vitamin D quartile showed a markedly increased prevalence of MS with an OR of 4.1 (CI 1.2–13.7, $p = 0.02$) compared to those in the highest quartile.
Conclusions: A powerful association exists between hypovitaminosis D and MS in obese patients independently from body fat mass and its clinical correlates. This indicates that the association between low serum 25(OH)vitamin D_3 levels and MS is not merely induced by vitamin D deposition in fat tissue and reinforce the hypothesis that hypovitaminosis D represent a crucial independent determinant of MS.

Association between CDX2 polymorphism of Vitamin D Receptor (VDR) and type 2 diabetes

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Background: It is known that vitamin D is capable to facilitate the insulin action through its specific receptor (VDR) expressed both in adipose tissue and skeletal muscle, where the active vitamin D induces the expression of GLUT-4 and stimulate, therefore, the insulin-induced glucose uptake. Other studies demonstrated the presence of VDRs on pancreatic β cells, where vitamin D modulates insulin secretion in response to glucose-load, not interfering with basal insulin release and fasting blood glucose. The presence of polymorphisms of the main genes regulating vitamin D metabolism has been previously investigated in diabetic patients, whereas no data are available on the Cdx2 VDR polymorphism. Therefore, aim of this study was to evaluate the frequency of the Cdx2 polymorphism in an Italian population of subjects with and without type 2 diabetes mellitus (T2D).
Methods: For this purpose, 570 consecutive subjects attending our Diabetes and Internal Medicine outpatients' clinics for metabolic evaluation were enrolled. Subjects at high risk of T2D (n = 406) underwent OGTT, with calculation of insulin-resistance and insulin-secretion indexes. (HOMA-IR, ISI, CIR30, Disposition Index). The Cdx2 variant was genotyped by PCR–RFLP (restriction fragment length polymorphism) technique. A fragment of 214-bp was amplified, digested by restriction enzyme HpyCH4III and separated on 3.5 % agarose gel.
Results: Patients affected by T2D (n = 178) had significantly higher prevalence of Cdx2 A/A genotype compared with non-diabetic subjects (9.2 vs. 4.2 %, $p = 0.04$) with OR: 2.07 (CI = 1.03–4.2). The means comparison test showed that the A/A homozygosis was associated with higher blood glucose levels at 120 min from the glucose load compared with A/G and G/G subjects (156.9 ± 53.7 mg/dl vs. 136 ± 48.8 mg/dl, $p = 0.03$). No significant difference was observed in fasting blood glucose, basal insulin, and insulin-resistance/sensitivity calculated indices between A/A and non-A/A groups.
Conclusions: The VDR Cdx2 A/A homozygosity is significantly associated with the diagnosis of T2D and with glycaemia 120 min after glucose-load; indeed, this polymorphism may modulate insulin secretion and/or glucose uptake by peripheral tissues in response to blood glucose levels.

Insulinemic response curve after oral glucose tolerance test identifies early alterations of glucose metabolism in patients affected by chronic liver disease

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Background and Aims: Patients affected by liver cirrhosis frequently develop glucose intolerance and diabetes mellitus (DM), a condition named "hepatogenous diabetes", associated with a poor prognosis. However, alterations of glucose metabolism in compensated chronic liver diseases (CLD) are subclinical and difficult to recognize. We aimed to verify whether different biomarkers of insulin sensitivity/resistance and of metabolic control would be useful to identify glucose metabolism alterations in patients with compensated CLD.
Patients and Methods: We enrolled 51 patients affected by stable CLD (Metavir F2-F3) without glucose intolerance or DM and 20 healthy subjects. Fasting serum glucose and insulin were measured and Homeostasis Model Assessment (HOMA) for Insulin Resistance was calculated. Glycated haemoglobin (HbA1c) and fructosamine were also determined. Moreover, biochemical parameters for the evaluation of APRI index and FIBROTEST were determined. In addition, an oral glucose tolerance test (OGTT) followed by measurements of serum glucose and insulin at 0, 30, 60, 90 and 120 min was performed.
Results: Even though fasting serum glucose was normal, fasting serum insulin as well as HOMA index were higher in patients with CLD rather than controls. HbA1c and fructosamine were similar in CLD patients and healthy subjects. Linear regression analysis showed that fasting serum glucose and insulin, as well as HOMA index, were positively related to both APRI and FIBROTEST in hepatopathic patients. Finally, analysis of glycemic and insulinemic response curve after OGTT revealed that CLD patients exhibited higher glycemia after 60 ad 90, and higher insulinemia after 30, 60, 90 and 120 min of glucose administration, as shown in the following figures:

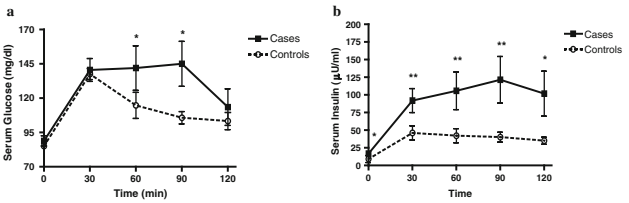

Fig. 1 Serum glucose (A) and insulin (B) after OGTT in healthy volunteers (Controls) versus hepatopathic patients(Cases)(* = $P < 0.05$; ** = $P < 0.01$)

Conclusions: Patients affected by compensated CLD present both fasting and OGTT normoglycemia, as well as normal HbA1c and fructosamine levels, but a hyperinsulinemic status. In such patients, metabolic glucose balance is maintained by higher insulin level, until insulin resistance occurs. Moreover, insulin level is associated with biomarkers of liver disease severity, suggesting that hyperinsulinemia could contribute to the development and progression of liver fibrosis.

In conclusion, the determination of fasting insulin levels and of both glycemic and insulinemic response curve to OGTT in patients with compensated CLD may reveal subclinical alterations of carbohydrate metabolism, which can not be evidenced through routine laboratory tests.

Lifestyle habits assessed by a specific questionnaire (MEDSTYLE): populations and worrisome trends

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As the prevalence of the metabolic syndrome (MS) is increasing worldwide at any age, the risk of diabetes mellitus, obesity, hypertension, cardiovascular diseases, and liver steatosis is also increasing. Little is known, however, about "real" lifestyles in a typical mediterranean area and in young people *before* stigmata of MS do manifest.
Aims: To assess lifestyles in young and adult subjects according to sex and health status.
Methods: 825 subjects were screened: 408 medical students (ST) (M:F = 174:234; mean age 22.3 ± SEM 0.19 and 21.7 ± 0.18 years, resp.), 138 healthy adults (HA) (M:F = 43:95; 32.2 ± 1.43 and 33.7 ± 1.04 years, resp.) and 279 "metabolic" adults (MA) (M:F = 93:186; 54.3 ± 1.57 and 52.7 ± 0.99 mean age) with at least 3 criteria of MS. The survey included: medical history, physical exam, administration of a custom-designed *MEDSTYLE* questionnaire investigating lifestyles as qualitative-quantitative food consumption, physical activity, use of "junk food", drinks, and social habits.
Results: A progressive increase ($p < 0.001$) was seen in both sexes for overweight (F 7 %ST, 10 % HA, 37 % MA; M 17 %ST, 16 %HA, 45 %MA), obesity (F 2 %ST, 6 %HA, 39 % MA; M 5 %ST, 7 %HA, 40 %MA) and visceral adiposity (ATPIII, IDF criteria). Concerning social habits, percent of overweight-obese relatives was significantly greater in MA with high BMI compared with HA and ST ($p = 0.0005$). Physical activity (Kcal/day, M vs. F) was 82 ± 8.4 vs. 43 ± 5 (ST), 74 ± 16 vs. 34 ± 6 (HA), 36 ± 10 vs. 23 ± 6 (MA) and greater in ST and HA M than F ($p = 0.0001$). Consumption of "junk" food decreased progressively in ST, HA and MA in both sexes ($P = 0.000000$). Fiber intake was significantly greater in F than M in MA (17 ± 0.6 vs. 15 ± 0.4 gr/day, $p = 0.03$). Olive oil consumption was 24.3 ± 0.5 g/day with a progressive increase noticed across the subgroups of ST, HA, MA in both sexes (from 20.8 ± 0.7 to 26.8 ± 1.1 to 28.2 ± 0.9 g/day; $p = 0.00000$ ST vs. HA/MA, $n = 825$). Alcohol consumption (as wine, beer, and spirits) was still low but significantly higher in M than F (42.3 ± 4.4 g/week, $n = 309$ vs. 18.6 ± 1.9 g/week, $n = 515$, $p = 0.000000$); consumption in M increased significantly in MA (61.4 ± 10.1 g/week) compared to HA (26.8 ± 5.2 g/week) and ST (36.0 ± 5.4 g/week) ($P = 0.01$).
Conclusion: In this preliminary survey, Medstyle questionnaire appears a simple, useful tool to accurately depict lifestyles in different age groups and populations. We found that obesity and sedentary life affect already our young healthy populations. Consumption of daily fibers is low while alcohol consumption, although low, increases with age in MS males (with subgroups already at risk). Our populations appear to shift their food consumption from junk food to "healthy" mediterranean (but hypercaloric) food. A metabolically unhealthy familiar environment contributes to the development of MS. Interventional studies to prevent chronic metabolic complications are urgently required with involvement of Internal Medicine Units across Italy.

Divergent effect of vitamin D supplementation on plasma concentration of total homocysteine

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The adverse health outcomes associated with vitamin D deficiency and increased plasma concentrations of total homocysteine (tHCY) partially overlap. To explore the relationship between vitamin D and tHCY, we performed a two-step pilot study.
Firstly, the relation of vitamin D status to tHCY was investigated in 50 Internal Medicine outpatients, 65.3 ± 11.3 year-old, who did not have acute medical conditions or correctable causes of hyperhomocysteinemia (e.g. atrophic gastritis) and had undergone measurement of tHCY, 25-hydroxyvitamin D [25(OH)D], 1,25-dihydroxyvitamin D [1,25(OH)2D], vitamin B12, and folate concentrations. A significant negative correlation between tHCY and 1,25(OH)2D was found in univariate analysis ($r -0.35$, $p = 0.01$), but not after accounting for age, sex, and estimated glomerular filtration rate (eGFR).
tHCY, 25(OH)D, 1,25(OH)2D, vitamin B12, and folates were then reassessed in 22 patients, after 12 weeks of 5,000 or 7,000 IU/week oral cholecalciferol (native vitamin D) for vitamin D deficiency.
As expected, treatment improved vitamin D status: mean level of 25(OH)D, the marker of vitamin D reserve in the body, rose by 13.3 ± 8.4 ng/mL ($p < 0.01$).
tHCY significantly decreased from 13.3 ± 2.7 to 11.2 ± 2.6 μM ($p < 0.05$) in 10 subjects starting from a value equal to or higher than the median of 10.3 μM, while it increased, although nonsignificantly, in the remaining 12 cases starting from less than 10.3 μM (from 8.4 ± 1.4 to 9.5 ± 1.9 μM). Female-to-male ratio, age, body mass index, eGFR, 25(OH)D, 1,25(OH)2D, vitamin B12, and folates were not significantly different in the two subgroups. Nor diet, BMI, eGFR, 1,25OH2D, vitamin B12, and folates changed significantly over the 12-week period. In linear regression analysis there was a trend for a significant interaction between baseline tHCY (< or ≥10.3 μM) and absolute changes in 25(OH)D in determining the magnitude of tHCY variation following treatment with cholecalciferol ($p = 0.06$).
In conclusion, vitamin D supplementation affected tHCY differentially depending on the starting value. Modulation of tHCY may account for some skeletal and extra-skeletal, especially cardiovascular, effects of vitamin D.

Association of soluble tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) with central adiposity and atherogenic lipid profile

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Objective: Tumor necrosis factor-Related Apoptosis-Inducing Ligand (TRAIL), in addition to having a prognostic value in patients with cardiovascular disease, seems to interact with adiposity, insulin resistance and other cardiovascular risk factors. However, the results of previous clinical studies, focused on the association of TRAIL with

selected metabolic or anthropometric indices were inconclusive. The aim of this study was to further investigate how soluble TRAIL concentrations independently correlate with major cardiovascular risk factors, including lipid, glycemic and anthropometric features.
Methods: We examined the associations between serum soluble TRAIL concentrations, measured by ELISA, and lipid, glycemic and anthropometric features in 199 subjects recruited at our Metabolic Outpatient Clinic.
Results: Soluble TRAIL concentrations had a significant and direct correlation with total cholesterol ($p = 0.046$), LDL-cholesterol ($p = 0.032$), triglycerides ($p = 0.01$), body mass index ($p = 0.046$), waist circumference ($p = 0.008$), fat mass ($p = 0.056$) and insulin ($p = 0.046$) and an inverse correlation with HDL-cholesterol ($p = 0.02$). In multivariable analyses adjusted for potential confounders, TRAIL levels continued to have an independent correlation with LDL-cholesterol and waist circumference.
Conclusions: Serum TRAIL levels were significantly and independently associated with waist circumference, a marker of visceral adiposity, and atherogenic lipid profile, especially with LDL-cholesterol. Further studies are needed to clarify the biological basis of these relationships.

Effectiveness of a counselling treatment carried out on groups of diabetics of type 2 suffering of serious obesity

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Introduction: Although the diabetes of type 2 is strictly related to obesity, which should be corrected by means of an adequate life style, most of diabetic people don't respect a correct diet and don't practise a regular sport activity.
Scope: Asses how a structured intervention on nutrition education, both at individual and at group level, could improve the biochemical, anthropometric and behavioural condition of patients affected by diabetes of type 2 with a serious obesity situation.
Methods: We have recruited patients affected by diabetes of type 2 with serious obesity situation belonging to the Diabetes Research Centre for physical examinations. The patients were never reached a metabolic control or a stable weight loss throughout the time. Those patients suffering of either tumour pathologies or serious comorbidity have been excluded. The recruited patients were split into three groups During the study, lasted over 6 months, the visits were carried out every 3 months. During the group meeting a counselling about the nutrition habits and the life style has been done in order to identify and correct the wrong habits. We proposed gradual changes in order to eliminate wrong habits. Moreover, the patients were strongly advised to practise a regular sport activity. Afterwards, we evaluated the energetic income, which is a quantitative objective of nutrition habits, by means of a "longitudinal" method. The three visits were structured as follows: *I Phase*. Anthropometric evaluation, with weight and height measurements, and therefore calculation of the body mass index (BMI): subsequently waistline and hips measurements were carried out in order to calculate and evaluate the changes in the relationship between them. This evaluation was always followed by a bioelectrical impedance weighted to track the muscle mass and the fat mass percentage in relation with the variation of the body weight. *II Phase*. Evaluation of the body functionality in relation with the nutritional state taking glycaemia measurements, in basal condition, of the post-prandial glycemia and glycated haemoglobin. We analysed the cholesterol and the triglyceridemia. Finally, the THS values and the blood pressure values were taken into consideration. *III Phase (first visit excluded)*. Vision of the "Alimentary Diary". Besides, informative material about the diabetes pathology associated to the obesity, the life style and physical activity has been offered to the considered patients at each of the meetings. Both the last provisions and the dialog between them, the practical nurse, the diabetologist and the nutritionist have promoted the patients participation involving them into the project.
Results: There were 33 patients recruited, whose average age was 64 [comprised between 41 and 78] and average value of HbA1c of 7.9 [comprised between 6.8 an 10.0]. About half of them have followed the programme carefully, the other ones have only partly modified their life style though, paying more attention to their alimentation. The average lost in weight is 5.6 kg. We have verified an average reduction of the waistline up to (5.9 cm) and of the fat mass percentage up to (2.3 %). A slight reduction in the blood pressure has been identified. In 16 patients the muscle mass has been kept, and in 11 of them has even increased. Only 6 patients have decreased lean body mass, whilst two of them have even increased their weight. Consequently also the glycated haemoglobin values, which were above the standards for all of the patients, have been decreased (−0.59) at the end of the intervention. Besides, the glycemia values, in condition of empty stomach and after 2 h since the last meal, from average values of 158 and 211 mg % have been decreased to 149 and 169 mg %.
Conclusions: Although diabetes pathology is partially strongly related to hereditary factors, we have had the chance to confirm how the correct life style could enhance the metabolic control in the subjects who are already affected by this disease, in proportional way correlated to their level of attention on the alimentation and to their constancy to practise physical activity. It will be of interest to follow these recruited patients in the future in order to evaluate the long-term effects of our educational intervention.

SOLVE™ study: efficacy, safety and effect on body weight of insulin detemir in patients with type 2 diabetes insulin-naïve: italian results

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The addition of basal insulin to oral agents is a method to initiate insulin therapy in diabetes mellitus type 2 (DM2) described by a large number of guidelines and commonly used in clinical practice. The basal analogue insulin detemir in Randomized Clinical Trials (RCT) showed a lower risk of hypoglycemia compared to NPH insulin and a better body weight profile compared with insulin glargine and NPH. SOLVE is a 24-week observational study in 10 countries evaluating the safety & effectiveness of once-daily insulin detemir in insulin naïve people with T2DM treated with one or more OADs. The purpose of this study is to evaluate the safety associated with the basal insulin detemir once daily in patients with type 2 diabetes treated with oral antidiabetic agents in conditions of real clinical practice.
Primary endpoint: incidence of SADR (serious adverse drug reactions), including serious hypoglycemia. At the initial visit, after 12 and 24 weeks, were recorded: HbA1c, FBG (glucose fasting), major and minor hypoglycemic events, ADR (adverse drug reactions), SADR, and body weight.
We enrolled 4624 patients with type 2 diabetes in 223 italian centers for diabetes care. At initial visit the mean age was 66.5 years, the

average duration of diabetes 13.3 years, average weight 79.0 kg and mean BMI 29.5 kg/m^2. In addition, patients had poor glycemic control: the mean FBG was 205 mg/dL and mean HbA1c was 9.2 %. In the starting the daily dose of insulin detemir was 0.16 U/kg. At the end of observation, glycemic control was improved with a reduction of 1.4 % in HbA1c ($p < 0.001$) and 70 mg/dl of FBG ($p < 0.001$)). The dosage of insulin detemir was equal to 0.23 U/kg and the percentage of patients in the ADA target (HbA1c < 7 %) was equal to 21.9 %. Only 3 SADR were reported in 2 patients (<0.1 %) and of which only 2 were major hypoglycemia. The percentage of patients with minor hypoglycemic events was 2.8 % at baseline and increased to 4.7 % at the end of the study with the same incidence. We observed a reduction of 0.5 kg of body weight ($p < 0.001$); dividing the patients for classes of BMI we have seen how the control of body weight was more pronounced in patients with higher starting level of BMI.
The results from the Italian cohort of SOLVE ™ show that insulin detemir, administered once-daily in starting therapy, improves glycemic control without increasing the incidence of hypoglycemic events and show a concomitant body weight reduction, confirming in the real clinical practice the results obtained in randomized clinical trials.

Study of Once-daily Levemir (SOLVE): Glycaemic control and impact of once-daily insulin detemir in real-life clinical practice: global results

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Aims: Despite treat-to-target trials demonstrating the effectiveness and simplicity of adding basal insulin to oral antidiabetic (OAD) therapy, insulin treatment is often initiated only after years of poor glycaemic control.
The aim of this analysis is to provide insights on the impact of initiating once-daily insulin detemir in real-life clinical practice in different countries around the world.
Methods: SOLVE is a 24-week observational study in 10 countries evaluating the safety and effectiveness of once-daily insulin detemir in insulin naïve people with T2DM treated with one or more OADs.
Hypoglycaemia episodes were defined as follows: major hypoglycaemia—requiring third party assistance, and minor hypoglycaemia—a daytime or nocturnal glucose measurement <3.1 mmol/L ± symptoms. Major hypoglycaemia was recorded as events recalled within the preceding 12 weeks (4 weeks in the UK), and minor hypoglycaemia as events recalled within the preceding 4 weeks (all countries).
Results: A total of 14,785 participants have been enrolled in the study. Of these, 10,786 patients have completed the 24-week study (53 % male, age 62 ± 11 years, BMI 29.6 ± 5.3, duration of diabetes of 10 ± 7 years, of which 9 ± 7 years was on OAD therapy). Pre-insulin HbA1c and FPG were 9.0 ± 1.6 % and 10.4 ± 3.2 mmol/L, respectively. After 24 weeks of treatment, HbA1c and FPG decreased by 1.4 ± 1.6 % to a mean 7.7 ± 1.2 % and by 3.3 ± 3.1 mmol/L to 7.1 ± 1.9 mmol/L, respectively. Insulin dose at the end of the study was 22 ± 16 U (0.27 ± 0.17 U/kg). The incidence of major hypoglycaemia fell from 3 episodes per 100 person years pre-insulin to 0.8 episodes per 100 person years at the end of study, whereas the incidence of minor hypoglycaemia increased from 1.4 to 1.8 episodes per person year.
Conclusion: Insulin initiation is delayed until late in the course of the disease. Using modest doses of once-daily insulin detemir, there were substantial improvements in HbA1c and FPG without increased risk of major hypoglycaemia.

Nuclear receptors LXRβ, PPARα and ERRα in PBMCs identify female subjects with Metabolic Syndrome and sustain their HDL-cholesterol

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Background: Nuclear receptors are a class of 48 ligand-activated transcription factors identified as key players of metabolic and developmental events. Most of these receptors are potential targets for pharmacological strategies in the Metabolic Syndrome (MS). Here we analyzed nuclear receptors in peripheral blood mononuclear cells (PBMCs) of patients with MS.
Methods: We enrolled 11 healthy controls (5F:6 M) and 20 naïve patients (10F:10M; >3 criteria for MS upon Adult Treatment Panel III) without signs of organ damage. We collected clinical and biochemical parameters. Using quantitative real-time PCR (RTqPCR), we assessed the expression patterns of the nuclear receptor family in PBMCs.
Results: MS patients showed increased BMI, abdominal circumference, blood pressure, insulinemia/insulin-resistance, triglyceridemia, erythrocyte sedimentation rate (ESR), and decreased levels of HDL cholesterol, leading to increased cardiovascular risk assessed by the Progetto Cuore score ($p < 0.05$). 35/48 nuclear receptors were significantly expressed in PBMCs. We performed a statistical analysis with classification threes and correlation studies; several hits were identified and a predictive core of expression patterns was depicted for MS subjects. In female subjects with MS, peroxisome proliferator-activated receptor α (PPARα), liver X receptor β (LXRβ) and estrogen receptor-related receptor α (ERRα) as well as their target genes carnitine palmitoyltransferase 1 (CPT1), ATP-binding cassette transporter A1 (ABCA1), ATP-binding cassette transporter G1 (ABCG1) and medium chain acyl-CoA dehydrogenase (MCAD) correlate significantly and positively with HDL-cholesterol, while being negatively correlated to triglycerides. Applying the Random Forest algorithm, modulation of PPARα, LXRβ and ERRα mRNA levels defined a strong (87 % of cases) prediction ability of the MS status in females.
Conclusions: We identified nuclear receptor expression patterns in PBMCs that predict the metabolic status. Our results point to an up-regulation of the LXRβ, PPARα and ERRα trio as a gender-specific adaptive response that might protect metabolic females from cardiovascular disease.

Prevalence of sarcopenia in a group of obese patients from southern Italy

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Background: Sarcopenia is a syndrome characterized by a progressive and generalised loss of skeletal muscle mass and function, associated with aging and implying a poor quality of life and a higher risk of physical disability and death. Though being mainly observed in older people, it can also be found in young adults and obesity. The combination of fat mass excess and muscle mass depletion is defined "sarcopenic obesity".

Aim of the study: To evaluate the prevalence of sarcopenia in a group of obese adults from Southern Italy, by using different skeletal muscle mass indexes.
Subjects and Methods: One hundred thirty-one (80 F, 51 M) obese (BMI $\geq$ 30 kg/m^2) adults, aging 45–67 years have been recruited at the Obesity outpatient Unit of Federico II University in Naples. Body composition was evaluated by bioimpedance analysis (BIA). Skeletal muscle mass (SM) was calculated using the BIA equation of Janssen[1] et al. 2002 (SM = [(height^2/BIA-resistance $\times$ 0.401) + (gender $\times$ 3.825) − (age $\times$ 0.071)] + 5.102). In order to evaluate the prevalence of moderate and severe sarcopenia, the sex-specific cut-off points of percentage skeletal muscle index (SMI % = SM/body mass $\times$ 100) have been first used. Therefore the sex-specific cut-off points of skeletal muscle mass index (SMI = SM/height^2) according the criteria of Janssen[2] et al. of 2004 have been used too.
Results: When the cut-off points of SMI were considered, 9.8 % of men and no women resulted to be moderately sarcopenic; neither men nor women met the definition of severe sarcopenia.
Whereas, with the cut-off points of SMI %, 100 % of both men and women had SMI % values suggestive of sarcopenia; the prevalence of moderate sarcopenia was 17.6 % in men and 45 % in women, while the prevalence of severe sarcopenia was 82.4 % in men and 55 % in women.
Conclusions: This study shows a high prevalence of sarcopenia in a population of obese patients in Southern Italy.
Obese subjects may have normal muscle mass, but inadequate for their total body mass. For this reason, SMI cut-offs could underestimate sarcopenia in obese subjects; SMI % could better describe sarcopenia in obese subjects, since it takes into account their total body mass. Using SMI %, 100 % of our patients can be considered in a "presarcopenia" stage.
The definition of sarcopenia needs to be improved with an evaluation of muscle function.

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Severe megaloblastic anemia induced by long-term metformin treatment: a case report

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Introduction: Metformin is actually considered the first choice drug for oral treatment in overweight and obese type 2 diabetic patients with normal kidney function, as recommended by the American Diabetes Association. It has been reported malabsorption of vitamin B12 and consequent Vitamin B12 deficiency in long-term treated patients.
Case Report: A 56-year-old type 2 diabetic woman, presented progressive weakness, fatigue and a severe anemia (HB 6.6 g/dl) that required a tranfusion of packet red blood cells at emergency department. Since 2 months the patient presented fatigue, walking difficulty, diarrhea, difficulty starting urination, reporting a conspicuous weight loss during last months. Findings on the physical examination were: blood pressure 160/70 mmHg, heart rate 72/minute, pallor, scleral icterus, gait ataxia and symmetric hyporeflexia. Neither liver nor spleen were appreciable. No palpable lymphonodes were found. She referred to be affected by diabetes since 13 years and to be treated since the beginning with an association of Glibenclamide 5 mg and Metformin 500 mg, three times a day. The results of the complete blood cell count (CBC) performed on admission were: RBC 2.16 $\times$ 10^6/mmc, Hb 7.5 g/dL; MCV 101 fl; RDW 24.2 %, WBC 2.750/mmc (33.5 % neutrophils, 61.7 % lymphocytes, 0.9 % monocytes, 1.9 % eosinophils, 0.2 % basophils); and platelets, 205,000/mmc. Blood tests revealed a severe macrocytic anaemia; leucopenia with neutropenia; high levels of : LDH 7483 U/L, bilirubin, almost all indirect, with total bilirubin 3.06 mg/dl and indirect bilirubin 2.64 mg/dl, ferritin with a value of 339.4 ng/ml; low level of reticulocytes (0.8 %) and an haptoglobin deficiency (6 mg/dl compared to a normal range 36–195). Thyroid function and lymphocyte typing appeared to be normal. Vitamin B12 and folate levels were tested, showing normal levels of folate (10.7 ng/ml) but a severe Vitamin B12 deficiency (52.2 pg/ml, normal values 197–866). The stool was negative for occult blood. Bone marrow smear was performed showing findings compatible with vitamin deficiency anaemia. We investigated all the most common causes of Vitamin B12 deficiency. No lack of vitamin B12 was reported in the diet. She was not an alcoholic drunker. She didn't refer any kind of gastrointestinal surgery, no long-term treatment with antiacids was reported. Both specific blood tests for antiparietal cells antibodies and for anti-intrinsic factor antibodies were negative. Esophagogastroduodenoscopy and pancolonoscopy were negative. A complete screening for autoimmune diseases was performed : C-ANCA, P-ANCA, RF, C3, C4, CRP, anti-TPO Ab, anti-Tg Ab, AMA, SMA, renal anti-LKM, hepatic anti-LKM, ANA, AGA-ab, EMA-ab, tTG-ab, anticardiolipin antibodies were all negative. A therapy with cyanocobalamin mcg 1000, daily, and N5-methyltetrahydrofolate calcium pentahydrate 15 mg, twice a week, was started. After 4 days of therapy the patient showed an increase of Hb value from 7.5 to 9.1 g/dl and symptoms like asthenia and fatigue ameliorated in a few days. Performance status was globally improved and the patient was discharged. Cyanocobalamin mcg 1000 was prescribed for other 10 days and her anti-diabetic therapy was replaced with Repaglinide 1 mg, twice a day. A follow-up visit was performed after 6 months showing a complete normalization of her laboratory values and a considerable improvement of her clinic conditions. Clinical and laboratory data of our patient argue for a severe megaloblastic anemia due to vitamin B12 deficiency. We investigated all possible causes of B12 deficiency. Then, excluding other causes, we hypothesized vitamin B12 deficiency due to metformin treatment. Such hypothesis was confirmed by follow-up of the patient with normalization of clinical and hematological picture 6 months after that metformin was stopped.
Conclusions: Vitamin B 12 deficiency in metformin treated patients is an unusual side effect of the chronic treatment. As the large proportion worldwide of diabetic patients undergone to metformin, clinicians must be aware of the possibility of drug-related vitamin B12 deficiency and of need for routine assessment in long-term treated subjects.

Liraglutide Provides Effective Glycemic Control, with Weight Loss and a Low Incidence of Hypoglycemia, in Patients with Type 2 Diabetes in Clinical Practice: First Available Audit Data

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Phase 3 trials with the once-daily human GLP-1 analog liraglutide demonstrated that it provides effective glycemic control with minimal

hypoglycemia, weight loss and reduced systolic blood pressure (SBP) in patients with type 2 diabetes. Insulin-naïve patients prescribed liraglutide at a center in Northern Ireland were audited to assess outcomes in clinical practice. Patients attending Ulster Hospital who were prescribed liraglutide (June 2009–September 2010) were assessed at baseline and first postinitiation visit. Patients providing data at both visits were included in the analysis. The primary endpoint was change in A1C from baseline. Changes in weight and blood pressure were also assessed, as was frequency of hypoglycemic events. Data from 143 patients are reported (baseline A1C 8.9 %, mean age 55.8 years, diabetes duration 7.7 years, BMI 39.4 kg/m^2, 67.8 % male). Average time to first visit after initiation was 14 weeks, at which point 15 patients (10.5 %) were still prescribed 0.6 mg liraglutide, and 128 (89.5 %) were prescribed 1.2 mg liraglutide. From initiation to first visit, mean change in A1C was −0.9 % and mean body weight change was 2.2 kg. Changes in blood pressure were SBP −2.2 mmHg, diastolic blood pressure +0.2 mmHg. Gastrointestinal side effects were experienced by 12.6 % of patients and were mainly transient. The number of patients experiencing minor hypoglycemic events was low (7.0 %), and no major events were reported. In conclusion, data from clinical studies translate into clinical practice: liraglutide provided improved glycemic control after 14 weeks' treatment, accompanied by weight loss and low incidence of hypoglycemia.

Palpebral ptosis, fixed mydriasis and exophthalmos

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A 60-year old women was admitted to our Department for new onset of diabetes, exacerbation of bronchial asthma and likely pulmonary infection. The patient reported fatigue, shortness of breath, cough, haemoptysis, polyuria, weight loss and fever 2 weeks before onset. The clinical history was characterized by bronchial asthma (III degree of severity of asthma) and bronchiectasis, treated with steroids and beta 2 agonists. The physical examination showed tachycardia, dry skin and mucoses, rhonchi and wheezing at lung auscultation, right palpebral ptosis with exophthalmos, fixed mydriasis and ocular abduction deficit (that, according to the patient, had been present since about 2 weeks), and a slight deficit in the lower right visual field. Laboratory tests revealed hyperglycemia (554 mg/dL), HbA1c 11.5 %, neutrophilic leukocytosis (15.140/dL), increased inflammatory markers (CRP 208 mg/L), normal renal and liver function, absence of ketones and normal acid–base balance. We started intravenous rehydration and insulin infusion, parenteral antibiotic therapy with Meropenem and enhanced steroid therapy with Methylprednisolone. We excluded the initial hypothesis of a possible malignancy, given the rapid onset of the exophthalmos. Considered the neurological signs, in the hypothesis of carotid sinus thrombosis a head CT scan was performed, showing the presence of a hypodensity in the right frontal-basal parenchyma. Therefore a head MRI with angiography of the intracranial vessels was required which showed an apparently ischemic lesion in the territory of anterior cerebral artery and opacification of the right maxillary sinus and mucosal thickening, so the initial hypothesis was excluded. Suspecting a severe sinusitis, a new CT scan was performed to study the facial sinuses and orbits, from which resulted an opacification of the frontal sinus bilaterally, right maxillary sinus, ethmoid cells and sphenoid sinuses partially opacated. Given the massive sinusitis, we associated Macrolides to antibiotic therapy according with ENT colleagues[1]. The patient showed a progressive reduction of inflammatory markers, although there was a further loss of vision. A contrast enhanced MRI showed an extension of the frontal-basal lesion with a purulent component, compatible with intracerebral abscess and back-orbital cellulitis. The consulting neurosurgeons, however, excluded the requirement of surgery. Given the rapid deterioration of clinical and radiological objectivity, the patient underwent an emergency FESS (Functional Endoscopic Sinus Surgery). Histological report showed mucoid material encapsulating fungal hyphae and spores, consistent with Aspergillus infection, so we started therapy with Voriconazole 300 mg/daily. However, despite current treatment, the clinical situation remained unchanged. In consideration of the no response to therapy, the rapid loss of vision of the right eye and the multiple bone erosions of the paranasal sinuses we debated with infectivologists colleagues about the initial diagnosis of Aspergillus, thinking of invasive Mucormycosis. The latter infact has the same histological pattern of the former, but different therapy. So the patient underwent a nasoendoscopy to repeat a bacterial culture and to perform a direct bacterioscopic examination, that revealed a Rhizopus spp infection. The treatment of these infections should be started promptly and high-dosage Amphotericin B (5–7 mg/kg/daily) is the only antifungal that has been proved to be effective. This treatment is limited by renal and systemic toxic effect, it may require long hospitalization, which must continue in specialized departments, and does not guarantee a clinical response[2]. The patient is still hospitalized and has undergone other two FESS revisions for recurrences of orbital cellulitis. The last CT scans of the paranasal sinuses are showing a progressive deterioration of the infection. In our patient in contrast to the literature[3], neither histology, nor the microbiological examination allowed us to make a diagnosis, but only the bacterioscopic examination isolated the pathogen.

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Cardiac mass (CM) is a reliable marker of lean body mass (LBM) in hospitalised patients: a pilot study

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Rationale: Assessment of patients' LBM is key to diagnose cachexia and predict outcome in wasting syndromes. The use of available tools (i.e., CT scan, DEXA, etc.) is limited by invasiveness and high cost. Since both cardiac function and LBM affect outcome, we investigated whether CM is related to LBM.
Methods: To test this hypothesis, cachectic patients (i.e., involuntary weight loss >5 % in 6 months 1) admitted to our Department were considered. Hypertension and heart failure were excluding criteria. After signing informed consent, CM (g/m^2) was assessed by bidimensional M-mode echocardiography and by using the Devereux regression formula 2 which integrates telediastolic diameter, posterior wall, and interventricular septum. LBM was assessed by DEXA (Lunar Prodigy, GE). Correlation between numerical variables was investigated by Pearson's test. A $p < 0.05$ was considered statistically significant. Data are presented as M ± SD.

Results: Patients with cancer (n = 7), or renal failure (n = 3) were studied (1 M:9F; 69.1 ± 16.9 years). Mean body weight was 50.2 ± 10.3 kg and weight loss in the preceding 6 months was 6.5 ± 4.5 kg. Mean CM and LBM were 121.8 ± 46.7 g/m2 and 33.5 ± 3.8 kg, respectively. Cardiac mass correlated significantly with LBM ($r = 0.84$, $p < 0.05$).
Conclusion: Our results show that CM is tightly related to LBM of wasted patients. Considering the accessibility of echocardiography, this tool could be used to routinely assess and monitor LBM of patients with cachexia or at risk of cachexia.

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Lipid abnormalities in type 2 diabetes mellitus patients and their relation to nailfold microangiopathy severity

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Coronary heart disease (CHD) and other manifestations of macrovascular disease are major causes of morbidity and mortality in patients with diabetes and are four times more frequent in diabetic than in non-diabetic patients.
Objective: This study was performed to evaluate the prevalence of coronary heart disease, cerebrovascular disease (CVD), peripheral obliterating arteriopathy disease (POAD) and the nailfold microangiopathy severity in a population of type 2 diabetic patients (T2DM)) with and without hyperlipemia.
Methods: Our study included 92 NIDDM patients, hospitalized in the Internal Medicine Unit between March 15 and June 30 2011. We studied 49 Females and 43 Males mean age 64.7 (range 40–91 years), mean duration of diabetes mellitus 15.84 ± 1.07 years. Mean fasting plasma glucose was 160.8 ± 51.7 mg/dl, HbA1c 8.2 ± 1.6 mg %, total cholesterol 221.9 ± 37.8 mg/dl, trigliceridemia 196.4 ± 75.3 mg/dl, HDL-Cholesterol 49.8 ± 12.5 mg/dl. The parameters examined in each patient were: BMI in kg/m^2, Whist-Hip-Ratio (WHR), microalbuminuria (20–300 mcg/min), arterial hypertension (>130/85 mmHg) or antihypertensive treatment. The clinical patient history included information on TIA, stroke and intermittent claudicatio. The criteria for CHD were stable angina pectoris, or previous myocardial infarction or coronary revascularisation. All the patients underwent an EcoColorDoppler examination of carotid arteries and lower limb arteries and a video microcapillaroscopy of the nail folds of hands and feet.
Results: High blood pressure (>130/85 mmHg) occurred in 56 patients 61 % (35 F, 21 M); obesity in 33 patients 36 % (19 F, 14 M), in particular we found in 57 % of males a mean BMI: >30, and in 52 % of females a mean BMI: > 33. Moreover 35 % of males had a whist hip Ratio > 1; and 63 % of females had a WHR > 0.8. The results of determinations of triglycerides and total cholesterol showed hyperlipemia in 44 patients 48 % (26 F, 18 M); but mostly, we found mixed hyperlipemia (increased levels of total cholesterol, increased levels of triglycerides, lower levels of HDL-cholesterol and Total-cholesterol-HDL-C ratio >5) in 10 F and 6 M (18 %). Nail fold capillaroscopic analysis revealed that the decrease in number of capillary loops (<9/mm) was more marked in T2DM patients with hyperlipemia (82 vs. 68 %). Apical and venular dilatations, arteriovenous sludge, oedema, and fleabite juxtacapillary microhemorrhages were found especially in the patients with hyperlipemia without statistical significance. The mean duration of diabetes was 16.91 years in the T2DM patients with hyperlipemia versus 14.47 years in T2DM patients without hyperlipemia. We revealed CHD in 16.2 % (T2DM with hyperlipemia) versus 4.4 % (T2DM patients without hyperlipemia) $p < 0.1$;POAD in 21 % versus 8 % $p < 0.1$; cerebrovascular disease in 8.1 % versus 4.8 % $p < 0.4$, We found a high prevalence of multiple sites of vascular disease in T2DM patients with hyperlipemia.
Conclusion: The analysis of nail fold capillaroscopic pictures showed that especially in T2DM patients with hyperlipemia and high blood pressure there were apical and venular dilatations, fleabite juxtacapillary microhemorrhages, arteriovenous sludge and oedema. The microvascular abnormalities were linked to the atherosclerotic nature of the disease, and characterized the morphological picture of the endotelial injury or dysfunction that is considered the "primum movens "of the cascade of events leading to an atherosclerotic plaque.

Osteoporosis, obesity and metabolic syndrome in postmenopausal women

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Osteoporosis is a skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with consequent increase in bone fragility and susceptibility to fractures. Obesity, characterized by an elevated body mass index (BMI), is classically considered one of the most important predictors of high bone mineral density (BMD), although it is a condition associated with an inflammatory condition characterized by increased production of osteoclastogenic cytokines, main mediators of osteoporosis. Metabolic syndrome is a common disease in postmenopausal women. It refers to a constellation of disturbances including glucose intolerance, central obesity, dyslipidemia (hypertriglyceridemia, elevated nonesterified fatty acids (NEFAs), and decreased high-density lipoprotein (HDL) cholesterol), and hypertension. A chronic low grade inflammation accompanies the metabolic syndrome and has been implicated as major player in its associated pathological consequences. In order to evaluate the relationship between osteoporosis and metabolic syndrome, we measured the BMD in 100 postmenopausal women with metabolic syndrome and 100 without metabolic syndrome. The BMD, evaluated as T-score, was measured at the calcaneus by quantitative ultrasound technique (QUS) with a Lunar Achilles Express densitometer. Subjects were classified as having metabolic syndrome if any three of the following five characteristics were present: abdominal obesity (waist circumference greater than 85 cm), hyperglycemia (fasting glucose >100 mg/dL and/or medication), hypertriglyceridemia (fasting triglyceride >150 mg/dL), low high-density lipoproteinemia (HDL < 50 mg/dL), and hypertension (>130/85 mmHg and/or medication). Values are expressed as number (%) or mean + standard deviation (SD). Statistical comparisons were performed using Student's t test. The study of our sample showed a positive correlation between BMD and BMI. However, even with higher BMD values, obese women had an increased risk of non-traumatic fracture than non-obese controls (20 vs. 12 %; $p < 0.05$). The T-score value of women with metabolic syndrome was significantly lower compared to women without metabolic syndrome ($-2.02 + 1.63$ vs. $-1.64 + 1.62$, $p < 0.05$). Moreover, 21 % of women with metabolic syndrome and 15 % without metabolic syndrome had history of osteoporotic fractures. These findings suggest

that metabolic syndrome might be an important risk factor for osteoporosis and related fractures. In addition obesity, as well as excessive thinness, may be considered another risk factor for osteoporosis, regardless of the value of BMD.

Maternal efficacy and safety outcomes in a randomized trial comparing insulin detemir NPH insulin in 310 pregnant women with type 1 diabetes

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The aim of this prospective, randomized, controlled, parallel-group, open-label trial was to compare the efficacy and safety of insulin detemir (IDet) vs. NPH (both with prandial insulin aspart) in pregnant women with type 1 diabetes (T1DM). T1DM women (HbA1c $\leq$ 8 % at pregnancy confirmation) were randomized to IDet (n = 152) or NPH (n = 158) up to 12 months before pregnancy or during pregnancy at 8–12 weeks gestation. The primary objective was to confirm efficacy of IDet by showing that IDet was non-inferior to NPH with respect to HbA1c at
36 gestational weeks (GWs) (primary endpoint). Non-inferiority was shown if the upper limit of the 95 % CI for the treatment difference of IDet vs. NPH was below the pre-specified non-inferiority margin of 0.4 % for both the Full Analysis Set (FAS) and Per Protocol Set (PP). The data were analyzed using linear regression. 79 and 83 women in the IDet and NPH groups, respectively, were pregnant at randomization while 73 and 75 women, respectively, became pregnant following randomization. Mean ± SD baseline demographics were: age 30.1 ± 4.4 years; BMI 24.8 ± 4.1 kg/m2; HbA1c 7.01 ± 0.79 %; fasting plasma glucose (FPG) 5.94 ± 3.25 mmol/L and diabetes duration 12.3 ± 8.0 years. For FAS, the estimated HbA1c at GW36 was 6.27 % for IDet and 6.33 % for NPH. IDet was declared non-inferior to NPH (FAS: −0.06 %, 95 % CI: −0.21; 0.08; PP: −0.151 %; 95 % CI: −0.34; 0.04). FPG was significantly lower with IDet vs. NPH (Table). Hypoglycemia rates were similar between groups. In summary, lower FPG, but comparable HbA1c in late pregnancy were obtained using insulin detemir in comparison to NPH insulin in women with type 1 diabetes.

	IDet, n = 152	NPH n = 158	
Estimated mean FPG (mmol/L)			Treatment difference, 95 % CI, *p* value
At GW24	5.38	6.32	-0.94 [-1.67; -0.21] $p = 0.012$
At GW36	4.76	5.41	-0.65 [-1.19; -0.12] $p = 0.017$
Hypoglycemia rates (episodes/yr)			Estimated mean rate ratio, 95 % CI, *p* value
Overall major	1.1	1.2	0.82 [0.39; 1.75] $p = 0.615$
Overall minor	104.4	101.0	1.10 [0.88; 1.37] $p = 0.393$
Nocturnal major	0.3	0.2	1.15 [0.40; 3.33] $p = 0.797$
Nocturnal minor	15.6	17.4	0.96 [0.72; 1.27] $p = 0.763$

Insulin resistance after laparoscopic adjustable gastric banding: preliminary results at 6-month follow-up

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Background: Laparoscopic Adjustable Gastric Banding (LABG) is a minimally invasive surgical option increasingly used in the treatment of morbid obesity. This procedure involves the placement of a inflatable silicone band around the upper part of the stomach to create a small pouch with a narrow outlet. LABG leads to marked and long-lasting weight reduction. However, the effects on the components of metabolic syndrome, including glucose and insulin metabolism, are poorly characterized.
Aims: The objective of this study was to investigate the medium-term effects of LABG on serum lipid levels, arterial blood pressure and insulin resistance.
Patients and Methods: Eleven morbidly obese patients (6 males, mean age 34.3 ± 4.1 years) were studied before and 6-months after LABG for serum lipid levels, arterial blood pressure and insulin resistance assessed by homeostasis model assessment (HOMA-IR).
Results: At 6 months after LABG, study patients showed a significant decrease in BMI, waist circumference, arterial pressure and total cholesterol. In addition, we observed a significant increase in HDL cholesterol and insulin sensitivity (**Table**).
Conclusions: LABG is a safe and effective treatment for morbid obesity. Our preliminary results suggest that LABG-induced weight loss may also positively affect several components of metabolic syndrome, including insulin resistance. Further studies are needed to investigate whether these changes will translate into long-term clinical benefits.

Variable	Baseline	6-months	
		after LABG	P value
BMI, kg/m^2	42.4 ± 1.5	37.8 ± 1.2	0.0001
Waist circumference, cm	126 ± 4	118 ± 4	0.001
Total cholesterol, mg/dL	197 ± 9	180 ± 4	0.03
HDL cholesterol, mg/dL	48 ± 6	54 ± 5	0.008
HOMA-IR	7.14 ± 1.31	4.69 ± 0.57	0.02
Systolic arterial pressure, mmHg	140 ± 7	129 ± 7	0.001
Diastolic arterial pressure, mmHg	90 ± 3	81 ± 3	0.005

Gender differences in the relationship between metabolic syndrome and anger expression

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Background: Several lines of evidence demonstrated the association between anger, metabolic syndrome (MS) and cardiovascular disease. Anger control may also play a role in the pathogenesis of the MS.

Serum leptin levels are usually higher in women than in men, and they are associated with MS and cardiovascular risk.
Aim of the Study: In this study we explored the potential relationships between anger expression, gender, metabolic syndrome and serum leptin levels.
Patients and methods: Ninety-four subjects (47 women, mean age: 54.3 ± 6.2 years; mean BMI: 27.1 ± 7.1) consecutively attending the outpatient clinic of the Department of Internal Medicine of Messina University, Italy were enrolled into the study. MS was defined according to the ATP-III criteria. Clinical and lifestyle data were collected from all participants with a standardized questionnaire. Lipid and metabolic laboratory parameters were measured according to standard methods; fasting insulin and leptin serum levels was measured by radioimmunoassay, and insulin-resistance was calculated by the homeostasis model assessment ($HOMA_{IR}$). All participants underwent a 57-items psychological assessment (STAXI test), which measures the intensity of anger as an emotional state (State Anger) and the disposition to experience angry feelings as a personality trait (Trait Anger).
Results: MS women had significantly higher state anger ($P = 0.01$) and anger-out expression levels ($P = 0.05$) when compared to women without MS; whereas, in men, MS was not associated with any variation in anger trait or expression. Serum leptin levels were significantly higher in both men and women with MS when compared to subjects without it of either genders ($P = 0.001$ for both comparisons).
Leptin levels were significantly correlated with anger-out expression ($P < 0.006$) in MS women, and with trait anger ($P < 0.02$) in MS men.
At multivariate analysis, leptin levels were independently associated with trait anger in men ($P = 0.02$), and with anger-out expression ($P = 0.04$) in women.
Conclusions: MS is associated with a gender-specific anger expression, and these associations may be mediated by different leptin levels in men and women with MS.

Avoidable hospitalizations for diabetes mellitus in Italy: 10-years of observation

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Background and Aims: Costs of hospitalization for diabetic people accounts for more than 50 % of direct costs of the disease. Whereas hospitalizations due to chronic complications depends on long term quality of care, most hospital admissions for acute diabetic complications would have been avoidable with an appropriate outpatient care. In this nationwide study we investigated the temporal trends, and regional variations, in hospitalization rates for preventable acute diabetic complications in the period 2001–2010.
Materials and Methods: National Health System data were used to identify diabetes-related hospital admissions in Italian people from 2001 to 2010 for acute diabetic complications selecting all records with a primary or secondary discharge diagnosis including either hyperglycemic state: ketoacidosis (ICD-9-CM code: 250.1), hyperosmolar state (ICD-9-CM code: 250.2), other coma (ICD-9-CM code: 250.3), or hypoglycemic coma (ICD-9-CM code: 251.0 in association with diabetes: 250.xx). Hospitalization rate was calculated as the ratio of the number of hospital discharges and resident population per 100,000, and standardized by age and gender on 2001 Italian population. Rates were calculated also on diabetic population (Istat estimates).
Results: A total of 20,876 hospitalizations for acute diabetic complications were recorded in Italy in 2010, representing 3.0 % of all diabetes-related hospital discharges. Most of hospitalizations (94.4 %) were due to hyperglycemic complications (51.5 % for ketoacidosis, 25.1 % for hyperosmolarity, 17.8 % for other coma), and 5.6 % for hypoglycemic coma. The involved persons were 19,282 (49.7 % men), with a mean age of 63.6 years (61.6 for men and 67.9 for women, $p < 0.001$).The 6.4 % of patients had more than one hospitalization for acute complications in the same year.
Over the study period, hospitalizations for acute complications decreased in Italy by 43 %, from 56.3 per 100,000 in 2001 to 32.4 in 2010 (p for trend < 0.001); the decrease was similar for hyperglycemic and hypoglycemic complications. If we consider rates expressed per 1,000 persons with diabetes, the reduction was 51 % (from 14.4 in 2001 to 7.1 in 2010). No differences were observed by gender. Large geographical variations were observed, with the lowest rate in the North (24.1 per 100,000 residents in 2010) compared to the Centre (33.3) and the South of Italy (42.2). Variations across geographic regions remained stable over the study period, with a 4.2-fold increase between the lowest and the highest regional rates in 2010, largely explained by regional variability in diabetes prevalence. Nonetheless, a ten-fold regional difference in hospitalization rates were found in people aged 0–19 years, which cannot be accounted for by differences in incidence rates of type 1 diabetes.
Conclusion: This study examining hospital admissions for acute complications in diabetic people covers the whole population of Italy over a quite long time period. Despite hospitalizations for acute diabetic complications decreased by 43 % over a 10 years period, 21,000 hospital discharges were still registered in 2010. Large geographic variations are evident within Italy, and the amount of this excess cannot be attributed exclusively to regional variability in incidence and prevalence of the disease. The observed regional variability is clinically important for a preventable complication with a significant potential for long-term morbidity and mortality. Prevention strategies are needed, particularly in areas identified with the highest rates.

Association between anti-HSP70 antibodies and plurimetabolic syndrome: the Casale Monferrato Study

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Background and Aims: The metabolic syndrome (MS), a cluster of metabolic abnormalities characterized by a low-grade inflammation and a pro-oxidant state, is associated with increased risk of developing both type 2 diabetes (T2DM) and cardiovascular disease. Heat shock protein 70 (HSP70) is an intracellular, highly conserved polypeptide important for cell survival. In stress conditions, HSP70 can be exposed on the plasma membrane and/or released into the circulation, eliciting an immune response. A reduction in HSPs has been proposed to contribute to impaired insulin signaling/responsiveness characteristic of T2DM. Our aim was to investigate the potential association between circulating anti-HSP70 and MS.
Materials and Methods: A nested case–control study was performed within the Casale Monferrato Study (CM). The CM study recruited 3,700 non-diabetic subjects, aged 45–74 years, randomly identified through the files of the resident Casale Monferrato population. The present analysis included subjects ($n = 1552$) with plasma creatinine levels < 2 mg/dl, CRP levels < 3 mg/dl, and without cardiovascular disease. Among them, we selected as cases ($n = 251$) those who had

MS (NCEP-ATPIII) and as controls (n = 170) those without any component of the MS. Stored plasma samples available for the analyses were 180 for cases and 136 for controls. The sample size provides a power of 82 % ($\alpha = 0.05$) to detect a difference in log-anti-HSP70 within the cohort of at lest one-third of standard deviation. Serum levels of anti-HSP70 were measured by a commercial ELISA kit (Stressgen).
Results: Anti-HSP70 levels were higher in subjects with MS than in those without MS (Table 1), even after adjustment for age and sex (118.2 vs. 106.1 μg/ml, p = 0.02). In logistic regression analyses, higher levels of log-anti-HSP70 conferred higher ORs for MS and this remained statistically significant after adjustment for age and sex [OR = 2.02 (1.12–3.66)]. In this model, trend of ORs across quartiles of anti-HSP70 was statistically significant (p = 0.04). Subjects with anti-HSP70 > 108.0 μg/ml had 77 % increased odds of having MS compared to those with levels ≤ 108.0 μg/ml (Table 2).
Conclusions: In this cohort of non-diabetic subjects at low cardiovascular risk, we found an independent association between anti-HSP70 and MS. This suggests that anti-HSP70 may be a novel marker of MS.

Table 1 Anti-HSP70 levels

	Anti-HSP-70 [media geometrica (RIQ)]
MS	122.6 (89.5–155.6)
without MS	107.1 (77.3–152.4)

Table 2 Logistic regression analyses

	Model 1	Model 2 Età, sesso	Model 3 + fumo, apoB,AER
	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)
Log-AntiHSP70	1.67 (1.02–2.73)	2.02 (1.12–3.66)	1.84 (0.97–3.50)
P for trend	0.12	0.04	0.13
Anti-HSP70 (μg/ml) ≤ 108.0	1	1	1
>108.0	1.53 (0.98–2.41)	1.77 (1.05–2.99)	1.67 (0.94–2.96)

Cardiometabolic control and weight reduction in diabetic patients treated with liraglutide or sitagliptin, both in association with metformin: experience in daily clinical practice

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Introduction: Type 2 diabetes mellitus and obesity are closely linked disease with rising prevalence and incidence in developed and developing countries. The glucagon-like-peptide-1 analogue, Liraglutide and the dipeptidyl peptidase-4 inhibitor, Sitagliptin, are approved for type 2 diabetes mellitus (T2DM) treatment and, several studies, demonstrated that the Liraglutide may be efficacious in obesity treatment.
Aim: The aim of this study has been to evaluate retrospectively, in daily clinical practice, the capacity of both Liraglutide and Sitagliptin, each added to metformin, to induce a cardiometabolic control and/or weight reduction in patients with type 2 diabetes.
Methods: We evaluated 34 patients with type 2 diabetes (21 men and 13 women). All the patients were previously treated with metformin mono-therapy (>1500 mg/day) for a minimum of 6 months but with non-optimal glycemic control (HbA1c > 7.5 %). The patients were than treated with either Liraglutide 1.8 mg/day subcutaneous injection (n = 16, 9 men and 7 women, age 58 ± 6 year) or Sitagliptin 100 mg/day orally (n = 18, 12 men and 6 women, age 58 ± 7 year). In our analysis, we examined only the patients in which the treatment has been performed for at least 52 weeks. In basal, after 26 and 52 weeks we evaluated, after 12-h fasting, anthropometrical parameters, including body mass index (BMI), and waist circumference, and a venous blood sample was drawn for biochemical determinations, including glycemia, HbA1C and lipid profile. Clinic blood pressure (BP) were obtained in the left arm of the supine patients, after five minutes of quiet rest, with a mercury sphygmomanometer. At baseline, no differences in age, fasting plasma glucose, HbA1c, systolic and diastolic blood pressure and treatments including lipid-lowering and antihypertensive therapy were present into two groups. Conversely, patients in treatment with Liraglutide showed, at baseline, higher values of body weight (100 ± 14 vs. 79.3 ± 12 kg), BMI (35.7 ± 5.8 vs. 28.3 ± 3.7 kg/m$^{2)}$ and waist circumference (114 ± 12 vs. 98.8 ± 9 cm) when compared with patients treated with Sitagliptin.
Results: After 52 weeks, in patients in treatment with Liraglutide we observed a reduction, even if no significant, in the body weight (100 ± 14 vs. 95.8 ± 14 kg, P = N.S.), waist circumference (114 ± 12 vs. 112 ± 8 cm, P = N.S.) and BMI (35.7 ± 5.8 vs. 34 ± 2 kg/m^2, P = N.S.); a significant improvement in fasting plasma glucose (181.8 ± 43 vs. 145 ± 30 mg/dl, $P = 0.009$.), HbA1c (8.7 ± 1.5 vs. 7.6 ± 1 %, $P < 0.05$) and systolic blood pressure (130.9 ± 6 vs. 124.6 ± 6 mmHg, $P < 0.05$) while no difference was present in diastolic blood pressure.
Similarly, in patients in treatment with Sitagliptin after 52 weeks we observed a slight reduction in the body weight (79.3 ± 12 vs. 78 ± 11 kg, P = N.S.), waist circumference (98.8 ± 9 vs. 96.8 ± 9 cm, P = N.S.) BMI (28.3 ± 3.7 vs. 27.3 ± 3.4 kg/m^2, P = N.S.) and a significant improvement in fasting plasma glucose (174, ± 28 vs. 133 ± 29 mg/dl, $P < 0.0001$.) and HbA1c (8 ± 0.9 vs. 7 ± 0.6 %, $P < 0.0001$). Conversely, no difference was present in the systolic and diastolic blood pressure.
In both groups of treatment no adverse events have been reported.
Conclusion: In conclusion, our data, confirm that also in daily clinical practice, both Liraglutide and Sitagliptin are able to improve glycemic control in patients with type 2 diabetes. However, in our experience, Liraglutide was not more effective for reducing fasting plasma glucose and HbA1c compared with Sitagliptin. Conversely, although not statistically significant, the weight loss was considerably greater in the patients in treatment with Liraglutide. In addition, the treatment with Liraglutide was able to reduce significantly systolic blood pressure.

Homa index is a marker of metabolic and vascular impairment

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Morbid obesity is associated with increased risk of death and atherosclerosis. Prospective studies have shown that bariatric surgery can

reduce the risk of death and the incidence of cardiovascular events in morbid obese subjects; particularly it has been shown that the major benefit in terms of risk reduction is related to high preoperative insulinemic levels (1).

The aim of our study was to evaluate early vascular impairment (flow mediated dilatation –FMD- and intima-media thickness –IMT-) in 60 morbidly obese subjects, 26 males, 34 females (BMI 45 ± 7 kg/m^2, waist 132 ± 18 cm), stratified on the basis of different values of HOMA-IR and body mass index.

In all subjects we determined glycemia, insulinemia and lipid profile. We used ultrasound for the evaluation of FMD (percentage change of the brachial arterial diameter from the baseline vessel size after reactive hyperemia), IMT (measured on common and internal carotid artery) and visceral fat area (VFA, as previously described by Hirooka et al.) (2).

The study population was stratified on the basis of HOMA-IR median values: ≥ 3.5 group 1, <3.5 group 2. Group 1, comparing to group 2, showed significantly higher levels of BMI (47±7 kg/m^2 vs. 43. ± 6 kg/m^2, p = 0.025), VFA (288 ± 61 cm^2 vs. 208±55 cm^2, p < 0.001), triglycerides (154 ± 117 mg/dl vs. 95 ± 34 mg/dl, p = 0.012) and IMT (0.9 ± 0.2 group 1 vs. 0.75 ± 0.2 p = 0.023); at the same time group 1, comparing to group 2, showed also significantly lower values of HDL-C (46 ± 10 mg/dl vs. 54 ± 12 mg/dl, p = 0.011) and of FMD (9 ± 6 % group 1 vs. 13 ± 7 % group 2 p = 0.035).

On the contrary, stratifying the study population on the basis of BMI median values, below and over 45 kg/m^2, we did not find any significant difference in triglycerides, HDL-C, FMD and IMT between the two groups. At the multivariate analysis age (β = −0.297, p = 0.019) and VFA (β = −0.362, p = 0.005) were the independent predictors of lower FMD; BMI, blood pressure, HDL-C, LDL-C and HOMA index were included in the model but did not enter the final equation. Age (β = −0.680, p < 0.001), LDL-C (β = −0.272, p = 0.002) and HOMA index (β = −0.268, p = 0.003) were the independent predictors of IMT; blood pressure, BMI, visceral fat area, triglycerides and HDL-C were included in the model but did entered in the final equation.

In subjects with morbid obesity, HOMA index, and not BMI, is the parameter able to quantify the degree of metabolic and vascular impairment. Visceral fat, closely linked to insulin resistance, and HOMA index are independently correlated to endothelial dysfunction and intima-media thickness, thus predicting higher risk of future cardiovascular events.

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Cardiovascular safety of liraglutide assessed in a patient-level pooled analysis of phase 2–3 liraglutide clinical development studies

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We assessed the cardiovascular safety of liraglutide, a glucagon-like peptide-1 receptor agonist, using existing clinical data. Patient-level results from all completed phase 2 and 3 studies from the liraglutide clinical development programme were pooled to determine rates of major adverse cardiovascular events (MACE): cardiovascular death, myocardial infarction, stroke. MACE were identified by querying the study database using Medical Dictionary for Regulatory Activities (MedDRA) terms combined with serious adverse events recorded by study investigators. Broad, narrow, and custom groups of MedDRA queries were used. Candidate events from each query were independently adjudicated post hoc. In 15 studies (6638 patients; 4257 liraglutide treated), there were 114 patients with MACE identified using the broad MedDRA query. Of these, 44 were classified as serious adverse events and 39 were adjudicated as MACE. The incidence ratio for adjudicated broad/serious MACE associated with liraglutide was 0.73 (95 % CI 0.38–1.41) versus all comparator drugs (metformin, glimepiride, rosiglitazone, insulin glargine, placebo), within cardiovascular safety limits defined by the United States Food & Drug Administration for diabetes therapies under current investigation.

Modulation of Adipogenesis profile in PBMC from HCV infected patients

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Background and Aims: Hepatitis C virus (HCV) is one of the leading causes of chronic liver diseases in Western countries. The World Health Organization estimates that 3 % of the world's population is chronically infected with HCV. Chronic HCV infection leads to a wide spectrum of liver diseases ranging from mild chronic hepatitis to end-stage cirrhosis and hepatocellular carcinoma.

Although hepatitis C virus (HCV) is considered essentially hepatotropic, recent studies suggest that it can also infect peripheral blood mononuclear cells (PBMC).

Furthermore, Hepatitis C virus (HCV) infection has been clinically associated with serum lipid abnormalities. The aim of this study is to analyze the possible roles of genes involved in HCV-mediated lipid metabolism in peripheral blood mononuclear cell (PBMC) from HCV infected patients.

Methods: Using The Human Adipogenesis RT2 Profiler TM PCR Array, we have analyzed the expression profile of 84 genes in chronic HCV PBMCs patients normalized with PBMCs from heathy donors. We compared results obtained from HCV + PBMCs with the HCV expression in the hepatocytes, to this aim we used a JFH1/HCV in vitro system 48 h post infection normalized with uninfected Huh 7.5.1 cell line.

Results: Out of 84 genes, about 40 genes are up-regulated in both of our system. Based on the results of microarray analysis, the expression of adipogenesis genes analyzed are significantly increased as well as in HCV PBMCs patients compared with PBMCs from healthy donors HCV in vitro system. In particular genes involved in lipid metabolism and angiogenesis are upregulated in HCV PBMCs and after JFH1 infection: Shh, SIRT1, SIRT 2, PPARs, FASN, SREBP1c, PRDM16, LMNA, FABP4 as well as the expression of the nuclear receptors LXRa, RXR and SHP1 for the first time associated with HCV infection in PBMCs.

Conclusions: These results confirm the ability of HCV to regulate, in the same manner, the transcriptional response of a high number of genes

involved in modulation, maintenance and adipogenesis regulation in lymphoid cells from HCV patient and in JFH1 HCV infection model. Moreover our data suggest the possibility that adipogenesis deregulation observed in HCV + PBMCs, may influence the host immune response during HCV infection.

Metabolic and nutritional evaluation on severely obese patients treated with laparoscopic gastric bypass: short, medium and long-term results

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Background: Obesity is a chronic and multifactorial disease, characterized by an increase of fat mass, due to an unbalance between energy intake and expenditure, with a background of predisposing genotype and environmental factors. Laparoscopic gastric bypass (LGBP) is one of the most common technique in surgical treatment of morbid obesity.
The aim of the study was to evaluate the trend of metabolic and nutritional parameters in a group of severely obese patients before LGBP and 6 weeks (about 10 % weight loss), 6 months (about 25 % weight loss) and 24 months (long-term evaluation) after surgery.
Methods: Twenty-eight (14 M, 14 F; age 41.71 ± 7 years) obese (BMI 49.76 ± 5.8 kg/m^2) patients were treated with LGBP. Resting metabolic rate (RMR) was measured by indirect calorimetry, body composition was estimated by bioimpedance analysis (BIA) and biochemical parameters were evaluated by ***routine laboratory*** analysis.
All evaluations were performed before surgery and after achieving ~10 % (A) and ~25 % (B) weight loss; fourteen patients were evaluated 24 months after surgery (C) as well.
Results: Body weight and BMI significantly decreased at 6 weeks, 6 months and 24 months after surgery (weight 137.6 ± 23.7 kgs at entry vs. 120.4 ± 20.6 kgs in A ($p < 0.05$) vs. 103.9 ± 19.6 in B and 93.24 ± 6.94 in C; ($p < 0.01$ vs. baseline for B and C).
As far as BMI, it was 49.8 ± 5.8 kg/m^2 at entry versus 43.8 ± 5.0 in A versus 37.4 ± 4.5 in B and 32.18 ± 2.09 in C ($p < 0.01$ for all values). Also RMR decreased during the repeated evaluations (2492 ± 388 kcal/24 h at entry vs. 2098 ± 346 in (A) vs. 2035 ± 312 in (B) and 1880 ± 105 in (C), $p < 0.01$ vs. baseline for all groups). RMR corrected for fat-free mass decreased too (R*MRc* = 35.7 ± 6.7 2 kcal/kg FFM/24 h at entry vs. 34.9 ± 9.0 in (A) vs. 33.5 ± 5.4 in (B) and 30.02 ± 7.2 in (C);($p < 0.05$ vs. baseline in B and C). Body composition analysis, evaluated by BIA, showed an increased fat free mass (*FFM*, 52.2 ± 6.2 % at entry vs. 51.5 ± 7.4 in (A) vs. 64.1 ± 8.9 in (B) and 67.08 ± 2.64 in (C); $p < 0.01$ vs. baseline in (B) and (C)) with a concomitant reduction in fat mass (*FM*, 47.8 ± 6.2 % at entry vs. 48.5 ± 7.4 % in (A) vs. 34.9 ± 9.0 in (B) and 32.92 ± 2.91 in (C); $p < 0.01$ vs. baseline in B and C). Moreover, a significant reduction in blood glucose ($p < 0.01$ vs. baseline for all evaluations), insulin ($p < 0.01$ for all evaluations), homeostasis model assessment (*HOMA)* index ($p < 0.01$ vs. baseline for all evaluations), and triglyceridemia ($p < 0.01$ vs. baseline in B and C) as well as an increase in HDL-Col ($p < 0.05$ in B and $p < 0.01$ in C) were observed.
Conclusions: Our study confirms that, in well selected severely obese patients, LGBP is responsible for the improvement in both body composition (reduction of FM) and some metabolic parameters. The long-term observation also confirms these results.

Antiplatelet therapy in diabetic patients with nephropathy in primary prevention for cardiovascular disease

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Background: ADA, as well as SID-AMD 2012 guidelines, suggests to consider anti-platelet therapy as a *primary prevention* strategy in patients with diabetes with increased cardiovascular risk (10-year risk 10 %). Several studies evidenced no advantages in primary prevention and a greater risk of bleeding and haemorrhagic stroke. In order to improve knowledge of this aspect of Diabetes treatment, we carried out a retrospective observational study.
Methods: We studied 564 patients, with T2DM and diabetic nephropathy (diagnosed with clinic criteria, i.e. microalbuminuria + diabetic retinopathy) in primary prevention for CVD. 242 of them were treated with anti-platelet drugs (group A) and 323 were not treated with anti-platelet drugs (group B). Patients underwent a follow-up visit every 6 months, for 8 years (2002–2010). We compared the number of MACE (Major Adverse Cardio-Vascular Events) occurred in patients treated to patients not treated by anti-platelet drugs. We used Kaplan–Meier survival curves to compare cumulative probability of survival between the two groups. The comparison between the two groups was performed using the Log-Rank test. Statistical significance was evaluated at 0.05. We used the Cox Regression model to assess the independent effect of covariates (anti-platelet therapy, smoke, HbA1c, BMI, total cholesterol, sex and blood pressure) for the primary endpoint (occurrence of MACE).
Results: MACE occurred in 49 patients from the group A and in 52 patients from the group B (OR = 1.32; IC 95 % = 0.86–2.04). Fatal MACE occurred in 22 patients from the group A and in 20 patients from the group B (OR = 1.52; IC 95 % = 0.81–2.85). Non fatal MACE occurred in 27 patients from the group A and in 32 patients from the group B (OR = 1.18; IC 95 % = 0.69–2.04). The analysis of the Kaplan–Meier survival curves did not show a lower incidence of MACE in the group A compared to group B. The analysis of the single covariates showed that anti-platelet therapy does not influence the incidence of MACE.
Discussion: This study did not show a reduction of MACE in diabetic patients with nephropathy in primary prevention for CVD treated with anti-platelet drugs, compared to the untreated, though also patients at high cardiovascular risk belonged to the population studied.

Relationship between renal function and hypoglycaemic drugs in a cohort of patients with type 2 diabetes mellitus

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Background: Evaluation of kidney function is essential in order to prescribe properly hypoglycaemic drugs, moreover early detection of chronic kidney disease is essential in patients with type 2 diabetes mellitus in order to identify subjects at risk of severe comorbidities. The National Kidney Foundation recommends the use of equations to estimate glomerular filtration rate (GFR). The aim of our study was to relate hypoglycaemic drugs prescription to main clinical parameters of renal dysfunction and long term glycaemic control in a cohort of type 2 diabetes mellitus (T2DM) outpatients.

Patients and Methods: This survey included all the outpatients with T2DM patients treated with hypoglycaemic drugs who were not taking insulin evaluated at the diabetic clinic of the Azienda Ospedaliera-Universitaria of Ferrara. Patients' treatment was classified in the following way: glitazones (group 1), metformin (group 2), repaglinide (group 3), sulphonylureas (group 4), sulphonylureas and metformin (group 5) and dipeptidyl peptidase 4 inhibitors (group 6). GFR was evaluated with the new CKD-EPI formula and subjects were classified in the five K/DOQI stages. Main clinical parameters, glycosylated haemoglobin A1c (HbA1c) and microalbuminuria (MA) were also evaluated. Univariate and logistic regression analysis was carried out. MA and HbA1c were considered dependent variable while the other parameters including the different hypoglycaemic drugs were considered as independent ones.

Results: The study included 1686 T2DM patients (57.1 % males), mean age was 68 ± 10 years, mean BMI 30 ± 5 kg/m^2, mean systolic and diastolic BP 138 ± 15 and 80 ± 9 mmHg, respectively. Mean fasting glucose level was 114 ± 51 mg/dl, glycated haemoglobin 8 ± 1 %, serum creatinine 1.03 ± 0.35 mg/dl. Mean GFR was 71.2 ± 21 ml/min/1.73 m^2 and in 504 (30 %) patients it was lower than 60 ml/min/1.73 m^2. As for their therapeutic regimen, 117 (7 %) were on glitazones, 665 (39.5 %) on metformin, 114 (6.8 %) on repaglinide, 178 (10.5 %) on sulphonylureas, 600 (35.5 %) on sulphonylureas and metformin, and 12 (0.7 %) on dipeptidyl peptidase 4 inhibitors. The different treatment groups had different GFR and hypoglycaemic drugs were prescribed differently in the different K/DOQI stages. 640 patients had MA, they had higher GFR than those without MA (75 ± 21 vs. 69 ± 21, $p < 0.0001$). MA was associated with LnBMI (OR 3.732, 95 %CI 1.993–6.988, $p < 0.0001$), age (OR 0.967, 95 %CI 0.955–0.979, $p < 0.0001$), stage IV K/DOQI (OR 0.198, 95 %CI 0.065–0.601, $p = 0.0042$), metformin treatment (OR 0.122, 95 %CI 0.061–0.246, $p < 0.0001$), sulphonylureas treatment (OR 0.421, 95 %CI 0.255–0.695, $p = 0.0007$), sulphonylureas and metformin treatment (OR 0.593, 95 %CI 0.391–0.901, $p = 0.0144$). HbA1c > 7 % was associated with LnBMI (OR 1.766, 95 %CI 1.029–3.030, $p = 0.0390$), systolic blood pressure (OR 1.010, 95 %CI 1.000–1.020, $p = 0.0415$), metformin treatment (OR 0.046, 95 %CI 0.015–0.140, $p < 0.0001$), repaglinide treatment (OR 0.157, 95 %CI 0.051–0.486, $p = 0.0013$), sulphonylureas treatment (OR 0.110, 95 %CI 0.038–0.319, $p < 0.0001$), sulphonylureas and metformin treatment (OR 0.287, 95 %CI 0.101–0.814, $p = 0.0188$).

Conclusion: Our results are in agree with data published by Koro et al. (Clin Ther 2009) reporting that 39.7 % of adults with T2DM in the United States had chronic kidney disease. Moreover, this survey demonstrates that GFR and hypoglycaemic drug prescription are poorly related. Hypoglycemic drug treatment appears to be a determinant of the main clinical parameters such as MA and HbA1c, reducing the risk of complications related to T2DM.

Effectiveness of rehabilitation treatment in combination with an additional aminoacids mixture (aminotrofic®) in patients undergoing cardiac surgery

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Introduction: The restoration and the maintenance of an optimal physical condition, compatible with below cardiac pathology, represent objective of the cardiopathy rehabilitation treatment in patients subordinates to cardiac surgery. Various studies, reported to patients with heart failure, have demonstrated that it exists, in this type of patients, a altered protein metabolism that negatively influences the quality of life and the tolerance to physical exercise. Therefore, an improvement of the nutrition and metabolic state by means of a proteinic supplement could represent a stimulus to a more immediate recovery of the physical condition. We think that in the cardiac surgery patients a supplement of a specific aminoacids mixture (with contained adapting in essential aminoacids) can represent an ulterior one stimulus to in combination improve the physical performance to the rehabilitation treatment.

Scope Study: To estimate the tiny tolerance to physical exercise by means of six walking test (6 MWT) in the patients subordinates to surgical operation before and after cycle of cardiological rehabilitation with and without oral dietetic supplement of a specific aminoacids mixture (aminotrofic®).

Materials and Methods: We have estimated in the period of time that goes from 1 september 2011 to December 2011, 27 patients with indication to cycle of cardiological rehabilitation treatment after cardiac surgery. Of these patients, 19 (12 M/7F 65.7 ± 12.3) have been subordinates to operation of myocardial revascularization by means of BPAC, remaining 8 (5 M/3F 69.8 ± 10.2) to participations of surgery to valvular. Before beginning the rehabilitation treatment, all the patients have been estimated clinical. The rehabilitation treatment, for every patient, is lasted 4 weeks and has been subordinates all to 6MWT to beginning and at the end of the rehabilitation treatment, uniforms in two groups with and without aminoacidica supplement detailed list to the dosage of 8 grams die (4 g to the morning and 4 g to the afternoon) (aminotrofic®).

Results: After the rehabilitation treatment, 24 patients have introduced an improvement of the 6MWT. The data to 248 ± 92 m bases them in the two groups was to place, while the data differed in the two after the treatment; in the group control an increment was taken place of 301 ± 99; in the treated group with aminoacids supplement 352 ± 128 ($p < 0.02$ regarding base them). To moment, data the meager number of patients, has not been gone to estimate if differences between the patients exist subordinates to BPAC regarding the patients with pathology to valvular.

Conclusions: The rehabilitation treatment, like demonstrated in other previous research, is in a position to improving the tolerance a physical exercise. From our job, holding account the meager number of patients, is evidenced as a specific aminoacids mixture determines an improvement of the physical ability in combination all' exercise to the rehabilitation treatment in the patients subordinates to cardiac surgery. In conclusion therefore, also in the patients subordinates to cardiac surgery, thus like in the patients with heart failure, exists a altered muscular metabolism that determines a insufficient tolerance a physical exercise, such condition can be improved with a specific dietetic supplement.

Something more than just a pancreatitis

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Background: When we deal with pancreatitis, we immediately think to cholelithiasis or alcoholism, but sometimes pancreatitis may be the expression of other major diseases

Clinical Case: MM, male, 38, smoker, non drinker, BMI 34, no major illnesses in his clinical history; is hospitalized because of abdominal pain.
Abnormal laboratory tests: WBC 14000; glucose 170, amylase 460, lipase 2948; chylous serum. *ECG, CXR* and *X-ray abdomen* within the limits; *abdominal echography* not practicable because of the abdominal pain; *abdomen CT*: Enlarged pancreas, with soft edges.
Further *tests* are then performed: Cholesterol 325 (HDLc 25), triglycerides 1140; ApoA 85, ApoB 134; then practiced deepening anamnestic about family history: *his father had myocardial infarction at 50 years, and his brothers are dyslipidemic.*
The patient is discharged on the sixth day, with the following diagnosis: "Acute pancreatitis in familial combined hyperlipidemia (FCH). Diabetes mellitus (DM) due to pancreatitis".
He is now in follow-up with good results, including the reduction of overall cardiovascular risk, no further episodes of pancreatitis.
Discussion: Cholelithiasis and alcohol are the main causes of pancreatitis, hypertriglyceridemia is responsible for 2–3 %. Hypertriglyceridemia may be primary (hyperchylomicronemia, family hypertriglyceridemia, dysbetalipoproteinemia and FCH), or secondary (alcohol, type II DM, obesity, medications).
Criteria for FCH: LDLc $>$ 160 mg/dl and/or triglycerides $>$ 200 mg/dl in the patient, associated with different phenotypes and/or early cardiovascular events in his first degree relatives. Further criterion: ApoB $>$ 125 in a patient with early CV familiarity.
Depending on levels of triglycerides, the risk of pancreatitis and/or cardiovascular disease can increase. There is high risk of acute pancreatitis for levels triglyceridemia $>$ 1000 mg/dl, while moderate hypertriglyceridemia is a marker of atherogenic dyslipidemia.
Conclusions: The case shows that pancreatitis should suggest, sometimes, also a possible metabolic disease and that the association with hypertriglyceridemia, frequent bio-humoral alteration, shouldn't be runned in a hasty manner, but should ask the doctor to identify possible systemic diseases, such as FCH, associated with high cardiovascular risk.

Liraglutide reduces carotid intima-media thickness in patients with type-2 diabetes

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Background: Liraglutide is in the Italian market since 18 months, and can be prescribed only in combination with oral hypoglycemic agents. There is currently interest on the non-glycemic effects of liraglutide, such as those on cardiovascular risk markers; yet, the effect on carotid intima-media thickness (IMT), a recognized marker of subclinical atherosclerosis, is still unknown.
Aim and Methods: We evaluated in our Italian center the effect of liraglutide on carotid IMT (as assessed by B-mode real-time ultrasound) in 33 patients with type-2 diabetes (58 % males, age: 59 $\pm$ 9 years), who were also receiving metformin at fixed dose of 1500/daily. Patients were newly diagnosed or previously treated subjects with oral hypoglycemic agents. The dose of liraglutide was 0.6 mg/daily for the first 2 weeks, followed by a dose of 1.2 mg/daily. Statistical analysis used paired *t* test and Spearman correlation method.
Results: At baseline patients weighted 82 $\pm$ 9 kg, with 9.5 $\pm$ 1.4 mmol/L of fasting glycemia and 8.3 $\pm$ 0.6 % of HbA1c. Significant changes in these parameters were recorded after 4 months of therapy: weight lowered by 3.1 kg, fasting glycemia by 2.3 mmol/l and HbA1c by 1.8 % ($p < 0.0001$ for all). Carotid IMT changed from 1.55 $\pm$ 0.45 mm to 1.36 $\pm$ 0.31 mm ($p = 0.0003$). Changes in carotid IMT did not correlate with changes in body weight, fasting glycemia or HbA1c.
Conclusions: Liraglutide is beneficial on subclinical atherosclerosis in type-2 diabetes after only 4 months of therapy. This effect seems to be achieved by mechanisms not involving glucose metabolism directly. Further studies are needed to further investigate the non-glycemic effects of liraglutide, as well as those of incretin-based therapies in general.

Sometimes they come back

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Vitamin deficiencies are considered unusual in western populations. At the present time these rare diseases are sometimes misdiagnosed. It is important to recognize signs and symptoms in order to avoid unnecessary medical tests, as well as missing a very simple treatment that can prevent even life threatening illnesses.
We describe the case of a 40-year-old woman admitted to our hospital in March 2012 presenting bruising on her lower extremities and buttocks, denying any history of recent trauma.
She presented with tiredness, fatigue, reduced exercise tolerance, lower limbs pain. The patient did not refer relevant medical history. She reported family history of Inflammatory Bowel Disease (one sibling was affected by Crohn's disease) but denied fever, weight loss, diarrhea. She was not taking any drug treatment.
On physical examination, she had normal vital parameters (HR 92/bpm e BP 110/80). The skin was pale and dehydrated, in the lower limbs were evident spontaneous ecchymoses, swelling from the feet up to the knees, and several nonpruritic and not palpable perifollicular petechial lesions. Examination of chest, abdomen and cardiovascular system was normal.
She was reluctant, apathetic and avoiding eye contact. Lack of emotional involvement and participation, restricted affectivity and inadequacy in relation to others emerged during interview. Family members reported her tendency to social isolation and eating disorders with many food restrictions and extremely limited food choices that were not clearly justified.
On laboratory testing she was found to have a severe normocytic-normochromic anemia (Hemoglobin: 4.9 g/dL, Hematocrit: 15.9 %, Mean corpuscular volume: 93.6 fl, Mean corpuscular haemoglobin: 28.8 pg), mild leukopenia (WBC 4180/mm^3, Neutrophils 77.4 %, Lymphocytes 18.0 %, Monocytes 2.9 %) and normal platelet count (274000/mm^3).
There were no alterations in the coagulation profile nor history or signs suggestive of acute or chronic bleeding. Anemia was further investigated with the assessment of serum ferritin, folic acid, B12 vitamin, haptoglobin levels, Coombs tests, G6PDH. All values were in the normal ranges excepted for folic acid that was reduced (2.20 ng/ml).
Peripheral blood smear showed neutrophil hypersegmentation, anisopoikilocytosis, macrocytosis with no evidence of abnormalities of platelets. Thyroid function tests were also normal.
The morphological features of cutaneous manifestations (perifollicular nonpalpable purpuric lesions of about 1–2 mm located in the

lower limbs) did not appear compatible with vasculitis, moreover in the absence of autoimmune disorders.
Duplex ultrasonography of the deep and superficial veins with colour flow Doppler assessment ruled out deep vein thrombosis and ultrasound of soft tissues excluded haematomas.
When diet was investigated, it resulted in peculiar dietary habits that, in association with low plasmatic levels of folic acid, oriented toward a strong suspicion of malnutrition related disease. This hypothesis was confirmed by reduced levels of albumin and prealbumin. Nutritional assessment reported protein-calorie malnutrition.
In order to exclude malabsorption we performed gastroscopy and endoscopic duodenal biopsy which indicated no significant lesions. Serology for anti-tissue transglutaminase antibodies was negative and total serum IgA level was normal.
Because of the severity of anemia in a symptomatic subject, multiple blood transfusions have been practiced up to the achievement of acceptable values of haemoglobin.
Clinical symptoms and objective signs listed above are often observed in patients with severe vitamin C deficiency caused by low dietary intake of fruits and vegetables. The patient's diet was indeed very poor with severe lack of these nutrients.
Replacement therapy with high dose ascorbic acid was started, initially parenterally and later orally, together with the implementation of a balanced diet. This intervention resulted in a rapid clinical improvement, progressive disappearance of skin lesions and peripheral edema, and reduction of behavioural problems.
Systemic manifestations of such entity are unusual in western countries and are more often detectable in people with poor social status. However uncommon diagnosis, such as scurvy, must not be underestimated in presence of very incorrect alimentary habits.

Dietary assessment and one-hour post-load plasma glucose in hypertensive patients

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The prevalence of type 2 diabetes (T2D) is rapidly increasing worldwide. Control of body weight by balancing energy intake and expenditure is of major importance for T2D prevention; however specific dietary factors may affect T2D appearance. According with this, several evidences have demonstrated that whole grains so as vegetables or nuts consumption is inversely associated with glucose and insulin responses, that may positively affect inflammation and endothelial activation biomarkers reducing the risk of T2D. Recently, a cutoff point of 155 mg/dl for the one-hour (1-h) post-load plasma glucose (PG), during an oral glucose tolerance test (OGTT), is able to identify subjects with normal glucose tolerance (NGT) at high risk for T2D and with subclinical organ damage. The aim of the study was to evaluate the relationship between dietary factors and 1-h post-load PG. We enrolled 53 never treated essential hypertensive patients with a mean age of 48.9 $\pm$ 5.6 years, defined NGT by OGTT, 27 were NGT with 1-h post-load PG $<$ 155 mg/dl (NGT $<$ 155) and 26 were NGT with 1-h post-load PG $\geq$ 155 mg/dl (NGT $\geq$ 155). In all patients usual dietary intake was quantified by a semiquantitative food frequency questionnaire (FFQ) developed and validated in the European Prospective Investigation into Cancer and Nutrition (EPIC) study and nutritional analysis was performed by an appropriate software. Insulin sensitivity was assessed by the Matsuda index. NGT $\geq$ 155 had significantly reduced insulin sensitivity in comparison with NGT $<$ 155 (42.8 $\pm$ 20.2 vs. 71.3 $\pm$ 29.6; $P < 0.001$). According to nutritional analysis, NGT $\geq$ 155 vs. NGT $<$ 155 had a greater intake of fructose (15.0 $\pm$ 3.7 g vs. 11.0 $\pm$ 4.0 g; $P < 0.001$), oligosaccharides (107.3 $\pm$ 21.9 g vs. 84.3 $\pm$ 23.1 g; $P < 0.001$) and saturated fatty acids (SFA) (29.1 $\pm$ 9.0 g vs. 21.7 $\pm$ 4.0 g; $P < 0.001$) and a reduced intake of starch (227.6 $\pm$ 45.5 g vs. 302.8 $\pm$ 59.9 g; $P < 0.001$) and polyunsaturated FA (PUFA) (13.9 $\pm$ 3.4 g vs. 17.0 $\pm$ 3.4 g; $P = 0.020$). According to a linear regression analysis between 1-h post-load PG and different nutritional covariates in the whole population, 1-h post-load PG was directly and significantly related with oligosaccharides ($r = 0.518$; $p < 0.0001$), fructose ($r = 0.473$; $p < 0.0001$) and SFA ($r = 0.259$; $p = 0.031$) and inversely correlated with starch ($r = -0.518$; $p < 0.0001$) and PUFA ($r = -0.418$; $p = 0.001$). At multiple regression analysis, starch was the major determinant of 1-h post load PG explaining a 26.9 % of its variation; fructose, PUFA and oligosaccharides also entered in the final model justifying 10.3 %, 9.7 % and 4.7 % of 1-h post-load PG variation, respectively. In conclusion, dietary pattern may affect 1-h post load PG. This evidence has clinical relevance because 1-h post load PG is associated with T2D increased risk and, in hypertensives, with subclinical organ damage, that represents a strong predictor of cardiovascular events.

Vitamin D and one-hour post-load plasma glucose in hypertensive patients

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It's known that vitamin D has pleiotropic effects beyond the simple regulation of mineral metabolism. Recent epidemiological evidence points to a potential association of low vitamin D levels with adverse metabolic risk, including type-2 diabetes (T2D). Recently, a cutoff point of 155 mg/dl for the one-hour (1-h) post-load plasma glucose (PG), during an oral glucose tolerance test (OGTT), is able to identify subjects with normal glucose tolerance (NGT) at high risk for T2D and with subclinical organ damage.
The aim of the study was to evaluate the relationship between vitamin D and 1-h post-load PG. We enrolled 151 never treated essential hypertensive patients with a mean age of 52.2 $\pm$ 10.4 years, 79 males and 72 females, with a normal kidney function evaluated by creatinine and estimated glomerular filtration rate (e-GFR). After an OGTT, 74 were NGT with 1-h post-load PG $<$ 155 mg/dl (NGT $<$ 155), 36 were NGT with 1-h post-load PG $\geq$ 155 mg/dl (NGT $\geq$ 155) and 41 were impaired glucose tolerant (IGT). Diabetic patients were excluded from the study. In all patients insulin sensitivity was assessed by the Matsuda index and 25-OH vitamin D, the best indicator of vitamin D status in patients with normal kidney function, was measured by chemiluminescence (Liaison-Diaforin).
NGT $\geq$ 155 subjects in comparison with NGT $<$ 155 had higher Matsuda index (52.0 $\pm$ 23.2 vs. 90.5 $\pm$ 44.5; $P < 0.0001$) and high sensitivity C-reactive protein (hs-PCR) values (3.3 $\pm$ 2.3 vs. 1.6 $\pm$ 0.9 mg/L; $P < 0.0001$), but not significantly different from IGT subjects(50.1 $\pm$ 20.9, $P = 0.706$ for Matsuda index and 3.5 $\pm$ 1.4 mg/L, $P = 0.642$ for hs-CRP). Moreover, NGT $\geq$ 155 subjects had lower 25-OH vitamin D levels than NGT $<$ 155 (24.2 $\pm$ 6.6 ng/ml vs. 28.3 $\pm$ 8.3 ng/ml; $P < 0.0001$) but similar to IGT (23.4 + 7.8 ng/ml, $P = 0.631$). According to a linear regression analysis between 1-h post-load PG and different covariates in the whole population, 1-h post-load PG was inversely and significantly

related with 25-OH vitamin D ($r = -0.498$; $P < 0.0001$) and e-GFR ($r = -0.162$; $P = 0.024$) and directly correlated with hs-PCR ($r = 0.466$; $P < 0.0001$). At multiple regression analysis, 25-OH vitamin D was the major determinant of 1-h post load PG in the whole population, in NGT < 155, NGT ≥ 155 and IGT, explaining a 24.8, 13.2, 29.5 and 36.5 % of its variation, respectively.
In conclusion, vitamin D levels were strongly associated with 1-h post-load PG a predictor of T2D and, in hypertensives, of subclinical organ damage. Thus, it can be argued that vitamin D deficiency should not be considered only as a feature of osteo-mineral disorders, but also a biomarker and a risk factor for metabolic derangements as well as cardiovascular disease.

Pleiotropic effect of incretin-based therapy on cardiovascular risk factors in type 2 diabetes

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Background and Aims: Individuals with type 2 diabetes are at increased risk for developing cardiovascular disease (CVD), and coronary heart disease (CHD) is the leading cause of death in these patients. The higher CVD risk in diabetics is partially dependent on the prevalence of several factors, such as obesity, dyslipidemia and hypertension. Diabetic patients present dyslipidemia consisting in high triglyceride levels, low high-density lipoprotein cholesterol (HDL-C), and increased non-high-density lipoprotein cholesterol (non-HDL-C), which leads to an increase in atherogenic lipoprotein particles. The joint European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines recommend new low-density lipoprotein cholesterol (LDL-C) targets for diabetic patients. Incretin-based therapies are designed to target the metabolic effects of type 2 diabetes mellitus. We aimed to verify the effect of different incretin-based therapies on lipid profile of type 2 diabetes patients compared to insulin.
Patients and Methods: Eighty-one diabetic patients (mean age 65.9 years, range 51–86) with no history of cardiovascular disease were evaluated retrospectively. Only patients who reached the glycaemic control (HbA1c < 7 %) were considered in the analysis. They were divided into three main groups: 1) treated with DPP4 inhibitors (N = 33, M/F = 20/13, age = 66.97 ± 8.79); 2) treated with incretin mimetics/GLP-1 analogues (N = 21, M/F = 15/7, age = 62.81 ± 5.57); 3) treated with insulin (N = 27, M/F = 13/14, age = 67.04 ± 9.22). Body mass index (BMI), triglycerides, total cholesterol (TC), LDL-C and HDL-C were assessed at baseline and after 6 months of starting therapy. A 2-way analysis of variance was performed to compare the effects of the three treatments at the time points considered.
Results: BMI was reduced after 6 months in patients treated with incretin mimetics/GLP-1 analogues, while it was unchanged by DPP4 inhibitors and slightly increased by insulin. Of note, while cholesterol was significantly reduced by all the treatments, LDL-C and triglycerides decrease was observed in patients treated with incretin mimetics/GLP-1 analogues and DPP-4 inhibitors, but not with insulin; on the contrary, insulin-treated patients showed a marked increase in HDL-C levels after 6 months.
Discussion: We evaluated the impact of incretins and insulin-based therapy on metabolic factors of cardiovascular risk. Weight loss in patients treated with incretin mimetics/GLP-1 analogues was associated with improvements of lipid profile suggesting that incretin-based therapy not only improves glucose metabolism but also positively impacts lipid homeostasis. The exact molecular mechanisms remain to be elucidated, but current studies underline the concept that DPP-4 inhibitors and GLP-1 may exert pleiotropic action on cardiovascular risk in type 2 diabetes, independently from their incretin effect.

Liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results (LEADER®) trial: rationale and study design

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Liraglutide is a once-daily human glucagon-like peptide-1 analogue approved for use in patients with type 2 diabetes (T2D). Although liraglutide is associated with significant reductions in fasting glucose, haemoglobin A1C, weight, and systolic blood pressure, its effect on cardiovascular (CV) outcomes is unknown. LEADER® is an international, multicenter, randomized, double-blind, placebo-controlled trial designed to investigate the hypothesis that liraglutide is non-inferior to placebo, both in combination with standard of care, for a composite of major adverse cardiovascular (CV) events in patients with T2D. Approximately 9000 patients with T2D and at high CV risk will be enrolled in >30 countries. Patients are randomized 1:1 to once daily liraglutide 1.8 mg or placebo plus standard of care for 3.5–5 years. Assessments are being performed at enrolment, randomization, and every 6 months. The primary endpoint is time from randomization to an adjudicated composite outcome of CV death, non-fatal MI, or non-fatal stroke. The study is event- and time-driven and will not end until 611 events have accrued and a minimum duration of drug exposure has reached 42 months. Secondary outcomes include an expanded composite CV outcome, all-cause mortality, composite microvascular outcome (eye + kidney), foot ulcers, and various surrogate parameters for metabolic control and CV risk. Events will be adjudicated by independent committees blinded to treatment. Non-inferiority of liraglutide will be established if the upper bound of the 95 % CI is <1.3. If non-inferiority is demonstrated, a test for superiority will be performed. The first patient was enrolled in September 2010; results are expected in 2016. LEADER® is the first trial to test the long-term effects of liraglutide on CV outcomes in patients with T2D.

Therapeutic Plasma exchange in patients with severe Hypertriglyceridemia

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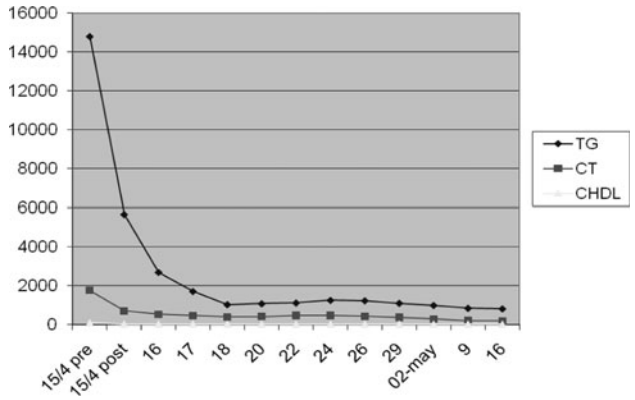
Extremely high plasma triglyceride (TG) level is a recognized risk factor for acute pancreatitis (AP). To evaluate the therapeutic efficacy of plasma-exchange in treating patients with severe hypertriglyceridemia (sHTG), 9 patients who had not responded to conventional medical therapy (fat-free diet plus drugs) were referred for therapeutic plasma exchange (TPE). One- hundred- four TPE sessions were performed. The youngest patient in this sample-2nd case ever described- is a newborn (♀) aged 3 months, with genetically

determined non functional LPL activity. Plasma TG and total cholesterol levels dramatic reductions after TPE are reported in the figure. Plasma HDL-cholesterol level already low when the extracorporeal treatment was initiated, did not show appreciable change. In most cases, the interval between treatments was related to the clinical presentation and individual circumstances.



The removal of TG-rich lipoproteins prevented relapses or insurgence of AP. In this case series, TPE is confirmed as a safe and reliable method for treating patients with refractory sHTG when a severe complication, such as AP, is clinically demonstrated or can be actively prevented. Therefore, in cases where standard medical approaches fail to promote the clearance of TGs from plasma and a high risk of first or second hypertriglyceridemic pancreatitis persists, TPE provides a therapeutic option for preventing life-threatening sHTG.

New possible mechanism involved in the pathogenesis of reactive hypoglycemia in obese and non obese subjects

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Introduction: Hypoglycemia is a common finding in daily clinical practice and, in obese or non-obese non-diabetic adult patients, may be related to drugs, critical illness, cortisol or glucagon insufficiency, non-islet cell tumour, insulinoma, or it may be surreptitious. Nevertheless, some hypoglycaemic episodes remain unexplained. Several factors (alteration in pancreatic beta-cell insulin secretion and/or alteration in pancreatic alpha-cell glucagon secretion) have been suggested to potentially play a role in the pathogenesis of reactive hypoglycemia in both obese and non-obese subjects. However, it is not known what is the role of the entero-hormone axis in the development of this condition.
Aim: Aim of this study was to evaluate the insulin, glucagon and GLP-1 levels in obese and non obese subjects, with or without hypoglycemia during oral glucose tolerance test (OGTT).
Methods: We have studied 28 non-diabetic subjects (15 men and 13 women) aged between 18–50 years. Subjects were excluded if they had history of cardiovascular disease including peripheral atherosclerosis, chronic gastrointestinal diseases associated with malabsorption, chronic pancreatitis, history of any malignant disease, history of alcohol or drug abuse, liver or kidney failure, and treatments able to modify glucose metabolism including lipid-lowering and antihypertensive therapy. On the first day, after 12-h fasting, subjects underwent anthropometrical evaluation, including body mass index (BMI), and waist circumference (WC), and a venous blood sample was drawn for biochemical and hormonal determinations. On the second day, after a 12-h fasting, a 75 g OGTT to 5 h was performed with sampling for plasma glucose, insulin, c-peptide, GLP-1 and glucagon. The insulin resistance has been evaluated by HOMA-IR and insulin sensitivity has been assessed by Matsuda index.
According to the onset of hypoglycemia (glycemia $\leq$ 70 mg/dl during OGTT) and BMI ($\geq$30 kg/m^2), the subjects was divided in 4 groups: obese with hypoglycemia (n = 6), obese without hypoglycemia (n = 7), non obese with hypoglycemia (n = 8) and non obese without hypoglycemia (n = 7).
Results: Obese subjects showed higher values of BMI, waist circumference, both basal and after 2 h during OGTT insulin levels and increased insulin resistance assessed by HOMA-IR when compared with non obese subjects. Moreover, in the 2 groups there were no differences in mean levels of basal GLP-1 and glucagon. In obese subjects with and without hypoglycemia, there were not differences in basal insulin levels and insulin sensitivity, but those presenting with hypoglycemia showed, despite low glucose levels, a reduced increase in glucagon during OGTT (AUC Glucagon = 55 vs. 101 pmol/L*h in obese with hypoglycemia vs. obese without hypoglycemia). Non obese subjects with hypoglycemia showed only increased insulin sensitivity when compared with non obese without hypoglycemia, while there were no differences in the others parameters. In these subjects was possibly to identify a subgroup of subjects that showed low basal levels of GLP-1 (6.36 vs. 13.3 pmol/L) and a reduced increase of glucagon during OGTT (AUC Glucagon = 58 vs. 100 pmol/L*h). In one case it was possible to demonstrate also reduced basal levels of glucagon (25 vs. 55.7 pmol/L), associated with an inappropriate secretion of GLP-1 during OGTT (AUC GLP-1 = 26 vs. 10 pmol/L*h).
Conclusion: In conclusion, our preliminary data seem to evidence the presence of new possible mechanisms involved in the pathogenesis of reactive hypoglycemia: one hand, an alteration of the alpha cells which results with a reduced response of glucagon to the hypoglycemia, on the other hand, a possible inappropriate secretion of GLP-1 in presence of low glycemic levels.

Miscellanea

Mechanical stimulation of the feet improves gait and increases cardiac vagal profile in Parkinson's disease

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Background: Alterations in sensorimotor central integration and/or peripheral sensory function might play a role in movement disorders in Parkinson's disease (PD). Body mechanical stimulations was recently found to improve gait in PD. In addition, alterations in cardiovascular autonomic control are common in PD, although their relationships with movement disorders have not been fully addressed.
Aims: We tested the hypothesis that bilateral plantar stimulation can improve gait and autonomic control of heart rate up to 24 h.
Methods: We studied 13 patients with idiopathic PD (mean age 66 $\pm$ 2 years, BMI 23 $\pm$ 1 kg/m^2, Hoehn-Yhar scale 2–4) on their habitual pharmacological treatment.
Every subject underwent mechanical pressure (0.8 kg/mm^2) at the big toe tip and at the big toe metatarsal joint (plantar stimulation, PL) on both feet.

Gait analysis and spectral analysis of heart rate variability provided quantitative indexes to assess movement disorders and cardiac autonomic profile (HF_{RR}, marker of cardiac vagal modulation) before and 24 h after plantar stimulation.
Results: Twenty-four hour after PL step mean length and gait velocity increased (23.3 ± 6.2 from 537.7 ± 40.8 mm and 0.06 ± 0.02 from 0.93 ± 0.09 m/sec, respectively) and clock-wise rotation time decreased (-1.8 ± 0.8 from 8.8 ± 1.2 s). In addition, HF_{RR} increased (1.2E−04 ± 2.7E−04 from 4.5E−04 ± 1.9E−04 ms^2) compared to baseline, suggesting an enhancement of the cardiac vagal modulation.
Conclusions: 24 h after plantar stimulation PD patients showed changes in step length, gait velocity and body rotation time consistent with an improvement of their movement disorder. Plantar stimulation induced a concomitant increase in the vagal modulatory activity of heart rate.

Dyskinetic syndrome in a patient with a family history of SMA

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We want to describe Dyskinetic syndrome in a patient with a family 'history of SMA
A female patient 60 years old came to our observation for widespread disease characterized by tremors, latent autoimmune thyroiditis with hypothyroidism, high blood pressure with partial compensation by therapy. During the anamnesis the patient showed emotional lability with frequent crying and during physical examination had intentional tremors with weakness in lower limbs. Presence of multi-nodular goitre palpable and visible has resulted. A brain MRI and a PET scan was performed in other hospital for suspected Parkinsonian syndrome. The first has revealed small-vessel lesions compatible with Hashimoto's encephalopathy. The second one did not give results worthy of note. We then prescribed an EMG and an ENG which showed an axonal damage of degenerative type. The subsequent history has shown the presence in the family, at least four generations of spinal muscular atrophy, but never was investigate like dominant pathology. Grandfather was affected, with early death (35 years of age) for unspecified myocardial disease: he had muscle atrophy in emisoma. Then male parents, sons and grandsons with muscle emisoma atrophy syndrome (that occurs after a febrile illness around the age of 15 years) were affected; all females of this family had autoimmune goiter, and this family had maternal grandmother's death from brain cancer. We made diagnosis of SMA. Genetic analyses are underway and we have advised the patient to practice continuous FKT as long as possible to maintain muscle activity.

Sub-acute beds in internal medicine wards: do they improve efficiency and reduce costs?

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In Italy, as in many other countries, the acute hospital sector accounts for a substantial share of expenditure on health care services, thus attempts to improve efficiency and reduce costs often begin in this sector.
In 2011, the Public Health Service of Lombardy Region reduced the number of acute beds, transforming part of them in sub-acute ones, intended for patients who still require some medical intervention, but below the level of an acute care institution, for a period no longer than 40 days. While acute beds are reimbursed by the DRG system, sub-acute beds are paid on a fixed per day reimbursement (1).
In our hospital, such an innovation consisted in transforming 10 beds (about 15 %) of the internal medicine ward in 10 sub-acute beds, activated in a contiguous area, still charged to internists, but with a reduced daily medical presence.
To be eligible for the sub-acute area, patients have to satisfy the following criteria: to be clinically stable, with a Modified Early Warning Score ≤ 2 (MEWS is a tool for bedside evaluation based on five physiological parameters: systolic blood pressure, pulse rate, respiratory rate, temperature and AVPU [Alert, Reacting to Voice, Reacting to Pain, Unresponsive]) (2); absence of Systemic Inflammatory Reaction Syndrome (SIRS criteria include body temperature, heart rate, respiratory rate, white blood cell count) (3); no need of invasive diagnostic procedures and/or continuous monitoring of infusion therapy; a Care Nursing Index ≥ 2 (CNI rates the needs of 10 functions [physiological and related to diagnostic/therapeutic procedures] according to a 4-point scale, from 1 = no need to 4 = completely dependent).
Here we present some preliminary data concerning the first 50 patients admitted to the sub-acute area in 2012, all coming from the acute ward, i.e. 10 % of discharged from this ward in the same period. Their median age was 81 years (range 47–101), with a little predominance of females (52 %). They had been admitted to hospital, through emergency, for pulmonary diseases (30 %), cardiovascular (22 %), gastro-intestinal (14 %), neurologic (10 %), and other causes (24 %). Their average length of stay (LOS) in the acute area had been 10.6 days (range 2–34).
At admission to the sub-acute area, their MEWS was 0 in 64 %, 1 in 16 %, 2 in 20 %; CNI was 2 in 24 %, 3 in 64 %, and 4 in 12 %. Their average LOS in the sub-acute area was 15.0 days (range 4–35). Thirty-one patients were discharged to home (22 % with home care assistance), 12 to a nursing home, long-term or hospice care facility. Five patients returned to the acute area, for unexpected complications (acute renal failure, stroke, gastrointestinal hemorrhage, pneumonia, worsening of a diabetic foot ulcer requiring surgery). Two patients died: one suddenly, during rehabilitation therapy; and one for hepatic failure, while waiting for admission to hospice.
In our experience, patients who can benefit from sub-acute beds are mainly older subjects, due to the presence of comorbidities and higher levels of disability, still requiring some medical intervention. Noteworthy, social issues, such as lack of appropriate housing and community care services, are not per se adequate reasons for admission of patients to sub-acute beds. This limitation, along with the strict clinical criteria cited above, can explain why the index of bed occupancy was only 64 %. Nevertheless, we observed a reduction in the average LOS in our acute ward from 11.4 days in the first trimester of 2011 to 10.5 days in the same period of 2012. A longer period of observation and more data are needed to evaluate if sub-acute beds are really able to reduce overall costs of hospitalization.

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When exams never end

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Here, we describe the case of a 72 years old man who came to our observation for a fever of unknown origin (FUO). The clinical history was not significant until 2006, when he was diagnosed with "chronic HCV-related hepatitis." In the same year, he had the first transient fever episode occurring after an antipneumococcical vaccine. Since then he has reported recurrent episodes of fever (initially 2–3 a month, then 5–6) preceded by shivering and lasting about 4–5 days with a maximum temperature of 40 °C, responsive to paracetamol. Fever was associated with systemic symptoms, including asthenia, arthralgias, myalgias and hyporexia resulting in weight loss. For these reasons the patient had been repeatedly hospitalized over the next 3 years in several internal medicine divisions, where he was subjected to various laboratory and instrumental tests. The haematological tests performed during the febrile episodes showed pancytopenia, elevation of inflammatory markers (ESR up to 109, CRP up to 13), mild reduction of folate, hypergammaglobulinemia, and hyperferritinemia. All tests performed to identify an infectious origin of fever, including mycoplasma, viruses, Toxoplasma, Rickettsia, Legionella, Borrelia, Bartonella, Leptospira and Leishmania, either in blood, urine, feces or bone marrow, were repeatedly negative. The search for monoclonal components (in serum and urine), autoantibodies, cryoglobulins, as well as the genetic analysis for hemochromatosis were negative. Similarly, serum procacitonin and tumor markers values felt within normal ranges. The HLA haplotype was the following: Class I: A1, A11, B35, B55, BW6, CW3, CW4, Class II: DR13, DRW52, DQ6, DQ7. The search for genetic mutations in the MEFV gene gave rise to negative results. TTE and TEE excluded the presence of cardiac valvular vegetations. Abdominal ultrasound showed no more than a liver with inhomogeneous echotexture and a total body CT showed only an enlarged prostate volume and the presence of left kidney stones. Furthermore, both full body scintigraphy and endoscopic examinations did not show any alterations worthy of note. During the period of observation, the patient was subjected to different biopsies: at the level of temporal artery, where no histological alteration typical of giant cell arteritis was found; of bone-marrow, showing only mild erythrocytosis, and of the liver which confirmed a chronic HCV-related hepatitis grade 1 and stage 2.

Since clinical conditions of the patient were getting worse an "ex juvantibus" treatment with colchicine (1 cp bid) was begun. Following this therapy, it was reported a marked reduction of febrile episodes: two episodes after 1 month of therapy, the second with a duration of 2 days with a temperature of 38.5 °C; two episodes in the second month; no episode in the third month; one episode in the fourth and fifth month, no later episodes except for one episode with a temperature of 37.8 °C after the patient had discontinued colchicine on his own for a day. Currently, the patient is taking 1 cp bid colchicine, a well tolerated dosage with the exception of few episodes of diarrhea, and his clinical conditions have improved considerably, with an increase in body weight.

The Familial Mediterranean Fever is a recessive disorder characterized by recurrent and brief episodes of fever and inflammation of the serosa with the subsequent development of amyloidosis. The only gene known to be associated is MEFV, which consists of 10 exons, located on chromosome 16, encoding a protein expressed in mature neutrophils during the activation phase. It controls inflammation by acting as a negative regulator. However, genetic test does not identify all the relevant mutations. This case demonstrates once again, the importance of clinical judgment and the opportunity for a therapeutic approach to confirm the suspected diagnosis.

Error and prejudice: how many errors are present in the most authoritative medical journals?

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Background: The editorial and peer review processes should guarantee readers about the reliability of published data. The first step of these processes is to check for errors.

Aim of our study was to look for the presence of objective errors in consecutive articles published by three of the most authoritative clinical journals.

Methods: Two reviewers evaluated the presence of any error in 200 consecutive original articles containing at least two tables, allowing a reanalysis of the data, published between October 2010 and April 2011. Error was considered any action different from what was planned. Errors were listed as methodological, numerical and slips. They were considered as severe if numbers in the abstract were completely different from numbers reported in the full text.

Results: Among the 125 articles included in the study, 102 (82 %, 95 % CI 74–88 %) contained some kind of errors, even multiple. Nine articles (7 %, 95 % CI 3–13 %) contained one slip, 92 articles (74 %, 95 % CI 65–81 %) contained at least one numerical error, and 22 articles (18 %, 95 % CI 11–25 %) contained one methodological error. Five articles (4 %, 95 % CI 1–9 %) contained one serious error. None of the errors retrieved (0 %, 95 % CI 0–2 %) would have changed the results of the studies.

Conclusion: Most of the articles published in the most important medical journals present mistakes. Our results could be a clue of the editorial and peer review systems system weakness. A debate within the scientific medical community about these systems and a possible alternative adjustments is needed.

Circulating BDNF levels in elderly patients with Depression, Alzheimer Disease (AD), comorbid AD and depression and in healthy age-matched and young subjects

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Introduction: Recent preclinical and clinical findings have suggested that neurotrophins, and in particular Brain Derived Neurotrophic Factor (BDNF), could be involved in some aspects characterizing the pathogenesis of neurodegenerative diseases and major depression. In fact, BDNF has a pivotal role in regulating neuronal function and affects neuronal outgrowth, synaptic connectivity and neuronal repair. Alzheimer's Disease (AD) is characterized by cognitive decline and loss of neurons in specific brain regions. Evidence in the literature suggests that neuronal degeneration begins 20 years before the onset

of the first clinical symptoms. The early identification of the process through specifical biomarker or imaging studies is a specific target of the research. Depression is an affective disorder that has a complex relationship with AD: it may affect individuals with AD with high incidence, preceding the onset of the dementia and masking its symptoms (pseudodepression). Moreover, geriatric depression is an independent risk factor for the development of AD.

It is well known that BDNF is present outside the central nervous system (CNS) and circulates systemically but the role of serum BDNF in the pathological (psychiatric and degenerative) conditions of aging is still matter of debate.

The aim of this study was to evaluate the circulating BDNF levels in healthy (elderly and young) subjects and in elderly patients with depression, AD and comorbid diseases (depression and AD).

Methods: We enrolled 18 patients with AD (group A. males/females, M/F = 2/16, mean ± standard deviation, m ± SD 86.4 ± 6.2 years), 17 patients with comorbid AD and depression (group B, M/F = 5/12, 79.4 ± 5.4 years), 17 patients with depression (group C, M/F = 5/12, 76.6 ± 7.9 years), 18 elderly (group D, M/F = 14/4, 80.1 ± 4.3 years) and 18 young (group E, M/F = 9/9, 27.4 ± 4.5 years) healthy subjects. Patients taking antidepressant or colinesterase inhibitors treatment were excluded. Diagnosis of probable AD was carried out using the NINCDS-ADRDA criteria and the diagnosis of geriatric depression was carried out using the DSM-IV criteria. Cognitive functions were evaluated using Mini Mental State Examination (MMSE). The severity of geriatric depression was evaluated using Geriatric Depression Scale (GDS) or Cornell Scale for Depression in AD patients with severe cognitive impairment (MMSE $\leq$ 20). Serum BDNF levels were determined using the enzyme-linked immunosorbent assay (ELISA) method.

Statistical analysis was performed by one-way analysis of variance (ANOVA) between groups. The relationship between the neuropsychological scores and BDNF was evaluated by the means of Spearman's rank correlation. A $p < 0.05$ was considered as significant.

Results: The MMSE scores were 11.3 ± 9.3 (m ± SD) in group A, 18.2 ± 6.2 in group B, 25.5 ± 3.2 in group C, 28.3 ± 1.2 in group D and 30 ± 0 in group E ($p < 0.001$).

The GDS scores were 4.2 ± 1.5 (m ± SD) in group A, 9.3 ± 1.7 in group B, 8.6 ± 2.6 in group C, 1.4 ± 1.2 in group D ($p < 0.001$).

The serum BDNF levels were 10.1 ± 2.5 (m ± SD) in group A, 11.7 ± 2.6 in group B, 12.0 ± 3.3 in group C, compared to the BDNF levels of 13.7 ± 3.7 and 14.0 ± 2.9 ng/ml in group D and E, respectively ($F = 4.94$, $p < 0.01$).

The circulating BDNF levels were significantly related to age ($p < 0.025$) and neuropsychological scores (MMSE) ($p < 0.01$).

Conclusion: The results of this study suggests that BDNF is involved in the pathophysiology of cognitive decline and AD in elderly subjects. Our data confirmed that BDNF is a promising candidate as a biological marker for the evaluation of the neuropsychiatric disorders in aging.

Giant bladder stone

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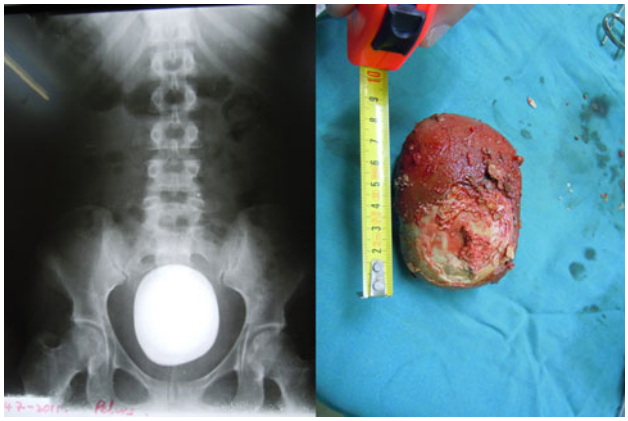
A 31-year-old woman was hospitalized in a Kenyan Mission Hospital after suffering from lower abdominal pains for 2 weeks. She had suffering from recurrent lower urinary tract infections, hematuria, dysuria, pollakiuria and urgency for nearly 15 years. She had undergone cesarean section 18 years before. Physical examination revealed suprapubic tenderness. Hemogram showed mild leukocytosis; blood urea nitrogen and serum creatinine levels were normal. Urine analysis showed pyuria and microscopic hematuria. Urine colture was not available. The ultrasonographic examination showed, in the pelvis, a hyperechoic wall with an acoustic shadow, not distinguishable from the bladder wall. There was no hydronephrosis. Abdominal plain radiography revealed a huge elliptical calcified mass in the pelvis. The patient underwent open cystotomy with removal of a giant stone adherent to the bladder wall. The stone weighed 350 g and measured 8.5 × 5.5 × 4.5 cm. The break section revealed a central core and a progressively increased stratified lamellar structure. Postoperative period was uneventful and the patient was discharged without symptoms.



Diagnostic role of ultrasonography and contrast enhanced ultrasonography

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A 64-year-old woman was admitted to our department because of abdominal pain and nausea. The patient had no previous history of relevant diseases. On physical examination, blood pressure, pulse rate and remnant vital parameters were normal as well as the cardiac and respiratory examination. The abdomen was distended without tenderness suggesting the presence of ascites. Laboratory tests revealed increased serum creatinine (1.3 mg/dl), and elevated tumor markers: CA 19-9 1131 UI/ml, CA 125 432 UI/ml. Abdominal ultrasonography (US) confirmed the presence of ascites and showed marked thickness of the gastric wall with the typical target pattern defined "pseudokidney", lymph-node enlargement nearby the pancreas and aorta, and bilateral hydronephrosis. Liver texture was homogeneous and portal venous flow resulted normal at color-doppler evaluation. US examination was extended to the lower abdomen and a 6 × 2.5 cm in homogeneously hyperechoic mass with irregular borders was detected in the right adnexal region. A primary or metastatic ovarian cancer was suspected. Contrast-enhanced ultrasonography (CEUS) was then performed to better define the vascularisation of both the adnexal lesion and gastric wall. An 8 microliters/ml solution of sulfur hexafluoride microbubbles stabilized by a phospholipids shell (SonoVue, Bracco, Milan, Italy) was used as US contrast agent. After an i.v. bolus of 2.4 mL of Sonovue, CEUS examination showed contrast enhancement of both the gastric wall and ovarian mass in the arterial phase, followed by wash-out in the late venous phase, that is the typical CEUS behavior of malignant lesions of the liver and other abdominal organs. Based on

both US and CEUS findings, the diagnosis of gastric cancer with right adnexal metastasis (Krukenberg syndrome) was inferred, and the patient underwent US-guided paracentesis for cytological examination and esophagogastroduodenoscopy (EGDS). Cytologic examination of the peritoneal fluid documented the presence of signet-ring cells, and EGDS showed stiffness and thickening of the gastric mucosal folds with mosaic pattern and multiple nodular lesions suggestive of linitis plastica. Endoscopic biopsy revealed poorly differentiated primary gastric mucus-producing adenocarcinoma with signet-ring cells. Thoracoabdominal computed tomography (CT) was performed to better assess tumor extension, but it did not yield any additional information and the final diagnosis was Krukenberg tumor originating from a gastric cancer. Surgery was not considered due to the advanced stage of the primary tumor and bilateral internal ureteral stents were placed.

To the best of our knowledge, this is the first case of Krukenberg syndrome inferred on the basis of US and CEUS findings. US identified both the pathological thickening of the gastric wall and the ovarian mass, and CEUS played a key role in depicting a vascular pattern strongly suggestive of malignancy in both lesions, promptly addressing the further diagnostic work-up. Although transvaginal US is undoubtedly the method of choice to evaluate ovarian tumors, transabdominal US allows to extent the examination throughout the abdomen to search for primary tumors in other organs, and CEUS enables to depict the vascular pattern of the lesions. If confirmed by further reports, such capabilities could play some useful role in the diagnostic workup of adnexal masses.

Association between high sensitivity C-reactive protein, heart rate variability and corrected QT interval in patients with chronic inflammatory arthritis

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Objective: The risk of sudden cardiac death is increased in chronic inflammatory arthritis, particularly rheumatoid arthritis (RA). To evaluate the putative effect of systemic inflammation on heart rate variability (HRV) and ventricular repolarization in chronic inflammatory arthritis, we analyzed in these patients the possible relationship among HRV parameters, QT interval, and high sensitivity C-reactive protein (hsCRP).

Methods: One hundred-one patients with chronic inflammatory arthritis underwent a 15-min ambulatory twelve-channel electrocardiogram-recording, to evaluate HRV and QT interval, as well as a venous withdrawal for hsCRP as an estimation of ongoing systemic inflammation.

Results: In patients with chronic inflammatory arthritis, hsCRP is inversely correlated with HRV and directly with QTc duration, but while hsCRP is associated with HRV independently from any other investigated factor, the association between hsCRP and QTc seems to be an indirect consequence of the autonomic dysfunction itself. Within the whole cohort of patients, those subjects having elevated hsCRP levels displayed both a significant reduction in HRV and a prolongation of QTc with respect to patients with a normal hsCRP value. A similar, although less marked, degree of HRV depression and QTc prolongation was found in RA patients when compared to subjects with spondyloarthritis (SpA) and healthy controls.

Conclusion: These data provide evidence of a link between systemic inflammation and the arrhythmic risk in patients with chronic inflammatory arthritis, also putatively explaining, at least in part, how the different inflammatory load characterizing RA and SpA parallels the different risk of cardiovascular death in these two conditions.

Role of bedside ultrasonography: our experience in an internal medicine ward

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Introduction: Bedside ultrasound scanning is increasingly recognized by Internal Medicine specialists as a valid alternative to ambulatorial ultrasound. Clinicians have often referred to ultrasound technology as the "stethoscope of the future" and now the day has arrived. We describe our experience of elective and emergency bedside ultrasound scanning.

Aim: To assess the utility of bedside scanning today, in the light of the state-of-the-art technologies available, and of the greater incidence of disabilities, comorbidities and severe illness in patients admitted to the Internal Medicine ward.

Materials and Methods: We reviewed all patients admitted between 01 July 2011 and 30 April 2012 to the Internal medicine Operative Unit "C.Frugoni": among 735 patients, 511 needed ultrasound scanning. Of these, 146 (100 F, 46 M, aged between 21 and 101 years, mean age 76) underwent bedside scanning, using a portable Esaote My lab 25 gold, equipped with 2 linear LA 523 variable frequency (4–13 MHz) probes, and a CA 631 variable frequency (1–8 MHz) convex probe.

Results: Bedside US scanning was done in both an elective and an emergency setting, the former for patients defined as "non transportable" to our US Unit. In the emergency setting, it was performed at the clinician's discretion to confirm diagnostic suspicions, or when organizational or staff problems would have prevented completion of the diagnostic workup. Finally, the patients category that benefited from bedside US for elective or emergency invasive diagnostic-therapeutic procedures was defined. When possible, US scanning was later repeated at the US Unit, to confirm the bedside US diagnosis.

Conclusions: Bedside US scanning is now a valid, timely, low cost method with a high diagnostic value in an Internal medicine Department, that is often performed as an alternative to ambulatorial US, as dictated by the circumstances.

Successful multimodal analgesic treatment of moderate-severe pain in 33 patients affected by Scleroderma ischemic skin ulcers

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Freedom from pain is a substantial element of quality of life. Competent and adequate relief of pain in all stages of life is a basic

characteristic of a humane medicine oriented to the quality and meaning of life for people. Chronic vascular ulcers are often painful and they result in a poor quality of life, interference with sleep and daily activities. Scleroderma ischemic skin ulcers are among the most painful vascular ulcers and as all ischemic ulcers are usually difficult to treat for the severe associated pain. Treating pain improves the patients' life's quality but is also essential in the healing's process. Multimodal analgesia is based upon the use of multiple analgesic drug classes or techniques to target different points in the neurological pathways relevant to pain perception. We proposed a treatment with analgesic drugs commonly used World Health Organization's Pain Ladd (WHO Scale) in clinical setting but using a specifical algorithm based on the available data of multimodal analgesic treatment with good response on quality of life and sleep, no toxicity and good compliance. The perception of the pain remains completely subjective and can be only measured by asking the patient. Therefore, a few validated instruments have been developed ranging from the simple intensity rating scales up to sophisticated questionnaires. Thirty-three patients with Systemic Sclerosis (SSc) and painful ischemic skin ulcers, lasting from at least 6 weeks, admitted to the Unit from December 2009 to September 2011 were treated for 4 weeks. At admission, they presented decrease assessment of sleep and visual analogue scale (VAS) ranged from 65–95 % (Moderate severe pain) despite assumption and alarming abuse of non steroidal anti-inflammatory drugs. The Thirty-three patients were treated in the following way: -during the first 3 days Tramadol/paracetamol 37.5 mg/325 mg were administrated two times a day, 1 tablet at the 8 in the morning (am) and 1 tablet at the 8 in the evening(pm); pregabalin 50 mg 1 tablet at 8 pm and Citalopram 8 mg (4 gtt) at 7 pm;-from the fourth day Tramadolo/paracetamolo 37.5 mg/325 mg were administrated three times a day (8 am;2 pm;8 pm); Citalopram 8 mg (4 gtt) at 7 pm; pregabalin 50 mg 1 tablet two times a day at the 8 am and at the 8 pm.

Values of the Visual Analogue Scale (VAS) for the assessment of pain during the day and the night at the baseline and at the end of the first week and at the end of the fourth week were expressed as mean and standard deviation and were compared using Friedman's test followed by Wilcoxon's matched pair test; Change in sleep pattern (increased, not changed or decreased) at baseline at the end of the first week and at the end of the fourth week were compared using the Fisher' exact test. All total mean VAS scores for pain improved and significantly decreased at the end of the first week of therapy ($P < 0.05$). All patients keeped showing significantly improvement and restoring the sleep at the end of the first week of therapy and at the end of the fourth follow up week also if ulcers didn't heal yet. No adverse event was reported.

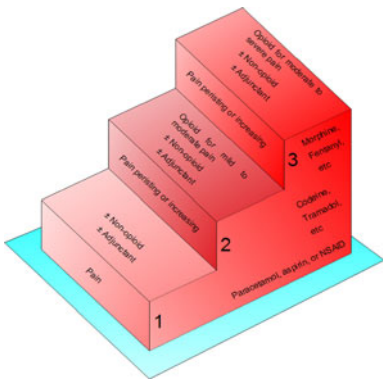

Fig. 1 Pain ladder

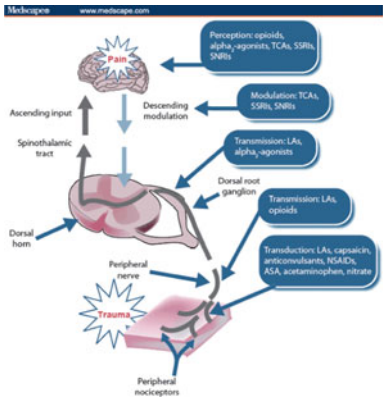

Fig. 2 Multimodal Analgesia

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A case of emphysematous pyelonephritis successfully treated with antibiotics alone in a diabetic man

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Introduction: Emphysematous pyelonephritis (EP) is a rare and life-threatening infection involving renal parenchyma, collecting tubes and pararenal tissue, due to gas-forming bacteria. Most of patients present an unilateral form, while that bilateral is very infrequent. Mortality rate is high, as can rise 70 % of cases, especially in bilateral forms. The most common pathogen is Escherichia Coli, and diabetes mellitus is the main risk factor. Surgical treatment is currently advocated as the treatment of choice in most of the patients. Anyhow nephrectomy, surgical drainage and antibiotic treatment are bases of the treatment. Cases treated with antibiotics alone are rare.

Aim: We describe a case of EP in a male sixty-one diabetic patient successfully treated with antibiotic therapy alone.

Description of the case: the patient came to our emergency department for a syncope complicated with craniofacial trauma, ocular trauma, and right lower limb fractures interesting malleolus and fibula. He presented a status of septic shock, hyperglycaemia, severe renal failure (GRF: 27 ml/min), jaundice, increase of neutrophil and platelet depletion. Abdominal CT-scan showed a collecting of gas in

the left renal pelvis and parenchyma, and perirenal tissue edema. It showed also gallbladder empyema. Aggressive antibiotic therapy, inotropic support and fluid-electrolyte replacement were immediately began. The course of the illness was complicated by atrial fibrillation, paralytic ileus and anasarcatic status. Moreover ocular trauma evaluation evidenced choroidal detachment for which was indicated cryo therapy. Nevertheless, in the course of the following days, the patient experienced a slow but sensitive clinical improvement, with channeling alvus, correction of the hypoalbuminemia and electrolyte disorders, regression of the anasarca. We are not able to find anatomic predisposing causes of the urinary infection (urolitiasis, or neoplasia). Three weeks later, the patient was discharged in good status, with the recommendation to return for correcting damage of the ciliary body and the removal of the leg cast.

Discussion and Conclusion: In EP, clinical indicators of poor prognosis include development of acute renal failure and thrombocytopenia. Both of these were present in this case. Most of patients with EP are diabetics, and unilateral form is much more frequent (>90 %). Our patient is diabetic, and presented an unilateral form. But in the most of cases EP is cured with a combined approach consisting on surgery and antibiotic therapy. In our case, the patient was successfully cured with antibiotics alone. This eventuality is rarely described in literature. The choice of do not perform drainage or nephrectomy was justify with absence of obstructive uropathy and the prompt improvement of clinical status after beginning of antibiotics: an immediate surgical option would be considered if the antibiotic treatment failed.

Possible role of ambulatory blood pressure monitoring in obstructive sleep apnea syndrome

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Background: Obstructive Sleep Apnea (OSA) is a common disorder affecting 5 to 25 % of men and women worldwide, a prevalence reported to be equivalent to that of diabetes. This syndrome is more frequent in carrier of nasal congestion, rhinitis, chronic sinusitis, nasopharyngeal and craniofacial anatomic abnormalities such as micrognathia and retrognathia. However the carriers of sleep apnea present excessive daytime somnolence, insomnia and parasomnia and his bed partners often describe breathing cessation rather than obstructed breathing. The patients are aware of snore and, especially when they sleep supine, they complain of choking and dyspnea. OSA is defined as an apnea-hypopnea index (AHI: namely the average number of apneic and hypopneic events per hour of sleep that represent the most common metric for assessment of the severity of OSA) of at least five episodes lasting 10 s or more per hour of sleep, and 1 in 15 adults had OSA of a more severe degree with an AHI of 30 or more. This is characterized by repetitive upper airway obstruction during sleep, resulting in profound effects on cardiovascular function with a poor quality of life. Epidemiologic studies show that OSA is an important risk factor for the development of cardiovascular diseases especially systemic hypertension. The exact mechanisms for this association are incompletely understood: increased sympathetic activity, endothelial dysfunction, inflammation, and disorder of metabolism seem to play an important role. Supporting of this OSA is strongly associated with obesity, increased insulin resistance, high levels of leptin, and finally metabolic syndrome which promote cardiovascular risk via multiple pathways. Very strong is the association with the resistant hypertension, but the magnitude of this phenomenon and its independence of confounding have not been yet established. Whatever in the United States and in West Countries OSA seems to be the most common cause of reversible hypertension; however this is infrequently diagnosed because most people with OSA do not undergo polysomnography which is the current gold standard test for the diagnosis of sleep-disordered breathing. Unluckily to obtain polysomnography in the large number of patients with cardiovascular disease who probably have OSA, it is necessary to consider the high costs, the trouble to access to specialized sleep laboratory and its poor spread. At present ongoing discussions continue among the expert organizations with the aim to determine the appropriate characteristics of the ideal screening and diagnostic modalities for OSA.

Objective: Our aim is to check a possible role, for a primary screening in hypertensive patients with resistant hypertension or suspected to have a sleep apnea, of the ambulatory blood pressure monitoring (ABPM) for the dynamic control of blood pressure during the waking and asleep, combined with pulse oximetry, a method used to determine the O_2 saturation (SaO_2) and desaturation of blood in a continuous noninvasive fashion, through the noninvasive assessment of arterial hemoglobin-bound O_2 saturation.

Materials and Methods: We have examined 10 ambulatory patients, seven men and three women, aged between 55 and 70, affected by essential hypertension apparently drug resistant or poorly responder, with distinctive characters of metabolic syndrome (and particularly android obesity, body mass index (BMI) greater than 28, impaired glucose tolerance or diabetes and dyslipidemia), and anamnestic suspicion of possible sleep apnea syndrome. Each of them has been submitted to pulse oximetry and ABPM.

Results: In all our patients many serious episodes of desaturation were recorded during the sleep; however the ABPM revealed high mean values of systolic and diastolic blood pressure, nondipping BP during the sleep and accentuated morning surge of BP, finally high nocturnal variability of the heart rate.

Discussion and Conclusions: The true prevalence of OSA in the population is unknown because few patients undergo to polysomnography and therefore the syndrome is undiagnosed. High prevalence of the association with both several cardiovascular diseases (i.e. hypertension, coronary artery disease, heart failure with systolic dysfunction, acute stroke, atrial fibrillation etc.) and metabolic syndrome, dyslipidemia etc. grant to OSA a role of an important problem of public health. Polysomnography is the current gold standard test for the diagnosis of OSA, but it is expensive and still unlikely applicable on a large scale. Therefore in selected patients, as preliminary screening, the ABPM and pulse oximetry can give interesting report for the purpose of identify the eligible patients for polysomnography in the sleep laboratory, which can be undergone subsequently to PAP the current first-line therapy for OSA. It lowers the AHI, decreases oxygen desaturation, improves sleep efficiency relieving nocturnal hypoxemia; decreases however sympathetic activity, and during sleep and daytime, especially in patients with hypertension drug resistant. Besides the benefit coming from PAP therapy could be found in patients with coronary disease or heart failure and at high risk for stroke and sudden death, large randomized controlled trials, at present, not have demonstrated whether it will reduce cardiovascular events or mortality. Nevertheless the improvement of the cognitive functions, in its turn, decreases the risk of motor vehicle accidents and usually improves the quality of life particularly in the patients undergone to systematic cognitive behavioral and educational strategies, as well as strategies that address the specific issues of individual patients.

SPA balneotherapy of chronic venous insufficiency of the inferior limbs

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The Chronic Venous Insufficiency (CVI) of inferior limbs is a widespread disease, with an increasing incidence as a consequence of longer life expectance, life-style, obesity, smoking, use of drugs as oestrogens and progestins and working conditions.
Medical therapy, as bioflavonoids, tri-idrossimetilrutoside, troxerutine, diosmine, minor antithrombotics, is still lacking for evidence of efficacy, and compression therapy is useful only in preventing a worsening of this condition. Surgical treatment is the only radical therapy effective for the advanced phases of the disease. In this context spa balneotherapy can be considered as a possible chance to improve some subjective and objective symptoms of CVI of inferior limbs, and to prevent worsening of this condition.
It has been performed a review of the relevant scientific literature concerning the treatment of CVI of inferior limbs with mineral water balneotherapy, in order to evaluate its effects on objective and subjective symptoms and its effectiveness to prevent further worsening. We searched the PubMed, Medline, Cochrane Library, Embase, Web of Science databases for articles published between 1990 and 2011 on this topic with any of the following key words: *balneotherapy and vascular diseases, venous disease, spa therapy, mineral waters*.
We found few studies belonging to the criteria of controlled clinical trials and many others performed as case–control ones; patients affected from CVI of inferior limbs were treated with balneotherapy at health spas with sulphureous, sulphate, salsojodic or salsobromojodic mineral waters. Baths in mineral waters were often associated with idromassotherapy and vascular pathway. Effects of spa balneotherapy are related to some aspecific properties, like hydrostatic pressure, osmotic pressure and water temperature, partly related with specific chemical-physical characteristics of the adopted mineral water (the anion and cation content, the presence of undissociated salts and oligoelements, the electric conductivity).
The controlled clinical studies on spa therapy showed significant improvement of subjective (such as itch, paresthesias, pain, heaviness) and objective symptoms (namely edema and skin discromias).These studies suggest that spa balneotherapy may give a good chance of secondary prevention and effective therapy of CVI of inferior limbs, but also that it needs of other clinical controlled trials.

The new skills of the Internist in the perioperative care of surgical patient

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Centro Chirurgico Toscano is a private surgical centre that in the last few years has significantly increased the activities that are oriented toward Orthopaedic Surgery and Urological Surgery but the entire Surgical Field.
The numbers of orthopaedic surgical procedures has increased from 732 in 2009 to 914 in 2011, with parallel increased of prosthetic surgical procedures from 245 to 386 also Urological interventions have increased from 315 in 2009 to 456 in 2011.
The projections of the first quarter of 2012 predicts of an increase in this tendency.
Consequently there appears to be an increase of the medium age of the patients that are exposed to major surgical procedures that often requires the necessity of a competent Internist to manage these problems.
Because of the above, Centro Chirurgico Toscano has adopted a model of managements which require the following:
The modification of the inpatient areas according to the depth of intensive of care related to the complexity of the surgical procedure
A total 24 h presence of a Physician (Hospitalist) who specialized as an Internist who must complement the activities of the Surgeon, Anaesthesiologist and Cardiologist in managing the perioperative care of these patients.
We maintain that Internal Medicine, according to the virtues of specific methods and contents, will undertake the pre and post-operative care of the surgical patients allowing the Surgeon to concentrate his skills in undergoing the present operative procedure.
Therefore the new managerial role of the Internist implies integrating the anaesthesiologist capacity and by training to integrate his professional skills because, in an Hospital organized by Intensive of care, the Internist should prepare the Patient to the surgical procedure, manage the post-operative care of the patient and subsequently follow the patient until their discharge from the Hospital.

Effects of general anesthesia on non linear indexes of HRV during abdominal surgery

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The Heart Rate Variability(HRV) signal contains mass information, which concerns the cardiovascular nervous system and the analysis of the HRV signal is one of the key techniques for the clinical studying and diagnosing the cardiovascular diseases. Newer HRV measures are model independent, suitable for nonlinear processes, and measure aspects of HRV different from the traditional methods.
The aim of this study was to evaluate the effects of deep general anesthesia on the HRV using non linear analysis in patients undergone to abdominal surgery.
Materials and Methods: We studied 7 subjects of both sexes (5 women) with a mean age of 54.4 $\pm$ 5.8 years with digestive diseases. None of the patients used drugs or was suffering from cardiovascular or metabolic disease.
The patient was anesthetized after endotracheal intubation. The recording was performed before anesthesia induction and after 5 min after the start of maintenance. The third measurement was performed at 24 h after surgery. ECG signal recording, lasting 5 min each, were made using a digital ECG with dedicated software (Xai-Medica) for PC storage and off-line analysis (Kubios HRV).
Nonlinear Methods: Poincarè Plots: Two-dimensional vector analysis was used to quantify the shape of the plots. In this quantitative method, short-term (SD1) and long-term R-R interval variability (SD2) and the ellipse area of the plot are separately quantified. The Detrended fluctuation analysis (DFA) was used to quantify the fractal scaling properties of short- and intermediate-term R-R interval time series. The

HR correlations were defined separately for short-term (<11 beats, α1) and longer-term (>11 beats, α2) R-R interval data. Thus, fractal analysis can be considered as an improvement of spectral analysis, without any interference of environmental and physiological changes, such as respiration and physical activity. Finally we analyzed the ApproximativeEntropy (ApEn) that is another nonlinear method for to quantify the amount of complexity in the time series data. Lower ApEn values indicate a more regular (less complex) signal; higher values indicate more irregularity (greater complexity)

		Basal	Anesthesia	24 h
LF/HF		5.3 ± 1.4	2.1 ± 0.9*	3.6 ± 1.2
SD1	ms	10.17 ± 1.5	3.69 ± 1.4*	10.4 ± 1.4
SD2	ms	59.27 ± 18.8	54.54 ± 14.3	45.93 ± 8.3
α1		1.409 ± 0.07	1.091 ± 0.19	1.284 ± 0.11
α2		1.157 ± 0.11	1.476 ± 0.07*	1.087 ± 0.07
ApEn		0.991 ± 0.09	0.489 ± 0.08*	1.021 ± 0.07

Statistics: One way anova. A p value of 0.05 has been considered significant. Data are expressed as mean ± ESM.
Results: Our data indicate, during deep anesthesia, a significant reduction of LF/HF ratio, and SD1 index of the Poincarè plots. Also the α2 index of DFA shows a significant reduction.
The Entropy expressed as Approximative Entropy shows a significant reduction of the signal complexity.
Because it has been suggested that the sympathetic modulation on the HRV is reduced by deep anesthesia, maybe the same results is possible to see using nonlinear methods.
The novel methods assessing heart rate dynamics have shown new insights into the abnormalities in heart rate behaviour in various pathological conditions, providing additional prognostic information when compared with traditional HRV measures. but more clinical studies by using new and traditional methods of HRV will be needed before the clinical applicability of these methods can be definitively established.

Migrain with aura: is there a new role for ASA?

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Aim: Our study aims assessing efficacy and tolerability of Acetylsalicylic acid (ASA) in migraine with aura (MA) management, in a sample afferent to the Headache Centre of San Giovanni Battista University-Hospital of Torino.
Materials and Methods: To this purpose, we analyzed the medical records of 1946 patients, consecutively offering to our Centre in the period 1995–2007 and receiving a prophylactic treatment, divided in two groups: those who received ASA (90) and those who were treated with other therapies (106). Primary endpoint was to evaluate the improvement in MA crisis frequency in the two groups. A binary logistic regression model was used to identify possible factors associated with the positive response to treatment.
Results: The mean age was 32.1 (±9.9) in ASA group and 36.8 (±14.9) in no-ASA group. Positive response to treatment (measured as a reduction of at least the 50 % of crisis with aura) was reported by 85.6 % of patients in the ASA group and 51.9 % in the control group ($p < 0.001$). Multivariate analysis showed, as only variable related with a positive response to treatment, the group (ASA Group: OR 6.26, $p = 0.006$), while there were no relationships with gender, age or typology of aura.
Discussion: In the past, other studies compared the effectiveness of ASA in migraine versus other prophylactic therapies, but they often considered very small samples, mixing MA and migraine without aura together. In those setting ASA appeared to be mildly effective. Our results show a large positive response to the treatment with Acetylsalicylic acid, whose probability of success was about six times greater than the one associated with other therapies.
Conclusions: According to our results, ASA is not only effective in the majority of MA cases, but the response is usually evident in a short time. A double blind study with a larger sample is needed to ascertain these findings.

Ghanaian rural patients: not only malaria

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We report our medical experience which took place in a clinic for outpatients called Baobab Medical Center in a rural area in the middle of the Central Region in Ghana, where two of us spent 3 weeks during a trainee for the school of Internal Medicine.
We visited 619 patients aging between 5 months and 96 years in a period of 3 weeks from 22nd May and 12th June 2011. We made diagnosis of malaria in 38 % of patients, followed by diabetes (about 7 %) and blood hypertension (8 %). The rest of the patients admitted were affected by impetigo (7 %), gastroenteritis (5 %), bronchitis (4 %), urinary tract infection (3 %), and arthritis (3 %). Moreover, we diagnosed some cases of sickle cell disease, scabies, severe anaemia, arthritis and conjunctivitis, tuberculosis and heart failure.
The aim of our observational study was to collect data about the vascular and neurological complications in diabetic patients of lower socio-economic conditions. The majority of our 41 diabetic patients was female (68 %), aged 43–89 years. Diabetes mellitus type 2 (DM2) was a known diagnosis only in a small percentage of them; moreover rate of hypertension was high among our DM2 patients.
In addition to a complete physical examination, special attention was given to relevant aspects such as weight, blood pressure, peripheral pulses and neuropathy. We evaluated the prevalence of peripheral vascular disease (PAD) calculating the Ankle Brachial Pressure Index (ABI), that is the ratio between the highest ankle and brachial artery pressure; this measure can be used to predict the severity of PAD. An $ABI < 0.8$ indicates the presence of PAD and is a predictor of the risk to develop arterial ulcers; ABI between 0.9 and 1.2 is normal (that is free from significant PAD) while $ABI > 1.3$ suggests incompressible vessels usually associated to venous ulcers. An abnormal ABI may reflect the burden of atherosclerosis.
At neurological evaluation we focused on symptoms and signs characteristic of the distal symmetric polyneuropathy commonly associated to DM, such as burning sensation and numbness usually confined to the feet and lower legs and sensory loss in the distal parts of the lower extremities together with muscular weakness and the reduction of tendon reflexes.

Results: the ABI was <0.8 in 43 % of the patients, it was normal in about 47 % and >1.3 in 10 %. Thirty of patients complained symptoms like numbness and burning sensation in the distal part of the legs and about the same percentage manifests reduction of superficial sensitive modalities and tendon reflexes and muscular weakness in arms and legs at neurological evaluation.
Our data collected in a Ghanaian rural population can be added to those previously observed in a study involving Ghanaian patients recruited in an urban area in order to point out the high prevalence of DM type II. The lower socio-economical conditions of our patient can be considered a specific risk factor for DM II. The ABI is a simple but useful and affordable instrument to evaluate the presence of PAD even in conditions of lack of technology.
Based on these results we introduced aspirin in patients with ABI < 0.8 and pregabalin 75 mg twice a day in those with neurological complications and tried to obtain best results on anti diabetic therapy optimizing the dosage of the only available drugs (metformin and glibenclamide).

Asyntomatic male with an elevated alkaline phosphatase: Paget's disease of bone unrecognized case

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Here is reported a case of asymptomatic patient who presented elevation of serum alkaline phosphatase during routine medical checkup. He is otherwise in good health and denies any history of hepatobiliary disease. The patient notes that he has been experiencing pain in both legs of the past few months. The pain is throbbing and persists for a few hours, and then subsides.
Relevant laboratory values include the following:

	Patient's value	Normal Range
Serum phosphate	3.2	2.7–4.5 mg/dL
Serum alkaline phosphatase	162	40–120 UI/L
Serum alkaline phosphatase isoenzyme Liver	23.1	% 17.0–72.0
Serum alkaline phosphatase isoenzyme Bone	76.8	20.0–75.0
Serum alkaline phosphatase isoenzyme Biliary	3.7	1.0–11.0
Serum alkaline phosphatase isoenzyme Bowel (1-2-3)	0.0	The total of three < 14 %
Serum Ca	9.69	8.40–10.20 mg/dL
Pyridinoline (PYD-urine)	68.1	20–52 pMol/CREur
Deoxypyridinoline (DPD-urine)	12.1	5–11 pMol/CREur
Hydroxyproline (urine)	42.6	12.30–31.00 mg/g Crea.ur

The X-ray of the pathological bone showed irregular cortical and trabecular thickening. Whole- body bone scintigraphy using ^{99}Tc-labeled methylene diphosphonate was performed, is noted scattered points of increased uptake along sacro, coccygeal, left sacro-iliac joint, ischium, left whirlbone. In this case relevant laboratory findings are alkaline phosphatase levels and urinary excretion of free deoxypyridinoline (free D-Pyr), pyridinoline and hydroxyproline significantly increased. As result of this approach the most likely diagnosis is Paget's disease of bone. Paget's disease of bone is the paradigm of bone focal distortion with accelerated bone turnover. The woven pagetic bone in patients with Paget's disease is characterized by an impaired degree of β-isomerization of C-telopeptides of type I collagen molecules, which results in a preferential urinary excretion of nonisomerized type I collagen C-telopeptide breakdown products (CTX). A number of different drugs have been used to control its activity but, since biphosphonates were introduced for the treatment of the disease, they have become the preferred treatment. We administered intravenous zoledronic acid (4 mg) in a single 15-min 5 mg infusion dose. The only side effect was a flu-like syndrome treated with paracetamolo. Thus, at 6 months, laboratory values are as follows:

	Patient's value	Normal Range
Serum alkaline phosphatase	30	40–120 UI/L
Serum alkaline phosphatase isoenzyme Liver	37.0	% 17.0–72.0
Serum alkaline phosphatase isoenzyme Bone	60.1	20.0–75.0
Serum alkaline phosphatase isoenzyme Biliary	2.9	1.0–11.0
Serum alkaline phosphatase isoenzyme Bowel (1-2-3)	0.0	The total of three < 14 %
Pyridinoline (PYD-urine)	32.2	20–52 pMol/CREur
Deoxypyridinoline (DPD-urine)	5.5	5–11 pMol/CREur
Hydroxyproline (urine)	12.9	12.30–31.00 mg/g Crea.ur

Conclusion: The present case shows that Paget's disease of bone is asymptomatic and the diagnosis is made incidentally by increased levels of bone metabolism markers, especially alkaline phosphatase and is confirmed by specific findings in radiographs and radionuclide bone scan, but also that zoledronic acid, apart from being safe and effective in Paget's disease, also appears to be able to achieve significantly remission.

Prevalence of brain white matter hyperintensities in 121 patients with primary headache

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Background: White matter hyperintensities are lesions of the brain which predict an increased risk of stroke, dementia, and death [1]. If migraine is a condition with an increased cardiovascular risk is still debated. Despite this, a higher prevalence of leukoencephalopathy has been documented in migraine patients (particularly those with aura) than in the general population [2]. Conflicting data have been reported for other primary headaches [3]. The purpose of our study was to investigate the relationship between white matter lesions and migraine (with and without aura) or tension-type headache and between the lesions and intensity and frequency of headache symptoms.

Methods: In the period January 2010-December 2011, we analyzed 2046 medical records of patients with headache, and we included those with a diagnosis of Primary Headache, according to the International Headache Society criteria, and with availability of a recent (less than 5 years) Brain Resonance Imaging. Both sexes were considered. Patients with neuralgia, mixed, cluster or secondary (e.g., from hemorrhage, neoplasia and meningitis) headaches were excluded. 121 patients (99 F, 22 M; mean age 34.93 ± 14.59 years), of which 74 with migraine without aura, 23 with migraine with aura and 24 with tension-type headache, were selected. Site, mean intensity of pain and number of crises per month were registered at the first visit. We compared the three groups relative to the MRI parameters (positivity vs. negativity for lesions, Chi-square test) and, within each group, the frequency and intensity of crises of MRI positive (MR +) and MRI negative (MR-) subgroups (Student's *t* test for unpaired samples).
Results: Among 74 patients with migraine without aura, 23 with aura and 24 with tension-type headache, MRI was positive in 21, 1 and 11, respectively. There was a statistically significant difference between the groups with migraine with and without aura ($p < 0.03$), and between the groups with migraine with aura and tension-type headache ($p < 0.002$). No statistically significant difference was found between the migraine without aura and tension-type headache groups. In both the migraine without aura and tension-type groups, the number (but not the intensity) of crises was significantly higher in the MR + than MR- subgroups ($0.04 < p < 0.05$).
Conclusion and Discussion: Our study shows a similar prevalence of brain white matter hyperintensities in migraine without aura and tension-type headache and a higher prevalence in these two types with respect to migraine with aura, in contrast to the data of the literature, which indicate the maximal expression of leukoencephalopathy in patients with migraine with aura. Our results also support the hypothesis of a major link between the frequency of crises and MRI positivity, irrespective of the diagnosis of primary headache.

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Peripheral nociceptor sensitization mediates allodynia in patients with distal symmetric polyneuropathy

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Background: Distal symmetric painful neuropathy is really common and well known to all clinicians. This is also the most common neurologic syndrome seen in diabetes, but several other systemic diseases can reveal this clinical picture, especially with regard to monoclonal gammopathy of uncertain significance (MGUS), or to malignant lymphoproliferative disease, namely multiple myeloma, solitary plasmacytoma, Waldenström's macroglobulinemia, chronic lymphocytic leukemia, primary amyloidosis or cryoglobulinemia. Sometimes the neuropathy is of unknown origin, genetic, or it is associated with vasculitis, chemotherapy, alcohol abuse, poor nutrition, allergic disorder etc. Patients with painful neuropathy frequently complain of pain in response to normally non-painful brushing, namely dynamic mechanical allodynia. Despite many animal studies suggesting that allodynia arises when the spontaneous firing in damaged nociceptive afferents sensitise second-order nociceptive neurons to Aβ-fibre input, no studies have sought to confirm this mechanism by investigating Aβ-fibre sparing in human patients with allodynia.
Aims: We aimed at gaining information on the mechanisms underlying allodynia in patients with painful neuropathy.
Methods: In this study we included patients with four different aetiologies: diabetes-related neuropathy, chemotherapy-induced neuropathy, crioglobulin-related neuropathy, and neuropathy of unknown origin. We compared data from Aβ-fibre mediated nerve conduction studies and nociceptive fibre-mediated laser evoked potentials (LEPs) in 200 patients with distal symmetric polyneuropathy (114 with neuropathic pain, 86 without).
Results: Of the 114 patients with painful neuropathy studied, 44 suffered from allodynia. Whereas no statistical difference was found in nerve conduction study data between patients with and without allodynia, LEP amplitudes were larger in patients with allodynia than in those without ($P < 0.01$ by Mann–Whitney U-test).
Discussion and Conclusions: The lack of difference in NCS data between patients with and without allodynia suggest that this type of pain rather than arising through second-order nociceptive neuron sensitization to Aβ-fibre input, might reflect a reduced mechanical threshold in sensitised intraepidermal nociceptive nerve terminals. The information from our study showing that allodynia in patients with distal symmetric polyneuropathy is associated with partially preserved nociceptive afferent fibres and unrelated to Aβ- fibres could be useful in designing new treatment strategies targeted to this type of pain.

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Hypercholesterolemia, hyperckemia and macro-creatine kinase: a case report

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Introduction: One of the pharmacological cause of increase of CK is the therapy with a statin. This increase may be asymptomatic or

associated with muscle disorders. CK values beyond 10 times ULNV are diagnostic for rhabdomyolysis and as such require the suspension of the drug. The Macro-CK is a cytoplasmatic complex of high molecular weight which results from the polymerization of isoenzyme of CK with IgG (Macro-CK type 1), or oligomers of mitochondrial CK (Macro-CK type 2). The high values of total CK distorted usually do not exceed 500 IU/L: levels between 1.000 and 2.000 results are still compatible with the presence of only macrocomplex. MacroCK-1 is found in healthy individuals, more rarely may be associated with hypothyroidism, cancer, autoimmune diseases, myositis, cardiovascular disease, COPD.

Type 2 appears in the tumors of colorectal, prostate, breast and liver disease; is often transient response

(1). In literature there are only two descriptions of macro-CK found during statins therapy, of which a case of rhabdomyolysis from pravastatin (2,3).

Case Report: A 59-year-old woman was admitted to our department for angina pectoris. It had a family history of ischemic heart disease and hypercholesterolemia. It In the medical history were hypertension, kidney stones, osteoporosis, reflux gastrohesofageal. Since 2003 had hypercholesterolemia (total 311-HDL 73-LDL 224 mg/dl). Coronary angiography investigation was negative. During therapy with simvastatin the cholesterol values were minimum of 203 mg/dl. The drug was discontinued after 1 year to the finding of persistently increased CK total (between 233 and 415 IU/L). In 2009 were assayed isoenzymes: BB fraction 0 %, MB 0 %, MM 59 %, presence of a atypical band (41 %) attributable to macrocomplex, macrocomplex also present 2 years after. Excluding the statin at the cause of hyperCKemia was started therapy with ezetimibe. A subsequent check shoved total chol. 25I, CK 286-329, TSH and inflammatory marker normal, ANA and anti-ENA negative. Abdominal ultrasound: only nephrolithiasis.

Echocardiography: fine calcification of aortic cusps and small nodular calcifications of mitral valve.

The patient presented in these 4 years neither clinical nor biochemical signs related to muscle disorders, hypothyroidism, autoimmune or neoplastic diseases. A study of family members found hypercholesterolemia and hyperCKemia: two sister and a son have increased of CK. A 66 yr-old sister is suffering of hypothyroidism, hypercholesterolemia treated with simvastatin + ezetimibe; CK 236–451, MM 100 %.

Conclusions: We describe the clinical case of a patient with asymptomatic persistent hyperCKemia, probably familial, initially considered idiopathic, after referring to macro-creatine kinase. The anomaly has been observed after statin therapy withdrawal. In the follow up of 4 years did not identify clinical or biochemical suspicion. The control of CK is desirable before starting HMG-CoA reductase inhibitors.

In the presence of hyperCKemia not otherwise attributable, is indicated the dosage of the isoenzymes to exclude an underlying neuromuscular diseases and an increase also distorted, although rarely, by the presence of macrocomplex.

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A simple case of hyponatremia

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Background: Hyponatremia, defined as an excess of water in relation to the sodium in the extracellular fluid, is the most common electrolyte disorder in the hospitalized patients. Severe hyponatremia (<120 mmol/L) is important to recognize because of potential morbidity and because it can be a marker of underlying diseases, but it may be difficult to establish the real cause of a hyponatremia.

Case Report: A 76-year-old man, hypertensive and depressed, was admitted to our Division of Internal Medicine because of episodes of confusion, headache and weakness. Many years before he underwent a nephrectomy for a neoplasm of the left kidney and 3 months before he suffered a head trauma with subarachnoid hemorrhage. He was taking various drugs: the angiotensin-converting enzyme inhibitor perindopril to treat hypertension; dexamethasone to reducing cerebral edema and lowering intracranial pressure; nimodipine to prevent cerebral vasospasm; alprazolam, a second-generation antidepressant; allopurinol; oxcarbazepine as anticonvulsant. The physical examination was not significant and were performed some laboratory tests.

The serum sodium level was 116 mmol/L, the serum osmolality was 283 mOsm/Kg of water, the urinary osmolality was 324 mOsm/Kg of water, the urinary sodium 367 mmol/L and the urinary potassium was 73 mmol/L. Plasma uric acid was 3.1 mg/dl (in course of therapy with allopurinol). The thyroid function and the adrenal function were normal.

Differential Diagnosis: Anamnesis, symptoms and blood tests were evocative of a ***Syndrome of Inappropriate Antidiuresis (SIAD)*.** This is a condition characterized by hyponatremia, plasma osmolality < 275 mOsm/Kg of water, urinary osmolality > 100 mOsm/Kg of water, urinary sodium > 40 mmol/L, clinical euvolemia, no clinical signs of extracellular-fluid depletion, no edema or ascites, normal thyroid and adrenal function. The SIAD has a myriad of causes: malignant diseases, pulmonary diseases, disorders of the central nervous system (for example head traumas or subarachnoid hemorrhages). In addition, a variety of drugs (oxcarbazepine among them) can be the determining factor of a SIAD by means of the stimulation of the release of arginine vasopressin (AVP) or through an enhancement of its action.

Our patient fulfilled all the above-mentioned clinical features except for the plasma osmolality, which was not < 275 mOsm/Kg of water. SIAD may be difficult to distinguish from ***Cerebral Salt Wasting (CSW)***, a disorder characterized by relevant renal loss of sodium, hyponatremia and extracellular-fluid depletion than often occurs in patients with insults to the central nervous system, for instance a subarachnoid hemorrhage. The primary feature that differentiates CSW from SIAD is extracellular-fluid volume depletion, but our patient did not display this condition and was euvolemic. Besides, CSW appears acutely, soon after the cerebral event (1 to 10 days) and usually resolves in 3–4 weeks.

A third reasonable assumption was a "simple" ***hyatrogenic hyponatremia.*** Many drugs can determine hyponaremia: antidepressants and antipsychotics, nonsteroidal anti-inflammatory agents, anticancer agents, antiepileptic drugs as sodium valproate, lamotrigine, carbamazepine and oxcarbazepine.

Management: Acute symptomatic hyponatremia is routinely treated with hypertonic saline. In order to raise the serum sodium level, a hypertonic saline (3 %, the same concentration of sodium chloride

present in the sea) was infused to the patient. The administration of the saline solution was made very gradually because we know that a too aggressive correction of the sodium level carries a documented risk of serious neurological damage related to the osmotic demyelination syndromes. Moreover, we stopped oxcarbazepine therapy replacing it with levetiracetam, a new antiepileptic drug lacking serious adverse events.

Conclusions: A few days later, the patients felt well, his serum sodium level raised to 135 mmol/L and he was discharged from hospital.

Nephrology

Acute and chronic renal failure in HIV patients treated with tenofovir

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Introduction: The patients affected by HIV can present various types of nephropathy: the HIV correlated nephropathy, the nephropathy correlated with immunodepression or lymphoproliferative derived infections, the nephropathy secondary to the toxicity of antiretroviral drugs. Currently the most used drug is tenofovir (TDF), a nucleotidic analogue of the adenosine 5′ monophosphate. It's a drug of the first line therapy in the principal international guide lines. The renal elimination of tenofovir includes a glomerular phase and an active secretion tubular phase.

The tubular toxicity derived by the intracellular accumulation of the active metabolite, excreted in an unmodified form by the renal emunctory is a dose-dependent phenomenon. In literature there are univocal datas about the efficacy but not about the safety of this drug. Often, the presence of co-morbidity and confounding factors, among which the assumption of nephrotoxic drugs can make more difficult the interpretation of scientific results.

Materials and Methods: We have examined 22 patients (15 men and 5 women) with a mean age of 48 ± 4 aa, affected by HIV in treatment with tenofovir from 30 to 90 days, sent by infectologist for rising values of serum creatinine. The blood tests have confirmed a reduced glomerular filtration rate (analyzed with CKD-EPI, preferred by some authors in patients with HIV) with values between 30–50 ml/min, a mixed proteinuria in non-nephrotic range and a hypophosphatemia in all patients. The blood gas analysis and the renal echography were normal.

Results: 2 patients, affected by hypertension, presented a chronic kidney disease (CKD) of III stage KDOQI, 20 patients presented a normal renal function before initiating therapy, 3 of these had reported the recent assumption of NSAIDs and 2 had reported the recent onset of vomiting and diarrhea with subsequent dehydration. Following the immediate suspension of the drug, 17 patients had progressively regained a normal renal function over a period from 3 to 6 weeks, 5 patients presented a CKD even after 6 months from the suspension of therapy with a glomerular filtration rate GFR < 50 ml/min.

Conclusions: This study has demonstrated an elevated incidence of glomerulo-tubular damage in the patients affected by HIV in therapy with tenofovir, with a variable appearance compared to the beginning of the assumption, this shows both drug's dose dependence and the presence of possible Acute Kidney Injury (AKI) predisposing factors, like hypovolemia or the assumption of nephrotoxic drugs. The good general tolerability of the drug and its positioning in the first line therapy in the principal international guide lines impose an early identification of the predictive risk factors of organ damage in order to prevent the development of nephrotoxicity. Among non-modifiable risk factors we find the advanced age, African ethnic and some genetic polymorphisms that encode for transmembrane proteins. The use of protease inhibitors, didanosine or other drugs notoriously nephrotoxic, a reduced BMI, a low count of CD4, un elevated viral replication and the presence of comorbidity like HCV, diabetes and hypertension or a previous opportunistic infection, represent instead the acquired factors. The evaluation of the glomerular filtration rate, proteinuria and serum phosphate should be performed before starting the antiretroviral treatment, monitoring at first monthly and then every three months, with an early sending in nephrologic area. At the end it should be emphasized, given the close connection between renal injury and the atherosclerotic disease, a close monitoring of the both traditional and nontraditional cardiovascular risk factors.

Nephrotic syndrome and stroke

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Introduction: Arterial and venous thrombosis related to coagulation defects are potential complications of nephrotic syndrome.

Materials and Methods: A 71-years-old man went to Emergency Department for the onset of aphasia and crooked mouth.

His past medical history revealed pharmacologically treated hypertension and autoimmune haemolytic anemia on treatment with steroids.

Brain CT scan and carotid echocolorDoppler didn't show symptoms-related abnormalities.

Brain MR scan revealed bilateral peri-ventricular multiple ischemic areas and a recent wide left fronto-temporal-subcortical ischemic lesion. ECG and echocardiography were normal.

During hospitalization a condition of anasarca was associated with proteinuria, hypoalbuminemia and decrease of plasma proteins with normal renal function (creatinine 1.1 mg/dL).

Nephrotic range proteinuria was discovered by urinalysis (21 g/24 h).

Thrombophilia screening showed normal values of C Protein (125 %), increased fibrinogen (>660 mg/dL) and decrease of S Protein (56 %) and antithrombin III (59 %).

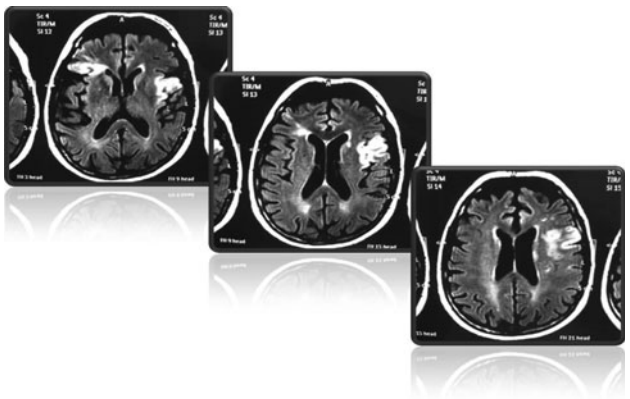
Therefore, renal biopsy was performed, showing diffuse membranous glomerulonephritis and mild atherosclerosis.

A full-body CT scan was negative, excluding a paraneoplastic syndrome.

He was discharged with the following therapy: prednisone (12.5 mg/die), cyclosporine (200 mg/die) and oral anticoagulants. Follow-up after six months revealed stable creatinine levels (1.2 mg/dL) and a significant decrease of proteinuria (0.74 g/24 h).

Conclusions: The hypercoagulability of patients with nephrotic syndrome could be an important trigger for arterial and venous

thrombotic events, especially if associated with a diagnosis of membranous glomerulonephritis.
Anticoagulant treatment is variable, depending on the individual patient's risk of thrombosis.



Ultrasound assessment of hemodialysis patients

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Introduction: Accurate determination of fluid balance to prevent both under- or overhydration, is an important issue in patients undergoing periodic haemodialysis (HD) for end-stage renal disease (ESRD). The correct "dry" weight is usually estimated clinically. Bioimpedance technologies are currently considered a reliable tool for technological assessment of volume in dialysis patients. Ultrasonographic evaluation of inferior vena cava (IVC) can asses the vessel's diameter and collapse index (expressed as the percentage of diameter reduction during spontaneous inspiration): both these measures estimate the central venous pressure (thus reflecting total intravascular volume). Lung ultrasound can evaluate extravascular lung water by identifying artefacts named B-lines, shown on ultrasound scan as vertical artifacts arising from the pleural line moving synchronously with respiratory acts. Our study was aimed to further clarify the usefulness of ultrasound in the assessment of volume status in patients undergoing HD.
Methods: 71 consecutive patients undergoing HD underwent immediately before and after dialysis lung and IVC ultrasound and bioimpedance spectroscopy (BIS). The number of B-lines was counted in each intercostal space at the parasternal, midclavicular, anterior axillary, and midaxillary lines for a total of 28 sectors examined. The inferior vena cava diameters was measured during a normal respiratory cycle at non forced end-expiratory and end-inspiratory phases; the collapsibility index was calculated. Fluid overload was assessed considering weight gain from the dry weight, which was in turn estimated from clinical parameters. Accumulated weight was defined as weight gain from dry weight. Weight loss was the difference between weight before and after dialysis. Residual weight was defined as difference between obtained weight after dialysis and dry weight. Every patients underwent a bioimpedance spectroscopy (BIS) with Body Composition Monitor (BCM- Fresenius^{TM}) before and after hemodialysis.
Results: There was a significant reduction in the number of B-lines and in IVC diameters during dialysis. No significant difference was detectable in the inferior vena cava collapsibility index. (Table 1)

Table 1 Ultrasonographic parameters pre and post dialysis (data are expressed as mean ± S.D.)

	Pre-dialysis	Post-dialysis	p
Number of B lines	3.13 ± 3.4	1.41 ± 2.47	0.000
End-expiratory vena cava diameter (mm)	1.71 ± 0.58	1.37 ± 0.55	0.000
End-inspiratory vena cava diameter (mm)	1.19 ± 0.59	0.95 ± 0.51	0.000
CCI (%)	30.9 ± 3.91,66	33.6 ± 3.90	0.695

The reduction of B lines correlated with weight reduction during dialysis; none of the parameters concerning the IVC correlated with fluid removal. (Table 2)

Table 2 Linear regression with weight loss

Correlation between weight loss and:	beta	P
B lines reduction (%)	0.36	0.007
End-expiratory vena cava diameter reduction (%)	0.14	0.24
End-inspiratory vena cava diameter reduction (%)	0.04	0.77
CCI reduction (%)	−0.03	0.81

At the end of the dialysis session the total number of B lines correlated with excess residual weight measured with BIS. (Table 3)

Table 3 Linear regression with weight excess post-dialysis (BIS)

Correlation between BIS Residual Weight and:	beta	P
Clinical Residual weight	−0.09	0.51
Number of B lines	0.40	0.002
End-expiratory vena cava diameter	0.10	0.46
End-inspiratory vena cava diameter	0.07	0.62
CCI	0.09	0.50

Discussion: The reduction of B lines correlated with fluid loss due to HD, despite the small pre-dialysis number, confirming that lung ultrasound can identify even modest variations in the pulmonary imbibition status. While lung ultrasound reflects the grade of imbibition in the lung interstitium, IVC ultrasound reflects the intravascular filling grade, and might be not enough sensitive to detect rapid volume decrease in HD. Clinically estimated dry weight had a poor correlation with both BIS and ultrasound techniques, thus confirming its imprecision. Post-dialysis B-lines number correlates with residual weight assessed with BIS, suggesting a role for ultrasound in managing HD patients.

Endothelial dysfunction, atherosclerosis and cardiovascular disease in chronic kidney disease: role of uricemia, homocysteine and NT pro-BNP in early stages of CKD

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Introduction: Cardiovascular complications represent the main cause of mortality in patients affected by chronic kidney disease. Accelerated Atherosclerosis in these patients is closely associated with endothelial dysfunction and systemic inflammation. Decline of estimated glomerular filtration rate (eGFR), left ventricular hypertrophy (LVH) and anemia are considered independent cardiovascular risk factors. Both homocysteinemia (an aminoacid considered as a new uremic toxin) and uricemia are emerging non-traditional cardiovascular risk factors, that promote inflammatory processes, endothelial dysfunction and smooth muscle cells proliferation, associated with increased cardiovascular risk. There are few scientific data available regarding the utility of NT pro-BNP dosage in early stages of CKD. The aim of our study is to identify the relationship between increased level of homocysteinemia, uricemia, NT pro-BNP and instrumental parameters as left ventricular mass index (LVMI), carotid intima-media thickness (cIMT) and brachial artery flow mediated dilation (FMD), in patient with earlier stages of CKD (KDOQI classification).
Materials and Methods: 34 patients affected by CKD, well controlled hypertension, without heart failure signs and symptoms and 6 control patients were consecutively selected. All patients, subdivided in 3 groups, 2 of them stratified on the basis of eGFR > 60 ml/min, eGFR < 60 ml/min and control group, underwent clinical, anthropometric, laboratory and instrumental examination. NT pro-BNP was dosed using automatic Analyzer Elecsys E2010. LVH, cIMT and FMD were assessed by Ultrasound Sonosite M Turbo Machine. LVMI was calculated by Devereux's formula. Data underwent univariate and multivariate analysis using SPSS statistic v17.0 software.
Results: The mean age of patients was 58 years old; there were not statistically significant differences in age, sex and BMI between groups. The multiple linear regression analysis confirmed an independent correlation between decline of eGFR and increment of NT pro-BNP concentration ($\beta = -0.227$, $p = 0.012$). The decrease of haemoglobin levels correlated with the increase of NT pro-BNP values ($\beta = -0.487$, $p < 0.001$). The increase of LVMI correlated with the reduction of eGFR ($r = -604$, $p < 0.001$) and of haemoglobin ($r = -0.433$, $p = 0.005$) and with the increase of NT pro-BNP ($\beta = 0.293$, $p = 0.015$). The median value of NT pro-BNP was significantly different between groups ($p < 0.001$) already at earlier stages of CKD (controls vs. eGFR > 60 ml/min group; $p < 0.001$). The medians value of cIMT, homocysteine, uricemia increased, whereas the median value of FMD reduced significantly during advancing of CKD (cIMT: $F = 53.8$, $p < 0.001$; homocysteine: $F = 18.5$, $p < 0.001$; uricemia: $F = 18.4$, $p < 0.001$; Ca*P: $F = 12.9$, $p < 0.001$; FMD:$F = 61.9$, $p < 0.001$).
Conclusions: Our study findings highlighted that the progressive increment of inflammatory indexes and endothelial dysfunction is already present at the early stages of CKD. There was also evidenced that the LVH, hemoglobin reduction and eGFR decline are independent factors correlated with increased serum NT pro-BNP levels. Hyperuricemia and hyperhomocysteinemia was associated with the increasing of cIMT and the reduction of FMD in the earliest stages of renal disease (I,II,III KDOQI stages), so they could be utilized as precocious systemic markers of subclinical atherosclerosis and endothelial dysfunction. Furthermore, study's results seem to support the utility of NT pro-BNP dosage, in patients affected by mild CKD, for the early evaluation of cardiovascular risk.

Association between Prealbumin and Visceral Fat Mass in Hemodialysis Patients

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Background: Both Albumin (ALB) and Prealbumin (PreAlb) are associated with malnutrition and inflammation in hemodialysis (HD) patients. Each have a residual effect on mortality outcomes when included in regression models that include the other. PreAlb, but not ALB is inversely associated with infectious and directly associated with vascular access hospitalizations. PreAlb has been reported to be increased in the obese mouse model as a consequence of stabilization of PreAlb by Retinol Binding Protein 4 (RTB4), secreted by adipocytes. We questioned if PreAlb was associated with adiposity in HD patients, independent of the effects of inflammation or nutrition.
Methods: We evaluated body composition in 48 prevalent HD patients by Magnetic Resonance Imaging, measuring total skeletal muscle mass (SM), visceral and subcutaneous adipose tissue (VAT and SAT), and serum ALB, PreAlb, RTB4, interleukin -6 (IL-6) concentrations. We used normalized protein catabolic rate (nPCR) to report nutrition and separately analyzed the determinants of ALB and then of PreAlb by multiple stepwise regression.
Results: 32 subjects were women, 16 were diabetic, median age 54.5, range 40–69. Median BMI (kg/m^2) 27.3, range 22.5–37.2. Median TAT 24.3 kg range 11.5–40.1 kg, median VAT 3.25 kg range 0.5 5.8 kg. PreAlb was positively associated with VAT ($p = 0.002$), nPCR ($p = 0.0001$) and RTB4 ($p = 0.05$), and negatively associated with IL-6 ($p < 0.003$) and white race ($p < 0.001$). r^2 for the model was 0.66. By contrast ALB was positively associated only with nPCR and negatively with Log IL $= 6$. r^2 for the model was 0.18.
Conclusions: PreAlb, like ALB, is associated with markers of nutrition (nPCR) and inflammation (IL-6), but unlike ALB, PreAlb is strongly associated with adiposity.

Low serum creatinine in end stage liver disease: association with acute kidney injury post-liver transplantation

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Introduction: End Stage Liver Disease (ESLD) is a common disorder of multiple aetiologies associated with high mortality. Liver transplantation (LT) is the only effective therapy that increases the survival of these patients. While the expanded use of LT has changed the outcome for patients with ESLD, Acute Kidney Injury (AKI) has rised interest because of its association with poor prognosis and increased mortality rate.

The Model for End-stage Liver Disease (MELD) is a score of mortality in ESLD patients and it's based on bilirubin, INR and creatinine values. Serum creatinine (sCr), a surrogate of renal function, is considered a bias in ESLD patients because of decreased hepatic synthesis of creatine, malnutrition, reduced muscle mass, low body mass index (BMI). The development of AKI, occurring in first week post-LT, seems to be mainly influenced by more serious pre-LT hepatic insufficiency, presence of ascites, higher MELD score, prolonged intra-operative hypotension and dysfunction of liver graft.

Purpose is to evaluate the prevalence of AKI post-LT and its association with pre-LT factors linked to hepatic dysfunction.

Methods: Data from 71 consecutive patients who underwent LT were collected (2008–2011). Patients' characteristics such as age, gender, etiology of liver disease, infectious state, presence of ascites were recorded. Pre-LT hepatic function evaluation included: bilirubin, INR, albumin, and laboratory-MELD. Renal function was recorded before and after LT, evaluated on the basis of sCr, estimated glomerular filtration rate (eGFR) based on Modification of Diet in Renal Disease (MDRD4) formula, serum sodium. AKI was defined and classified by AKIN criteria in stages (S) on the basis of sCr changes from baseline: Risk-S1 (1.5–2-fold), Injury-S2 (2–3-fold) and Failure-S3 (>3-fold).

Results and conclusions: The incidence of AKI was 61 % (43/71 patients), of these 53.5 % (23/43) developed S1, 39.5 % (17/43) S2 and 18.6 % (8/43) S3. Differences were found between patients developing S3 compared to the others as a group (no-AKI + S1 + S2).

In S3 group, pre-LT MELD, bilirubin and INR were higher ($p = 0.002$, $p = 0.003$, $p = 0.04$, respectively), while sCr and MDRD were abnormally low and high, respectively ($p < 0.001$ and $p = 0.002$). No differences were found in BMI and other patients' characteristics. Considering the abnormal values of renal indices, pre-LT sCr < 0.65 mg/dl and eGRF > 115 ml/min seem to be predictive values for post-LT development of AKI Stage 3 was obtained (sCr AUC = 0.902; eGRF AUC = 0.857).

Development of AKI post-LT concerned more than half of patients in our study. It's known the multifactorial etiology of AKI in the setting of LT, but in our series we found an association between the worst degree of AKI (Stage 3) and worse pre-LT hepatic function. The highest MELD score, not due to high sCr, indicates the poor clinical conditions and the advanced state of end stage liver disease in these patients.

The abnormal sCr and GFR may result from the markedly reduced creatine hepatic synthesis due to the advanced cirrhosis. The abnormally low sCr and high eGRF pre-LT could be considered a predictive factor for the development of AKI post-LT.

Changes from baseline versus absolute values of serum creatinine to diagnose and classify acute renal failure in end stage liver disease

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Introduction: Renal failure in patients with cirrhosis is primarily related to disturbances in circulatory function, activation of vasoconstrictor systems and non-osmotic hyper-secretion of antidiuretic hormone leading to sodium and solute-free water retention and eventually to renal failure due to intra-renal vasoconstriction and hypoperfusion. Acute kidney injury (AKI) is a frequent complication in patients with end-stage liver disease (ESLD) associated with increased mortality and commonly identified by serum creatinine (sCr) > 1.5 mg/dL. The hepatorenal syndrome type I (HRS-I) is a specific form of AKI recognized on the basis of the International Ascites Club (IAC2007) criteria, including increase of sCr > 1.5 mg/dl. Levels of sCr in cirrhosis are influenced by decreased hepatic creatine synthesis and reduced muscle mass, with possible overestimation of renal function. AKIN criteria (KDIGO-2012) have been extensively validated for definition and stratification of AKI degree, based on modifications of sCr rather than absolute values: SCr > 150 % from baseline or ≥0.3 mg/dL in <48 h (Stage1), sCr > 200 % from baseline (Stage2), sCr > 300 % from baseline or sCr ≥ 4 mg/dL (Stage3). Application of AKIN criteria may implement the diagnosis of AKI in patients with ESLD, including cases not meeting HRS-I criteria. The aim of our study is to evaluate the prevalence of AKI, based on AKIN criteria in patients with ESLD.

Materials and methods: Single-centre study of 64 patients (53 M/11F) affected by ESLD and waiting liver transplantation. Clinical parameters (ascites, hypotension, no improvement of sCr after diuretic withdrawal volume expansion with albumin, use of nephrotoxic drugs) and laboratory parameters (sCr, urinalysis, proteinuria 24 h) were recorded. Definition and classification of AKI and HRS-I were performed on the basis of AKIN and IAC criteria respectively.

Results and conclusions: Mean age was 55.2 ± 8.8 years. Aetiology of liver disease: hepatitis C (39 %), hepatitis B (20.3 %), alcohol (15.7 %), other (25 %). AKI occurred in 13/64 patients (20 %); of these 3 patients developed Stage1, 1 patient Stage2 and 9 patients Stage3. HRS-I occurred in 2 patients, both with AKI Stage 3. Seven out of 13 patients with AKI showed sCr > 1.5 mg/dL. The diagnosis of AKI in ESLD was implemented according to AKIN criteria: 6/64 patients (9.4 %) developing AKI with values of sCr < 1.5 mg/dL would have not been recognized and consequently would have not received adequate treatment. The overall prevalence of AKI was 20 % and about 50 % of these patients would remain unrecognized outside AKIN criteria.

Uraemic dysgeusia: quality of life is even matter of good taste

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Introduction: The intake of several drugs, diabetes mellitus, vitamin B12 deficiency, zinc deficiency are among the most frequent causes of taste disturbance, from ageusìa (complete loss of taste), to dysgeusia (raised threshold of perception and distorted perception of taste).

The taste disturbances may affect the lifestyle of uremic patients (salt intake, weight gain, intake of phosphorus). We therefore wanted to assess the prevalence in a population of 78 patients on hemodialysis, comparing their responses to a standardized test with those of a control population, consisting of non-uremic age-matched hypertensive subjects.

Materials and Methods: The taste of sweet, savory, bitterness and acid were tested by scalar glucose, sodium chloride, caffeine and citric acid solutions. It was therefore assigned to each test a value of 4 (recognized at the lowest concentration) to 1 (not recognized). Each

subject then received a score of 4 (ageusia) to 16 (maximum capacity of discriminating tastes), obtained by the sum of individual scores.
Results: The control subjects had a total score between 11 and 16, with a median of 14 ± 1.6.
The hemodialysis patients had a total score between 6 and 16, with a median of 12 ± 2.9. No patient had ageusia, while 25 % of the sample accounted a score below 10 (dysgeusia).
The test score of dysgeusia correlated directly with levels of hemoglobin and inversely with those of phosphorus. In other words, patients with poor taste exhibited lower hemoglobin values and higher levels of phosphorus, while no significant correlations were apparent with the interdialytic weight gain with age and length of dialysis.
Conclusions: Dysgeusia appeared very frequent among patients on hemodialysis. It did not appear to influence the interdialytic weight gain, and seems to correlate with serum phosphorus, in an interesting ambivalence of cause-effect relationships.

Pneumology

Changes in the smoking habits of 300 regular smokers, not willing to quit, experimenting the Electronic-Cigarette

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Background: Recent evidence suggests that E-cigarettes may be an effective and safe aid to smoking cessation, and large randomized controlled trials are now required to confirm and expand these preliminary observations. We designed a double-blind, placebo-controlled, randomized clinical study to evaluate smoking reduction, smoking abstinence and adverse events in smokers not intending to quit experimenting two different nicotine strengths of a very popular E-cigarette brand ('Categoria'; Arbi Group, Italy).
Methods: A double-blind, sham-controlled, randomized, clinical trial of 300 smokers (unwilling to quit) was designed to assess the efficacy and safety of 'Categoria' E-cigarette (Arbi Group, Italy) loaded with 7.2 mg nicotine (study group A) and 4.8 mg nicotine (study group B) cartridges in comparison to no-nicotine containing cartridges (study group C). Study participants were invited to attend a total of nine study visits in 1-year during which product use, number of cigarettes smoked, and exhaled carbon monoxide (eCO) levels were recorded. Smoking reduction and abstinence rates were calculated. Adverse events and product preferences were also reviewed. Analyses were computed as per intention-to-treat.
Results: A significant reduction in mean cig/day use and eCO levels from baseline was recorded at all study visits in all three study groups. A mean of 2.0 cartridges/day was used in each study group up to the 3-month time point, but falling thereafter. 50 % reduction in the number of cig/day was shown in 21 % and 9 % participants in group A, in 16 % and 8 % in group B and in 19 % and 10 % in group C, at month-3 and -12 respectively. Smoking abstinence was observed in 11 % and 13 % participants in group A, in 17 % and 9 % in group B and in 4 % and 4 % in group C, at month-3 and -12 respectively. Only minor and transient adverse events were reported, including mouth and throat irritation, and dry cough. By and large, participants' perception and acceptance of the product was positive.
Conclusion: In smokers not intending to quit, the use of e-Cigarette decreased cigarette consumption and elicited enduring tobacco abstinence at 1-yr without causing significant side effects.

Pleural effusion in highly asbestos-polluted area: advantages of multidisciplinary management

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Pleural effusion represents a significant public health issue and frequently the first diagnosis is made in the Internal Medicine division. Often the pleural effusion is expression of cardiac failure or infectious disease, but in the Alessandria district with the epicentre in Casale M.to, the pleural effusion could be expression of malignant pleural mesothelioma (MM), almost 20 times higher than the average in Italy. In consideration that the multidisciplinary approach is emerging as the best way to define the optimal strategy to care the patient and to deal with this problem the Interdisciplinary Care Group (MM-ICG) has been constituted since 2009 by joining the efforts and expertise of specialists from Casale M.to and Alessandria Hospitals and a dedicated biological bank (MMBB) has been created in Alessandria Hospital. The MM-ICG is formed by all the specialists involved in MM diagnosis and treatment: radiologists, pneumologists, nuclear medicine specialists, pathologists, oncologists, internal medicine specialists, thoracic surgeons, general surgeons, psychologists, experts in palliative care. This working group expressed a diagnostic-therapeutic flow chart on the management of MM. In the Internal Medicine division all causes of pleural effusion are considered and the doubt of malignant pleural disease meet with a diagnostic protocol of MM-ICG, which has been based on the best available evidence. In diagnostic protocol the pleural fluid drenage is the first step, with samples for citologic, biochemical and cultural studies. The second step is the CT and radiologic study of pleural lesions. Only at this time, whenever possible, tumour samples along with pleural effusion fluid, blood and serum were collected and stored in the MM-BB. If MM is diagnosed the patient is referred to a database created to record the patient histories (DBmeso) linked to the regional MM registry of Piedmont. Fortnightly meetings are held to discuss the most notable cases. In our countries, asbestos-polluted, the critical observation of pleural effusion is particulary useful for diagnosis of some aspecific pleural effusion: in 2010 in 11 patients with pleural effusion only 5 are malignant pleural effusions, in 2011 14 patients was affected of undefined pleural effusion and in 7 patients was diagnosed MM. The diagnosis was formulated in 5–6 days; the difficult diagnosis are discussed by the team and rapidly investigated.
In our experience the major attention united to a major cooperation is advantage for the patient but also could be useful for the health economy.

An atypical case of chronic pneumonia

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Hydroxyurea is a cytotoxic agent widely used in the treatment of myeloproliferative disorders. It is considered a-well-tolerated antineoplastic drug, with a dose-related bone marrow suppression as main adverse effect. This report describes a patient with essential thrombocythemia who developed an interstitial pneumonitis with pulmonary fibrosis within 4 years of beginning therapy with hydroxyurea. After 4 years of hydroxyurea treatment, the patient

presented severe dyspnea, shortness of breath on exertion and dry cough. She was afebrile. One week before she was treated with levofloxacin 750 mg daily and prednisolone 25 mg for 10 days without any clinical improvement. Her clinical examination showed bilateral basal velcro-like "crackles" at both lung bases. Arterial blood gas analysis showed mild hypoxaemia: pO2 61 mmHg, pCO2 38 mmHg, pH 7.42, HCO3- 24.6 mmol/l on air. A chest X-Ray showed multiple bilateral opacities, flowing together at both lung bases. Cultures from blood and sputum were negative. Serological findings for viral infection (varicella-zoster, CMV, herpes simplex 1, herpes simplex 2, adenovirus) and for *Legionella pneumophila*, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* were negative. Lung function tests showed a restrictive pattern: FVC 1.63 l (71 % predicted), FEV1 1.44 l (77 % predicted), FEV1/FVC 0.88, DLCO 10.2 (51 % predicted), TLC 3.62 l (72 % predicted). A chest CT (HRCT) scan showed pulmonary fibrosis, more evident at lung bases and in the subpleuric zones with several small areas of ground-glass at the upper lobes. Bronchoscopy showed normal bronchial tree and bronchoalveolar lavage did not find any yeast, hyphae or pneumocystis. Bacterioscopic and coltural tests for *Mycobacterium tuberculosis* on bronchoalveolar lavage and an autoimmunity screening were negative. Hydroxyurea was discontinued and the patient started treatment with prednisone (40 mg/day) and N-Acetyl-Cysteine (600 mg 3 times/day). At two-months follow-up there was a significant improvement in symptoms and CT scan findings. Arterial blood gas analysis performed on room air showed an improvement: pO2 78 mmHg, pCO2 39 mmHg, pH 7.42, HCO3- 25 mmol/l. After two years of follow-up no relapse occurs. Hydroxyurea-induced pulmonary toxicity is extremely rare: literature reported cases consists mainly of acute alveolitis or interstitial pneumonitis. Interstitial lung disease may be related to infective or autoimmune diseases, environmental exposure, radiations, aspiration or idiopathic. In our patient, HRCT findings were compatible with a diagnosis of interstitial pneumonitis evolving into pulmonary fibrosis. In our case an infectious cause was virtually excluded, autoimmunity tests resulted negative and she didn't have a positive medical history for environmental exposure; she also never received radiotherapy or be accidentally exposed to environmental radiations. Drug-induced pneumonitis is a diagnosis of exclusion and we believed that hydroxyurea could be the most likely culprit of the process. Discontinuing the drug, we assisted to a dramatic improvement of clinical and radiological findings. This is the first case in which clinical symptoms and radiological signs developed after 4 years since hydroxyurea was started. Hydroxyurea is a well tolerate chemioterapic drug with few significant side effects. It has been rarely reported a pulmonary toxicity, mainly in an acute or subacute onset. Our case reports a possible pulmonary toxicity associated with long term therapy with this drug. In patients treated with hydroxyurea, a pharmacologic etiology of interstitial pneumonitis should always be considered. In this subset of patients, hydroxyurea discontinuation with or without addition of steroids results in a clear improvement of clinical and radiological conditions.

Hospital management of community-acquired pneumonia (CAP): a clinical audit

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Background: The estimated incidence rate of CAP in Italy is 3–5 cases per 1,000 person-years with a 12 % mortality rate in hospitalized patients. Clinical and technical management of inpatients may be affected by high variability leading to both clinical (mortality, morbidity, complications) and economical poor outcomes. Medical scientific literature provides high quality evidence-based documents which can be used to implement quality improving planes based on clinical audit methodology

Aim: we created a clinical audit system concerning management of inpatients admitted to Clinica Medica ward with CAP, in order to achieve:

- Clinical outcomes improvement, minimizing hospital stay-related adverse events
- Organizational outcome improvement, particularly regarding length-of-stay and overall costs
- Training of medical and nursing staff.

Study Design: Clinical audit divided in three different stages:

- usual practice data collection
- implementation of recommendation and training
- post implementation data collection.

Inclusion criteria: patients admitted to Clinica Medica ward with CAP from April 2011 to April 2012.

Exclusion criteria: patients receiving cancer chemotherapy or long-term high-dose corticosteroid treatment, age 18 or younger, patients infected with HIV or A/H1N1 influenza, solid organ, bone marrow, or stem cell transplant recipients.

Referral guideline: IDSA/ATS Guidelines on the management of community-acquired pneumonia in adults 2007

Quality indicators: 8 validated process and outcome indicators will be evaluated distributed from ward admission to hospital discharge. When possible standards were extracted from the referral guideline or, if lacking, high quality evidence based documents were used anyway. The gap between standards and real practice will be recorded and analyzed.

Implementation tools: training-retraining, audit-feedback, creation of ad hoc pocket reminders and posters. A specific website (www.polmonitiancona.net76.net) was built too.

Data obtained from the first phase, available since july 2012, will be presented.

Clinical outcome of two patients with "complicated" pneumonia treated with Tigecycline

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In this report, we describe the clinical outcome of two patients with severe pneumonia (multifocal, bilateral, resistant to common empiric poly-antibiotic therapy), complicated by serious comorbidities.

In the first case an 83-year-old patient with cachexia, diabetes, heart disease, and also affected by chronic pancreatitis, was referred from the General Surgery Unit of Bari University Hospital. He had recently undergone cholecystectomy for gallbladder empyema. Although asymptomatic, at chest CT he presented areas of parenchymal consolidation of the superior lung lobes bilaterally, as well as bilateral pleural effusion. Blood tests showed neutrophilic leukocytosis and increased inflammatory markers. He was administered ciprofloxacin, piperacillin/tazobactam and clarithromycin. At radiographic control 1 week later, the findings persisted and a new paracardiac bronchopneumonia focus had appeared on the right. The treatment was changed to levofloxacin, clarithromycin and imipenem and pleural drainage was positioned on the left. At CT control after 7 days, the

parenchymal consolidation was still evident and another bronchopneumonia focus had appeared in the posterobasal site of the inferior left lobe, with a reduced pleural effusion on the left. At this stage, tigecycline for 10 days was introduced according to the table below; the bronchopneumonia completely resolved.
The second case was an 87-year-old patient affected by idiopathic pulmonary fibrosis, who presented a right basal bronchopneumonia focus at chest X-ray. Blood tests showed leukocytosis and increased inflammatory markers, with hyperpyrexia (max 38.3 °C). Within 2 days of onset of the symptoms, treatment with levofloxacin, clarithromycin and ceftriaxone was administered. After 72 h the patient showed a worsening clinical picture with a temperature of 39.7 °C. The antibiotic therapy was suspended in favor of tigecycline, as illustrated in the table below. After 48 h the temperature had returned to normal. After 7 days, chest X-ray showed resolution of the bronchopneumonia and normal blood chemistry tests, with normalizing inflammatory markers.
To date, there are no indications for the use of tigecycline in infections of the lower airways. However, cost-benefit analysis of antibiotic and tigecycline therapy in our two patients surprisingly showed that the latter was more economical than the antibiotic associations commonly administered. Although the costs of tigecycline were higher than the sum of the other antibiotics, the shorter hospitalization due to the therapeutic success of tigecycline was economically more convenient. In conclusion, this preliminary report suggests that in patients with grave comorbidities and pulmonary infections resistant to common antibiotic polytherapy this drug may offer a new therapeutic option that warrants clinical validation in large case series.

Never underestimate the most likely disease!

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Introduction: Each smoker should be investigated by pulmonary function tests (PFT), diagnostic "gold standard". Composite indices to assess the prognosis are validated. The most important is the "BODE index" that includes, along with BMI, even the perception of dyspnea and exercise tolerance, measured by MMRC and 6'MWT. Too often this is not done and the most frequent pathology disease due to smoking is not recognized and is untreated until an advanced stage.
Case Report: P.A., 65, male, 10 years before: NSTEMI ACS, undergoing PTCA, and since then treated with ASA, ACEInh, NTG. On that occasion, he stopped smoking (before: over 20 p/y). Never any more detailed respiratory diagnostic investigation until October 2010 when, because of the onset of fever, cough and asthenia, he practices chest-X-ray: parenchymal thickening on the left side.
So the patient is hospitalized in Day Hospital for more detailed diagnosis.

- A/B balance: pH 7.38, $PaCO_2$ 46, PaO_2 67, HCO_3^- 27.3;
- Chest CT: diffuse emphysema in both lungs;
- PFT: moderately severe obstructive alteration and absence of significant broncho-dynamic.

Therapy, antibiotics and steroids, solves the acute problem.
Diagnosis: COPD, GOLD stage 2 (moderate), previously unrecognized.
In addition to treatment for heart disease, beta-agonists and anti-muscarinic long-acting (LABA and LAMA) are prescribed.
Discussion: COPD is the fourth leading cause of mortality/morbidity in the world. It's associated with serious co-morbidity, primarily cardiovascular. The primary cause of COPD is smoking. We must always seek the symptoms of COPD (cough, phlegm, and wheezing) in a smoker. So every smoker should be investigated using pulmonary function tests (PFT), "gold standard" for COPD diagnosis.
As a proper hygienic-dietary (lifestyle) and pharmacology therapy (according to GOLD and AGENAS guidelines) is delayed, COPD worsens the more quickly.
Conclusions: The case shows that hospital and territorial doctors don't even consider that COPD is a serious disease, but early treatable. COPD is not currently diagnosed and treated adequately. So we need to reduce the diagnostic deficit, and therefore the therapeutic deficit. In fact, among the chronic diseases, COPD is the only one with a trend of increasing incidence, so that, according to the WHO, by 2020 will be the third leading cause of mortality/disability in the world.

Chronic co-morbidities and undiagnosed metabolic syndrome in elderly patients with COPD

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Objective: We investigated the prevalence of chronic co-morbidities associated with COPD in elderly patients.
Methods: We examined 100 COPD outpatients according to Global Initiative for Obstructive Lung Disease (GOLD) guidelines, in stable condition, aged ≥65 years, ex- or current smokers with ≥20 pack/years, and calculated both the Charlson Comorbidity Index (CCI) and the COTE Index (Divo M, et al.AJRCCM 2012May3). Each patient was also investigated for assessing the severity of breathlessness by the mMRC scale and the impact of respiratory symptoms on daily life activities by the COPD assessment test (CAT). Metabolic syndrome was defined according to AHA/NHLBI (2005;112:2735–52). All subjects underwent echocardiography, carotid ultrasonography and CT scan of the chest.
Results: Patients had mean age 72 years (range 65–82), mean pack/years 50.8, mean body mass index 28.4, mean waist circumference 103 cm. Sixteen patients were GOLD I, 52 II, 30 III and 2 IV. Symptoms of chronic bronchitis were present in 66 %. Mean mMRC was 1.2 (range 0–4), mean CAT was 13.6 (range 3–40). Mean CCI age-adjusted was 4.9 (range 3–10), and mean COTE Index was 0.68 (range 0–4). 88 % patients had ≥1 chronic co-morbidity (**Figure 1**). The most frequent co-morbidities were hypertension (66 %), metabolic syndrome (38 %), ischemic heart disease (22 %), peripheral arterial disease (20 %), depression (16 %), non-pulmonary malignancies (14 %) and diabetes (12 %) (**Figure 2**). Interestingly, 15 of the 38 (40 %) patients with metabolic syndrome were never investigated before for metabolic syndrome.
Conclusions: These results confirm the high prevalence of chronic co-morbidities associated to COPD. Metabolic syndrome seems to be under-diagnosed and therefore under-treated in elderly overweight heavy smokers COPD patients. Management of COPD patients should include active search and treatment of chronic co-morbidities, particularly metabolic syndrome.

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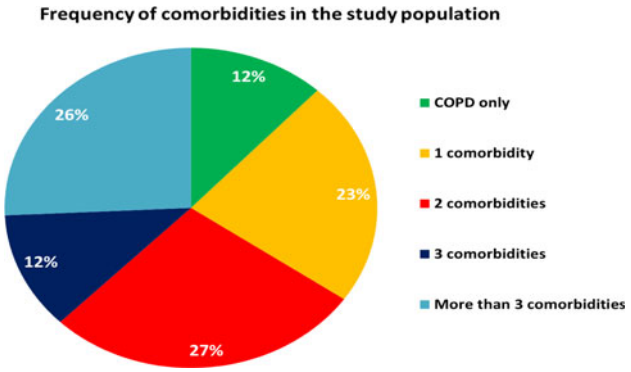

Figure 1

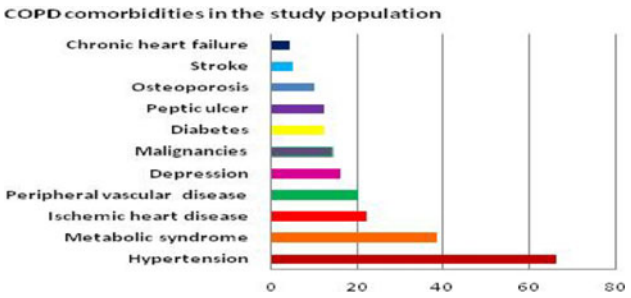

Figure 2

Rheumatology

Clinical observation of oxycodone/naloxone prolonged-release treatment in fibromyalgic syndrome: preliminary results

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Introduction: Fibromyalgia (FM) is a pain syndrome characterized by chronic widespread pain throughout the musculoskeletal system[1]. It is often accompanied by extraskeletal symptoms such as disturbed sleep, fatigue and psychophysiological distress. It affects 2 % of the general population with predominance in women. Unfortunately no laboratory tests which correlate with the subset and activity have been appropriately validated for FM, so the diagnosis is essentially clinical[2]. Several observations support the hypothesis of a central origin of pain with a characteristic time variation. Based on the discrete results obtained with opioid drugs, we decided to submit our patients to 16 weeks of treatment twice a day with 5/2.5 mg oxycodone/naloxone prolonged-release tablets[3].

Patients and Methods: A total of 47 FM outpatients were recruited (8 Males/39 Females, mean age 39.40 ± 15.30 years), who fulfilled ACR criteria by positivity of over 11 Trigger Points (TP) on a map of 18,. Each trigger point was rated from 0 point (no pain) to 3 points (most severe pain). TP score was assessed by finger pressure with the thumb or index finger, applying a gradually progressive force (about 4 kg/cm^2). The sum of the 18 tender points was calculated as the total myalgic score (TMS). Secondary measures included Pain Visual Analog Scale (VAS) and Fatigue VAS. The primary endpoint was the percentage of patients who reported a reduction in Pain Visual Analog Scale (VAS)≥40 % from baseline to week 16 and a decrease in the number of areas of hyperalgesia (TMS) by an average of 50 %.

Results: Five cases dropped out after 2 weeks because of AEs such as dizziness, nausea, anxiety, somnolence, while the other patients completed the period of therapy. 5/2.5 mg oxycodone/naloxone prolonged-release tablets treatment showed a satisfying reduction in Pain VAS. The treatment also obtained a significant improvement in fatigue as measured by Fatigue VAS. Overall, the treatment had a significant effect on improvement in sleep quality with a notable reduction of the impact of sleepiness and tiredness on daily activity. Even on a limited number of patients and for a short time, our preliminary results validate the efficacy and safety of 5/2.5 mg oxycodone/naloxone prolonged-release tablets twice a day in the treatment of pain, sleep disturbance, fatigue and activity in FM patients.

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Poly-arthralgia, persistent fever and neutrophilic leukocytosis: the case for misdiagnosing

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A 66-year old woman was admitted to our department because of intermittent-fever, symmetrical polyarthralgias, fatigue and itching skin erythema on the trunk, which had begun 6 months before. One month before admission reported a worsening of the above symptoms, associated with continuous-remittent fever, with peaks of 40 °C in the evening.

Her medical history was relevant for hypertension, diabetes mellitus, thalassemia trait. She reported, 2 years before, hospitalization for similar symptoms with diagnosis at discharge "Persistent fever".

At the admission, physical examination revealed salmon skin rash at the upper limbs and jugular-sternal region. A reduction of bibasal vesicular murmur was present, while cardiac, abdomen and neurological objectivity were normal.

Blood chemistry showed moderate neutrophilic leucocytosis, positive inflammatory markers (serum ferritin 32579 ng/ml, C-reactive protein 13 mg/dl, erythrocyte sedimentation rate 34, alpha-2 proteins 13, microcytic anemia (Hb 8.3 g/dl), high transaminases and thrombocytopenia (49000/mmc), normal thyroid and renal function. Chest X-ray and echocardiography were unremarkable, while total body CT scan showed bilateral basal pleural effusion and diffuse lymphadenopathy, with a maximum diameter of 3 cm. Axillary lymph node excision was performed and it was histologically reactive in nature.

The exclusion of infectious or neoplastic noxae and the presence of fever, rash, polyarthralgias, neutrophilic leukocytosis (major criteria), negativity for rheumatoid factor and ANA, increased transaminases,

and enlarged lymph nodes (minor criteria), were highly suggestive of Adult Still's Disease.
The diagnosis requires to fulfil at least 5 criteria, including at least 3 major ones.
Therapy with Prednisone (1 mg/kg/day) and Methotrexate (10 mg/weekly) was started with improvement of clinical and laboratory findings. The patient was therefore discharged, with indication to continue immunosuppressive treatment with top-down doses of corticosteroids and methotrexate.

Hypothyroidism and increased triglyceride levels in SSc patients

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The vascular damage in SSc consists mainly of microvascular changes, but recently macrovascular changes with dyslipidemia were recognized. A lipid profile is the result of complex metabolic process involving dietary habits, environmental influences and endocrine system function. Among the latter, thyroid function is of great interest with its influence on lipoprotein metabolism.
Objective: To evaluate the prevalence of clinical and subclinical thyroid diseases and to analyze lipid profile in a group of patients with SSc.
Methods: A total of 142 (122 F-20 M) unselected, consecutive pts with SSc were included in our study, with an average age of 58 years, 100 pts (70.4 %) with Limited SSc, 42 pts (29.6 %) with Diffuse SSc, and 40 healthy control group subjects. TSH, FT3, FT4, antithyroid peroxidase autoantibodies (AbTPO), thyroid ultrasonography, total cholesterol, HDL and LDL cholesterol levels, triglyceride levels were performed in all SSc patients and control group; and clinical data were carefully analyzed in all142 consecutive SSc patients.
Results: Higher prevalence of Thyroid autoimmune disorder we have seen in female pts versus male pts (12/1).SSc pts with Thyroid autoimmune disorder had longer disease duration (12 ± 7 vs. 5 ± 3 years $p < 0.005$. AbTPO 107 ± 286 IU/ml in SSc pts versus 24 ± 47 in control group ($p < 0.004$); FT3 4.4 ± 1.5 pmol/l versus 4.6 ± 0.8 (pNS);clinical hypothyroidism in 6 SSc pts (4.2 %) versus 1 control group (1.4 %) $p < 0.003$; subclinical hypothyroidism in 28 SSc pts (19.7 %) versus 4 control group (5.7 %) $p < 0.001$; Graves' disease in 2 SSc pts (1.40 %) versus 0 in control group; Thyroid volume <6 ml in48 SSc pts (33.8 %) versus in 16 control group (22.8 %);hypoechoic pattern in 76 SSc pts (53.5 %) versus 15 control group (21.4 %) $p < 0.001$ Comparing 34 pts with clinical and subclinical hypothyroidism (group A) versus 108 pts without clinical and subclinical hypothyroidism (Group B) we revealed: total cholesterol 213.1 ± 39.1 (group A) versus 173.4 ± 41.0 (group B); HDL- cholesterol 36.4 ± 8.1 versus 40.1 ± 4.2; triglyceridemia 175.1 ± 74.4 versus 110.7 ± 62.6; fibrinogenemia 392.1 ± 60.6 versus 380.3 ± 42.7 mg %. Digital ulcers in 19 pts (55.8 %) group A versus 16 pts(14.8 %) group B $p < 0.001$.
Conclusion: Hypothyroidism in SSc pts is significantly associated with a thyroid hypoechoic pattern by ultrasonography and a lower thyroid volume, AbTPO positivity was found in about half of SSc pts with Hypothyroidism. In cases of hypothyroidism, many SSc pts have elevations of both serum total cholesterol levels and triglyceride levels. The findings are of special importance in light of the increased prevalence of macrovascular disease observed in this group of pts.

Diagnosis of large vessel vasculitis with 18F-FDG PET-CT

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Case Report: Woman, 70 years, with history of hypertension, obesity and HCV positivity. The patient has been hospitalized because of fatigue, headache, arthralgia, fever (TC 37.8 °C) and normocytic anemia (8.7 g/dl) for a month. The medical examination didn't show any significant reports. The blood test stressed an increase of indices of inflammation (fibrinogen 616 mg/dl, D-Dimer 518 ug/L, PCR 79 mg/L, erythrocyte sedimentation rate 70 mm/h, ferritin 579 ng/ml, haptoglobin 4.07 g/L), negative blood cultures, Atc anti cyclic citrullinated peptide negative. Underwent endoscopy, echocardiography, and total body CT negative. On suspicion of giant cell arteritis (GCA) has been subjected to temporal artery biopsy was negative. For the high clinical suspicion of a vasculitic syndrome of the great vessels was also performed a ^{18}F-fluorodeoxyglucose-positron-emission tomography (^{18}F -FDG PET-CT) finding of "hypermetabolism of the wall all the large artery". After the diagnosis of vasculitis of large vessels began a therapy with Deltacortene 50 mg/day, that brought about a rapid clinical improvement and reduction of inflammatory markers. After 2 months of therapy ^{18}F -FDG PET-CT control: "low-level fixation of subclavian vessels indicative of therapeutic response is almost complete."
Conclusions: The two main large-vessel vasculitis are giant cell arteritis (GCA) and Takajasu's arteritis (TA). Both affect the aorta and its branches, including the temporal artery in GCA. The GCA occurs after 50 years and very often the clinic is typical, with headache, pain and/or temporal artery pulsatility deficits and the erythrocyte sedimentation rate is higher than 50 mm/h. The non-specific systemic symptoms are very common such as FUO, weight loss, the asthenia and anemia. The diagnosis is often difficult; but in recent years, the use of ^{18}F-FDG PET-CT can be helpful in diagnosing large-vessel vasculitis. The ^{18}F-FDG PET-CT is sensitive (77–92 %) and very specific (89–100 %) in the diagnosis of vasculitis of large vessels not treated with elevated markers of inflammation (Blockmans et al. Arthritis Rheum. 2006). Furthermore, this method is useful in monitoring the disease and response to therapy.

Effects of gabexate mesylate in pauci-immune vasculitis associated to disseminated intravascular coagulation

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Introduction: The vasculitis ANCA-associated are responsible for hypercoagulability, fibrinolysis, and increased bleeding tendency due to the release of pro-inflammatory cytokines.

Materials and Methods: A 69 years old man was admitted for renal failure (creatinine 7.1 mg/dL, urea 119 mg/dL), anemia (Hb 7.1 g/dL), thrombocytopenia, leg edema, purpura and splenomegaly. His medical history included diagnosis of short bowel syndrome from 16 years after car accident and since then in parental nutrition. Urinalysis documented hematuria and proteinuria of 1.2 g/24 h. The inflammatory markers were increased, the complement reduced (C3 470 mg/L) and ANCA negative. A rapidly progressive glomerulonephritis was suspected and a renal biopsy was performed showing a necrotizing small-vessel vasculitis pauci-immune type. Therefore steroid therapy was started. However, during the second week of hospitalization because of worsening of renal function (creatinine 9 mg/dL, urea 300 mg/dL) the patient was subject to three hemodialysis with reduction in creatinine to 4 mg/dL. For the simultaneous occurence of DIC (Fibrinogen 2.12 g/L, Ddimero 1908 ng/mL, INR 1.6, Ratio 1.61, platelets 45,000, ATIII 65.5 %) the patient was treated with several blood transfusions, with erythropoietin and plasma without improvement of hematological findings. However pancytopenia with bleeding tendency and hematuria persisted. A bone marrow biopsy showed hypocellularity of the three cell lines compatible with anemia iporigenerativa and for this reason immunosuppressive therapy could not bind to steroids for the treatment of vasculitis. The literature reported two cases of microscopic polyangiitis ANCA positive associated with DIC and treated with gabexate mesylate with improvement of hematological disorder. In our case report, even if in the presence of ANCA negative vasculitis, we treated coagulation disorder by administering gabexate mesylate at a dose of 600 mg/day × 2 weeks. After 2 weeks laboratory tests documented a good response (3.46 Fibrinogen g/L, Ddimero 708 ng/mL, INR 1.22, Ratio 1.22, PLT 99,000, ATIII 75.51 %) in the absence of gross hematuria.
Conclusions: Protease inhibitors may be a therapeutic option in patients with microscopic polyangiitis particularly when immunosuppressants are not feasible because of advanced age or when accompanied by DIC.

Helicobacter Pylori infection as a risk factor for disease severity in SSc patients

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Gastrointestinal tract (GI) disorders are recognized to be associated with great morbidity in SSc patients. Helicobacter pylori (HP) is suspected to be one of the factors triggering SSc.
Objective: The aim of this study was to determine the prevalence of upper GI manifestations associated with digestive clinical manifestations, gastric mucosal abnormalities on gastroscopy, and antroduodenal motor activity dysfunction on manometry oesophageal motor impairment and extradigestive manifestations and to assess the effect of HP eradication in SSc pts.
Methods: A total of 142 (122 F-20 M) unselected, consecutive pts with SSc were included in our study, with an average age of 58 years, 100 pts (70.4 %) with Limited SSc, 42 pts (29.6 %) with Diffuse SSc. We evaluated the disease severity using clinical and laboratory parameters according to the Medsger severity scale and the level of SSc activity was evaluated according to Valentini activity score. Upper GI involvement was assessed based on clinical symptoms such as regurgitation, pyrosis, solid and liquid dysphagia, bloating, nocturnal cough, gastroscopy and invasive test HP.
Results: 126 SSc pts (88.7 %) developed clinical symptoms of the upper GI involvement. Pyrosis (78 pts 61.9 %) was the most frequent symptom in upper GI. The prevalence of upper GI complications was similar between patients with Diffuse SSc 36 (85.7 %) and Limited SSc 89 (89 %).Gastroscopy was performed in all 126 SSc pts and invasive test for HP was positive in 72 SSc pts (61.9 %).We did not found any GI cancer, we found gastric ectasia in three pts and Barret oesophagus in five pts. Mucosal inflammation of oesophagus, stomach and duodenum was observed in 44,30,16 pts. In 28 cases, gastroscopy did not show any lesions. Severity of skin, GI, and joint/tendon involvement were different between H. pylori positive(72) and H. pylori-negative (54) SSc pts ($p < 0.001$ for skin involvement, $p = 0.002$ for GI involvement, $p = 0.003$ for joint/tendon involvement).Severity score according to Medsger was higher in H. pylori positive(72) and H. pylori-negative (54) SSc pts ($p < 0.001$).
Conclusion: GI involvement of SSc is common and widespread. Their effects on prognosis, morbility and life quality can be substantial. An early detection and treatment of GI disease will reduce the risk of complications. Our data suggest that helicobacter pylori infection correlates with severity of skin, GI and joint/tendon involvement in SSc pts. Helicobacter pylori positive SSc pts showed higher severity score compared with H. pylori negative SSc pts. Therefore Helicobacter pylori infection may play a role in the pathogenesis of SSc and can do prognostic information.

Clinical and radiological features of the hand and the foot in SSc patients

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Both the prognosis and the quality of life in SSc pts undoubtfully depend on the comorbidities. Arthritis is a commonly underestimated clinical problem.
Objective: We analyzed the clinical and radiological hand and foot features in a cohort of SSc pts at our centre and we examined the relationship with clinical parameters.
Methods: A total of 142 (122 F-20 M) unselected, consecutive pts with SSc were included in our study, with an average age of 58 years, 100 pts (70.4 %) with Limited SSc, 42 pts (29.6 %) with Diffuse SSc, and 40 healthy control group subjects. Clinical features of musculoskeletal manifestations, articular or periarticular pain, joint contractures, swelling were recorded. Tender and swollen joint counts, DAS-28 and the modified Rodnan Skin Score were compared with standard AP radiographs of the hand and foot and with contrast-enhanced low-field MRI of the metacarpophalangeal and metatarsophalangeal Joints. Hand disability was assessed by the Cochin Hand Function scale(CHFS).The severity of Joint effusion, synovitis, bone marrow oedema and erosions were analyzed using a 0–3 score(0: not detectable-3: severe). anti-citrullinated peptide antibodies (ACPA) and rheumatoid factor were determined in all SSc patients and control group; and clinical data were carefully analyzed in 142 consecutive SSc patients fulfilling Leroy and Medsger criteria. All the patients underwent clinical examination and X-ray.
Results: The mean CHFS for the entire group was 24.6. Foot features were Arthritis 23.9 % %, Erosive arthropathy 7.1 %,acro-osteolysis 7.1 %, and calcinosis 3 %.64/142 SSc pts (45 %)had arthralgias, 34 (23.9 %) had clinical arthritis; of 64 pts (45 %) with arthralgias: 42 pts had inflammatory MR findings with synovitis (78 %),tenosynovitis (14 %),erosion (66 %).Synovitis was more frequently detected on MRI (78 %) than clinically (18 %).Of 24(66 %) SSc pts with MRI erosions, only 9 SSc pts had radiographic erosions ($p < 0.01$) statistically significant association was found between positive ACPA and

erosion ($p = 0.0002$). ACPA were found in 30/142 (21.1 %) patients with SSc:14/72 with limited SSc, 16/42 with diffuse SSc; they were not found in control group. Significantly higher percentage of diffuse SSc had positive ACPA compared with others pts with SSc(26.2 vs. 7.1 % $p = 0.009$. Positive RF was found in 36/142 (25 %) SSc pts, RF not found in control group.

Conclusion: Osteoarticular and soft tissue involvement are more frequent in the hand and the foot and are a source of disability.

Prevalence of connective tissue diseases in italian patients hospitalized with FUO

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Background: Fever of unknown origin (FUO) is defined as a pattern of fever with temperature higher than 38.3 °C on several occasions over more than 3 weeks, in which the diagnosis remains uncertain after the initial diagnostic work-up [1]. FUO always represents diagnostic and therapeutic challenges [2]. It can be the initial symptom of connective tissue disease, an expression of the disease flare or unusual infections [3].

Objectives: Aim of our study was to estimate the prevalence of connective tissue diseases (CTD) in patients admitted to our Department with fever of unknown origin (FUO). We retrospectively analyzed the admission database of Internal Medicine Unit, University of Catanzaro, Italy.

Methods: We found 76 patients admitted in the years 2008–2011 with fever who fulfilled the Petersdorf and Beeson criteria for classification of FUO [4, 5]. Data were available about: full clinical assessment including full history taking, thorough clinical examination, laboratory investigations including the basic investigations for patients with prolonged fever, complete blood count, erythrocytes sedimentation rate, urine analysis and culture, blood culture, sputum culture and plain chest X ray. Further diagnostic work up and/or procedures were requested according to the potential diagnostic clues (PDC) present in every patient.

Results: Out of 76 FUO patients, 25 were found to have infectious diseases, 9 were found to have connective tissue diseases, 11 miscellaneous causes and 11 neoplastic diseases. In 21 patients no definite cause for FUO could be identified. Connective tissue patients were: 2 patients with psoriatic arthritis, 1 patient with systemic lupus patients, 1 patient with mixed connective tissue disease, 1 patient with familial mediterranean fever, 1 patient with erythema nodosum, 1 patients with Behcet disease, 1 patient with small vessels vasculitis, 1 patient with systemic amyloidosis.

Conclusions: Despite the advances in diagnostic technology, FUO remains a challenging medical problem. In our population infections were the most common cause of FUO, confirming the trends found in other parts of the world. Connective tissue disease, in general, accounts for a relatively small percentage of patients. However, within the category of CTD, no specific disease prevails over the others. Therefore, FUO may represent a form of nonspecific presentation of several different condition.

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Metabolic syndrome and its components in fibromyalgia patients

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Fibromyalgia is a rheumatic disease of uncertain aetiology characterized by chronic pain, fatigue, and insomnia. Patients with fibromyalgia commonly have an elevated body mass index and are physically inactive, 2 major risk factors for metabolic syndrome, a complex entity, characterized by the clustering of different cardiovascular risk condition such as atherogenic dyslipidemia, high blood pressure, visceral obesity and abnormal glucose metabolism. Yet little is known about the relationship between chronic pain conditions and metabolic disturbances. Aim of this work is to investigate the prevalence of metabolic syndrome in fibromyalgia patients.

In this study 103 consecutive fibromyalgia female patients referred to the Internal Medicine Unit, University of Catanzaro (Italy) for chronic widespread pain were recruited. Fibromyalgia was diagnosed by a single specialist according to 1990 American College of Rheumatology (ACR) Criteria. The presence of Metabolic Syndrome (MetS) was defined according to the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) criteria. These criteria define the presence of the MetS if three of the five following features are present: (1) Waist circumference $\geq$102 cm in men and $\geq$88 cm in women; (2) fasting triglycerides, $\geq$150 mg/dL or drug treatment for elevated triglycerides; (3) reduced high-density lipoprotein cholesterol (HDL-C), <40 mg/dL) in men and <50 mg/dL) in women, or drug treatment for reduced HDL-C; (4) blood pressure, $\geq$130 mmHg systolic blood pressure (SBP) or $\geq$85 mmHg diastolic blood pressure (DBP) or antihypertensive drug therapy; (5) fasting glucose, $\geq$100 mg/dL or drug treatment for hyperglycemia.

The mean age was 50.9 ± 9.0 years with a range from 32 up to 76 years. In our population, the prevalence of metabolic syndrome (MS) diagnosed according to AHA/NHLBI Guidelines was 40 %, with 41 out of 103 patients fulfilling at least three of the five features needed for diagnosing the syndrome.

Of our 41 patients diagnosed with metabolic syndrome (MetS+ group), 24 patients had three features, 14 patients had four, and 3 patients had five features. In the remaining patients (MetS− group), 34 had two features while only 6 had one feature and 22 had zero features.

Elevated waist circumference was found in 66/103 (64.02 %) patients; elevated triglycerides in 33/103 (32.01 %) patients; reduced HDL-cholesterol in 18/103 (17.46 %) patients; elevated blood pressure 69/103 (66.93 %); elevated fasting glucose in 31/103 (30.07 %). As expected, compared to the MetS−, MetS+ patients had a higher BMI (30.9 ± 4.9 vs. 27.5 ± 4.5, $p = 0.002$), fasting glucose (99.8 ± 13.6 vs. 89.1 ± 10.1, $p < 0.0001$) and fasting insulin levels (15.3 ± 9.7 vs. 9.5 ± 4.6, $p = 0.0001$). The number of positive tender points was significantly higher in MetS+ group ($p = 0.01$), while no statistical significant differences were found in ESR ($p = 0.28$) or CRP ($p = 0.32$) in MetS+ Vs MetS− patients. Female patients with fibromyalgia have increased prevalence of MetS. On the basis of our data and literature evidences seems plausible that

increased prevalence of MetS in patients with fibromyalgia is mainly due to an increased prevalence of high blood pressure and visceral obesity.

Central neurologic involvement in the course of systemic lupus erythematosus: reactivation of underlying disease or opportunistic infection?

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Background: Opportunistic infections in patients with systemic lupus erythematosus (SLE) represent diagnostic challenges. The risk factors of infections include immunosuppressive therapies and some manifestations of active SLE itself. These complications, though rare, are burdened by a high mortality rate. The central nervous system (CNS) is rare organ system of infections.
Case Report: We describe the case of a 29-year-old woman affected by SLE with cutaneous and haematological involvement, diagnosed in 2003. Throughout her history, the patient was treated with glucocorticoids and hydroxychloroquine, subsequently mycophenolate mofetil. In January 2011, following the onset of malaise, intense headache, and fever up to 38.8 °C not associated with shaking chills, the patient came to our observation. She had a poor headache response to therapy and a later onset of photophobia. Meningismus was noted. Laboratory examination showed mild neutrophilia, lymphopenia (320/mmc, with profound low CD4 count), ESR 42 mm/h, CRP = 6.3 mg/dl, no complement consumption, no significant proteinuria, all cultural and serological studies were negative for bacteria and fungi. Human immunodeficiency virus (HIV) serology was negative. Blood and urine cultures were negative. Cerebrospinal fluid (CSF) examination showed hypercellularity and increased protidorrachia. The research of JC virus in the liquor was negative. An India-ink preparation of the CSF was negative as a latex-agglutination test for cryptococcal antigen. The morphological investigations (brain CT and MRI) documented clustered enhancing nodules (diameter 5 mm) in the fronto-basal and cerebellar areas and a leptomeningitis pattern. Due to rapid clinical deterioration, with impaired consciousness and hydrocephalus, the patient was treated with CSF-leads in urgency. She was also treated with glucocorticoids for her SLE and with broad-spectrum antibiotics, with poor response. Infective serology data were not reliable due to the remarkable immunodeficiency state and it was not possible to perform additional investigations necessary to establish the diagnosis, such as biopsies to confirm or rule out some opportunistic infections.
Conclusions: This case has remained a medical mystery, suggesting the diagnostic difficulties in dealing with the differential diagnosis of opportunistic infections and neurological reactivation of SLE.

Diffuse idiopathic skeletal hyperostosis (DISH): a diagnostic challenge

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Introduction: Diffuse idiopathic skeletal hyperostosis (DISH) was first described by Forestier in 1950. The main characteristic of the disease is the calcification and the ossification of the anterior longitudinal spinal ligament. Peripheral enthesopathies, which often are ossified, are frequent findings. More common in men than women, its overall prevalence is reported to be greater than 10 % in subjects at age higher than 70 years old. Associated risk factors include obesity, type II diabetes, and hyperuricemia (1–5).
Clinical Case: A 53-year-old patient presented to our Hospital, worried about the occasional imaging findings of spondylitis on dorsal spine in a CT scan of the chest made for other reasons. His past medical history revealed a colon polypectomy with additional follow-up dependent upon the histological findings. Present personal and family history was not contributory. He denied fever, weight loss, lack of appetite, skin rash. General physical and systemic examination were normal for his age and lifestyle. Negative findings were found on musculoskeletal examinations. Complete blood count, erythrocyte sedimentation rate, serum level of calcium, liver enzymes, serum protein electrophoresis, and HLA-B27 were normal or non diagnostic. An X-ray of thoracic spine showed flowing ossification along anterior face of vertebral bodies separate from their anterior aspect. More than 4 levels were involved. An X-ray of the of the sacro-iliac joint excluded evidence for inflammatory sacroiliac disease. These findings are classic for DISH as defined by Resnick's criteria that require flowing calcification and ossification along the antero-lateral aspects of at least four contiguous vertebral bodies in absence of significant degenerative disk disease or inflammatory sacroiliac and facet changes.
The patient was reassured on the benignity of the disease and advised to replace amateur cycling with swimming and stretching exercises. Symptomatic treatment with NSAIDs was suggested only in presence of musculoskeletal pain. During the follow-up he was asymptomatic and maintained good health.
Discussion and Conclusions: Incidental imaging findings of spondylitis discovered in a chest CT scan supported the need of further investigations. The clinical history, physical examination, inconclusive laboratory tests, together with the classical findings on imaging of a thoracic spine X-ray, confirmed the suspect of DISH.

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Efficacy and safety of abatacept in patient with rheumatoid arthritis, comorbidities and intolerance to DMARDS

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Background: Rheumatoid arthritis (RA) is a chronic inflammatory disease, affecting about 1 % of the general population, with female predominance. In recent years the advent of anti-TNF biologic

therapies has actually changed the approach to the disease, by acting not only on a systemic treatment of disease, but also on the progression of joint damage. However, in clinical practice, already at 6 months, 50 % of patients treated with anti-TNF shows a poor response or intolerance occurs to the treatment, so that 1 out of 2 patient leaves the treatment at the same time frame.

Methods: The complete activation of T cells requires two signals: a main signal and a second signal, said co-stimulation. Abatacept as a humanized CTLA-4-immunoglobulin-Fc (CTLA-4-Ig) fusion protein, selectively modulates T cell co-stimulation. It prevents activation of T-cells by binding to the natural ligands CD 80 and CD86. In consequence, CD80 and CD86 cannot interact with CD28 on the T lymphocyte. As an important indirect effect within the inflammatory cascade, the production of cytokines and autoantibodies is inhibited. This helps to reduce inflammation, improving joint damage and other symptoms of the disease. Its use immediately after the methotrexate allows to achieve and maintain, in the follow-up clinical studies that currently come to 7 years, a low disease activity or remission.

Clinical Case: Male patient of 75 years, with a body weight of 70 kg, suffering from positive RA with high disease activity and comorbidities, which include chronic ischemic heart disease, pulmonary fibrosis for bullous emphysema, kidney failure, diabetes mellitus, duodenitis and recent episode of gastrointestinal bleeding from diverticulitis. In 1997, aged 60, was diagnosed with RA based on the clinical picture characterized by gradual onset pain and swelling at the level of the small joints of the hands, wrists, elbows, knees and ankles bilaterally, associated with long duration of morning stiffness, alteration of acute-phase reactants, positive for rheumatoid factor and antibodies anti CCP. The patient was initially treated with MTX (15 mg i.m. every 7 days) combined with low-dose corticosteroid and NSAIDs as needed. The MTX was discontinued after about 10 years due to alteration of liver function tests and nausea. Was introduced leflunomide 20 mg tablets (1cp/day). The therapy was discontinued after 3 months for the occurrence of dizziness, headache and paraesthesia. The patient was treated only with steroid and NSAIDs. In July 2011 the onset of pain and swelling at the level of the small joints of the hands, wrists, elbows, knees and ankles bilaterally, associated with morning stiffness and long-term functional impairment, fatigue, fever persisted. The patient was admitted to in the Department of Internal Medicine. Laboratory findings, at the entrance, were the following: ESR = 70 mm; CRP = 4 mg/dl; FR = 250 IU/l; Anti CCP = 300, Hb = 11.4 g/dl; increase in alpha1, alpha2, beta1 and beta2 globulins. Physical examination of the joints showed the following commitment: N° 22 tender joints, swollen joints N° 10, morning stiffness: 1 h. Disease activity(DAS 28) 7.3; SDAI 43. Because of worsening of clinical manifestations was introduced therapy with Abatacept 750 mg e.v. every 30 days, after induction with 750 mg e.v. at time 0.14 and 28 days. Concomitant therapy represented by low-dose corticosteroid and NSAIDs as needed in order to a synergistic action with biotechnology drug. Follow-up was made every 3 months by clinical and laboratoristic controls. The monitored clinically, in march of 2012, demonstrates into the joints considered the following results: tender joints N° 8, N° 3 swollen joints, morning stiffness: 30 min. The laboratory data were as follows: ESR = 35 mm, CRP = 1.5 mg/dl, normal blood count and QSP. Disease activity(DAS 28) 5.2; ICSD 18.

Conclusions: The introduction of Abatacept has helped to reduce the activity of disease, improve joint function and quality of life of the patient by reducing the dosage of cortisone even in the absence of therapy with DMARDS. In addition, there were no symptoms of intolerance or worsening of comorbidities.

Characteristics of arthritis in SSc patients

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In SSc, arthritis is a underestimated clinical problem.

Objective: We analyzed the prevalence and characteristics of arthritis in a cohort of SSc pts at our centre and we examined the relationship of Magnetic Resonance Imaging with clinical parameters.

Methods: A total of 142 (122 F-20 M) unselected, consecutive pts with SSc were included in our study, with an average age of 58 years, 100 pts (70.4 %) with Limited SSc, 42 pts (29.6 %) with Diffuse SSc, and 40 healthy control group subjects. Clinical features of musculoskeletal manifestations, articular or periarticular pain, joint contractures, swelling were recorded. Tender and swollen joint counts, DAS-28, functional capacity and the modified Rodnan Skin Score were compared with standard AP radiographs of the hand and wrist and with contrast-enhanced low-field MRI of the wrist and metacarpophalangeal Joints. The severity of Joint effusion, synovitis, bone marrow oedema and erosions were analyzed using a 0–3 score(0: not detectable- 3: severe). anti-citrullinated peptide antibodies (ACPA) and rheumatoid factor were determined in all SSc patients and control group; and clinical data were carefully analyzed in 142 consecutive SSc patients fulfilling Leroy and Medsger criteria.

Results: ACPA were found in 30/142 (21.1 %)patients with SSc:14/72 with limited SSc,16/42 with diffuse SSc; They were not found in control group. Significantly higher percentage of diffuse SSc had positive ACPA compared with others pts with SSc(26.2 %vs. 7.1 % $p = 0.009$. Positive RF was found in 36/142 (25 %) SSc pts, RF not found in control group. 64/142 SSc pts (45 %)had arthralgias, 34 (23.9 %) had clinical arthritis; of 64 pts (45 %) with arthralgias: 42 pts had inflammatory MR findings with synovitis (78 %),tenosynovitis (14 %),erosion (66 %).Synovitis was more frequently detected on MRI (78 %) than clinically (18 %).Of 24(66 %) SSc pts with MRI erosions, only 9 SSc pts had radiographic erosions ($p < 0.01$)Statistically significant association was found between positive ACPA and erosion ($p = 0.0002$).

Conclusion: Arthritis is a common finding in SSc even independent of clinical symptoms and signs.MRI is more sensitive method than clinical examination and radiological finding of inflammation in scleroderma. Our study demonstrates the presence of persistent, inflammatory, erosive arthropathy of the hand in SSc pts which is similar to RA.

Significant improvement of digital ulcers by bosentan in systemic sclerosis

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In Systemic Sclerosis (SSc), digital ischemia due to microvascular damage, sclerodactylia, and periodic vasospasm during Raynaud's attacks can lead to digital ulcers (DU), and bosentan has recently been proved to be efficacious for the prevention of new digital ulcers. Over the last 10 years controlled trials have shown clear benefits in the use of prostanoids.

Objectives: To assess the variation of digital ulcers number in SSc patients receiving a combined therapy with prostanoids and

endothelin receptor antagonist and to describe treatment outcomes and safety experiences.
Methods: Data were collected retrospectively from patients with DU, with and without pulmonary arterial hypertension, who were initiating bosentan + prostanoids therapy in 2004 (8 patients), in 2005 (6 patients), in 2006 (4 patients), in 2007 (10 patients),in 2008 (10 patients) and followed until December 2011. Relevant measures included number of DU, occurrence of new DU, overall DU clinical status: improved, stabilized, and worsened. We explored associations of disease subset, antibody profile, organ involvement, season, time interval after onset of Raynaud's phenomenon with development of DU and we describe potential risk factors for DU.
Results: 38 patients(29 F and 7 M) with SSc and DU were included. PAH was also present in 7 patients (18.4 %). At the start of combined therapy (bosentan + iloprost), the median number of DU was 3.0. More Digital Ulcers were present at the end of the cold season from February to May (p 0.036).DU clinical status was reported at 12° month of therapy: 32 patients (84.2 %) improved, in these patients digital ulcers healed within an observational period of 2.80 months (min 1, max 6 months), 3 patients (7.8 %) stabilized, 3 patients (7.8 %) had soft tissue infection requiring antibiotics, followed by gangrene and finally by surgical amputation. At 24° month of combined therapy 24 patients (63.1 %) did not develop any new DU, After the follow-ups at December 2011 3 patients were died for PAH, only 2 patients (7.2 %) had active digital ulcers and only Diffuse SSc, SCL-70 and lung fibrosis are significantly associated with DU.Our study showed a correlation between capillaroscopic damage and a higher degree of skin score, a higher prevalence of DU in pts with SSc who were male, and had diffuse cutaneous subset with anti-SCL-70 antibodies and cardiac and lung involvement ($p < 0.0001$).
Conclusion: The decreasing incidence of DU in follow-ups is ascribed to management of DU and we illustrated good long term outcomes through the utilization of combined treatment modalities. Bosentan is licensed for prevention rather than therapy of DU and in our study it also had a curative effect.

A 27 years old woman with ichthyoses and severe right flank pain

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A 27-year-old woman of Sardinian origin was admitted to hospital due to lymphadenopathy and fever .
The patient had a history of congenital ichthyoses and 5 months earlier had been admitted to another hospital due to polyserositis and lymphadenopathy. On that occasion, a laterocervical lymph node excisional biopsy showed aspecific lymphadenitis and the patient was treated with prednisone achieving clinical remission. Approximately 2 weeks before the admission, she suffered from a sore throat. In the following week, an intermittent high spiking fever exceeding 39 °C developed along with generalized myalgias and severe right flank pain, exacerbated by deep inspiration. No drug was introduced.
She didn't appear critically ill. Upon physical examination, widespread small lymphadenopathy were detectable. She didn't report respiratory symptoms, dysuria, headache, new onset of cutaneous manifestation or arthralgias. Blood pressure and oxygen saturation were normal, Laboratory tests detected normocytic anemia, normal reticulocytes count and elevated systemic inflammatory indicators (C reacting protein 108 mg/L, fibrinogen 8.89 g/L, D- Dimer 262 microg/L).Serum ferritin was normal (45 microg/l : reference range 30–400) White blood cell count was elevated (15.100/mm^3) and neutrophils were 13.500/mm^3; monocytosis was absent. Liver function test, CPK and LDH were normal. Blood cultures were sterile. Direct and indirect Coombs test was negative. Serum C3 and C4 were not decreased. Serological testing for the main possibly responsible infectious agents (viral Hepatitis, HIV, Cytomegalovirus, human Herpes virus, Rubella, Toxoplasma, Mycoplasma, Chlamydia pneumoniae, Adenovirus, Treponema pallidum, Vidal Wright, Weil Felix, Trichinella, Toxocara, Echinococcus, Borrelia, Quantiferon) and for autoimmunity (Anti Nuclear Antibody, antibodies, anti Extractable Nuclear Antiges, rhematoid factor, anti-citrullinated peptide antigen antibodies, and anticardiolipin, antiendomysial and antitransglutaminase antibodies) were negative. The measurement of thyroid hormones was normal.
Considering the available data, the initial diagnostic hypotheses were lymphoproliferative syndrome, leukemia, lymphoma, angioblastic lymphadenopathy, familiar Mediterranean fever, infectious endocarditis, granulomatous disorders, vasculitides, autoimmune seronegative disease, Inflammatory Bowel Disease or occult malignancies.
We performed computed tomography images of the chest, abdomen and pelvis after the intravenous administration of contrast material which showed widespread enlargement of lymph nodes, ranging from 10 to 14 mm (particulary bilateral axillary, pretracheal, mesenterial, along the right side, external right iliac right and bilateral inguinal lymph nodes were involved) but not relevant abnormalities of spleen, pancreas and adrenals; it also detected mild hepatomegaly without focal liver lesions, a small fluid collection in pelvis and adnexal cystis. The positron emission tomography showed minimal accumulation of tracer in some left sovraclavicolar lymphadenopathies and in anterior mediastinum compatible with inflammatory disease but did not reveal the presence of high metabolism disease.
The most likely diagnostic hypothesis, also considering the report of the lymph biopsy earlier performed, pointed to atypical onset of adult-onset Still disease with intermittent pattern (hyperferritinemia and rush were absent). The patient was initially treated with prednisone 50 mg/die—subsequently reduced—and showed no recurrence of symptoms during 18 months of surveillance.

Delayed systemic lupus erythematosus symptoms and increased survival by SerpinB3 in lupus-prone mice

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Introduction: Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease characterized by a loss of immunologic tolerance, production of anti-dsDNA antibodies and inflammatory damage in multiple organs. Defects of apoptosis and impaired clearance of apoptotic or necrotic cells are the main factors that influence the onset and the severity of the disease. SerpinB3 is a serine protease inhibitor that has been shown to inhibit apoptosis by preventing mitochondrial cytochrome c release. Recent data have described an impaired SERPINB3 expression in SLE patients, resulting in its absence on the surface of B lymphocytes.
Aim: Aim of the present study was to investigate the effect of the administration of SerpinB3 protein on the onset of lupus in a lupus-prone strain.
Materials and Methods: Sixteen NZB/NZWF1 female mice were injected with a total dose of 41.5 μg of recombinant SerpinB3 or of PBS. The recombinant protein was obtained by cloning the human SerpinB3 sequence in the pET101 expression vector, transformation into BL21 Star cells and purification of the obtained protein by

cationic exchange resin. Three intraperitoneal injections at 3 weeks interval were carried out starting from the age of 11 weeks. Urine samples were collected weekly and analyzed to determine the onset and the levels of proteinuria. Serial blood samples were collected and circulating anti-dsDNA and anti-C1q were analyzed by ELISA.
Results: A delayed onset of anti-dsDNA and anti-C1q antibodies were detectable in SerpinB3 treated mice compared to controls (week 28 vs. week 22) and their levels were significantly lower in treated animals ($p < 0.0001$). In keeping with these findings SerpinB3 treated mice showed a significantly delayed onset of proteinuria (week 42 vs. week 32, $p = 0.028$) and longer survival, with a gain of 10 weeks for the last mouse of each group ($p = 0.048$).
Conclusions: These results indicate that the administration of SerpinB3 to lupus-prone mice exerts a immunomodulatory and beneficial effect documented by a decrease in the onset of autoantibodies and of kidney damage, leading to increased survival.

Differential diagnosis of pain of the hips in a patient with a diagnosis of autoimmune liver disease

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A 43 years old man was referred to our attention for arthralgias at hands, feet, knees, and persistent pain of the hips with functional limitation. The patient had a previous diagnosis of autoimmune hepatitis treated with high dose corticosteroids and azathioprine.
Physical examination put in evidence signs of synovitis of the sacroiliac joints and ballottement of the right patella. Laboratory tests showed normality of hemochrome, liver and kidney function, whereas thyroid function tests indicated subclinical hypothyroidism (TSH: 17.3 MCU/ml with FT4 in the lower range of normality). Anti-thyroglobulin and anti-peroxidase antibodies were highly positive.
The diagnosis of autoimmune hepatitis had been formulated 4 months earlier for the presence of jaundice, hepatomegaly, dramatic increase of liver enzymes (x 30) and positive ANA (1/1024), in absence of markers of hepatic viral infections. Thus, the patient had been treated with prednisone (1 mg/kg), for 1 month, which was discontinued due to onset of diabetes mellitus and replaced with azathioprine (100 mg/day) with rapid normalization of liver enzymes and function.
Diagnostic hypotheses:

1. Arthralgias associated with autoimmune hepatitis;
2. Spondyloarthritis in a patient with a known family history of psoriasis;
3. Steroid-dependent, aseptic vascular necrosis of the femoral heads.

Previous diagnosis of autoimmune hepatitis was not confirmed because of (1) the acute onset of hepatitis, which is atypical of autoimmune liver diseases; (2) the rapid normalization of liver enzymes and function after short, high-dose steroid therapy; (3) the maintenance of remission after steroid withdrawal; (4) history of abuse of green tea, containing Camellia sinensis, a known hepatotoxic agent reported to induce acute toxic hepatitis 1.
The second diagnostic hypothesis was initially ruled out for negativity of inflammatory markers and presence on pelvis MRI, of avascular necrosis/aseptic osteonecrosis of both femoral heads, which confirmed the third diagnostic hypothesis. The patient was discharged with the diagnosis of bilateral aseptic necrosis of the femoral heads, chronic autoimmune thyroiditis, and previous acute toxic hepatitis. He was treated with high dose i.m. diphosphonate (100 mg disodium clodronate), thyroid hormone supplementation, and azathioprine was discontinued.
Three months after initiation of such therapy, the patient underwent X-rays of the pelvis showing absence of any structural alterations of the femoral heads but reduction of the hip joint. We started treatment with oral alendronate once/week and we confirmed the diagnosis of previous acute toxic hepatitis on the basis of normal liver enzymes and function after suspension of immunosuppressive therapy. One month later, the patient came again to our attention complaining about the onset of novel clinical manifestations: scalp lesions compatible with psoriasis, and hand arthralgias with signs of active synovitis. Laboratory testing showed increase of CRP and ESR. CASPAR criteria for psoriatic arthritis 2 diagnosis were met, and the patient started treatment with adalimumab 40 mg once/2 weeks with rapid amelioration of skin and joint involvement.

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Tocilizumab treatment in rheumatoid arthritis: results from a real-life retrospective cohort study

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Background: Tocilizumab (TCZ) is a novel anti-IL6 drug licensed for moderate to severe Rheumatoid Arthritis (RA). No data about its effectiveness and safety coming from real-life practice are still available in Italy.
Population: In this retrospective study we describe 39 patients, F/M 35/4, aged 61 years (median), duration of disease 8 years (median), who received TCZ 8 mg/kg every 4 weeks. Median follow-up is 12.5 months. 23/39 were treated in monotherapy. The most frequent combination therapy was Methotrexate (31 %). Only 20 % of the enrolled patients were naïve for previous biological treatments.
Results: We observed an high survival to the treatment (80 % at 12 month). All the drop-out (6 cases: lack of efficacy (2), adverse events (3) and other reasons (1)) were observed within the 8° month. Mean DAS-28 significantly decreased from 5.07 to 2.57 after 6 months (31 evaluable patients), with a further fall to 1.9 after 12 months (21 evaluable). Remission or low-disease activity was achieved in all pz after 1 year, either in monotherapy or combination. We observed 10 infectious events: 9 mild upper respiratory or mucocutaneous infections and 1 pneumonia requiring parenteral therapy. Furthermore we report mild neutropenia in 9 cases, transient increase of liver enzymes (5) and two minor infusional reactions (0.44 % of 451 infusions) leading to TCZ discontinuation.
Conclusions: Our experience is the first evaluation of TCZ efficacy and safety in a italian population followed in a real practice setting. Our data confirm the favorable safety and efficacy profile for this drug, even when used as monotherapy.