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HEMATOLOGY

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Polycythemia

DIFFERENTIAL DIAGNOSIS

SPURIOUS—stress (Geisböck's syndrome), decrease intravascular volume

PRIMARY—polycythemia rubra vera

SECONDARY ★HERA★

- **HYPOXIA**—obstructive sleep apnea, COPD, smoking, high altitude
- **EPO-SECRETING TUMORS**—renal, hepatoma, cerebellar, pheochromocytoma
- **RENAL**—polycystic kidney disease, hydronephrosis, post-transplant
- **ADRENAL**—Cushing's syndrome

PATHOPHYSIOLOGY

DEFINITION OF POLYCYTHEMIA—hematocrit >0.6 in ♂, hematocrit >0.5 in ♀

Related Topics

Hypoxemia (p. 92)

Myeloproliferative Disorders (p. 165)

CLINICAL FEATURES

HISTORY—hyperviscosity (headache, blurred vision, epistaxis), dyspnea, epigastric pain, weight loss, fever, night-sweats, pruritus, erythromelalgia, recent travel to high-altitude areas, past medical history (respiratory diseases, myeloproliferative disorders, myocardial infarction, stroke, pulmonary embolism, DVT, renal disorders, smoking), medications (androgens, EPO)

PHYSICAL—hypertension, oxygen saturation, facial plethora, conjunctival injections, engorgement of the veins of the optic fundus, abdominal mass, hepatomegaly, splenomegaly, excoriations, stigmata of a prior arterial or venous thrombotic event, gouty arthritis, and tophi

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, LAP, vitamin B12, RBC mass (total blood volume \times Hct, to rule out spurious causes), carboxyhemoglobin level, cortisol level, peripheral blood smear
- **IMAGING**—CXR

SPECIAL

- **JAK2 MUTATION**—JAK2 is a cytoplasmic tyrosine kinase activated by EPO binding to its receptor; the V617F mutation activates JAK2 and thereby drives EPO-independent erythropoiesis
- **EPO LEVEL**—low in PRV, high if secondary causes
- **HYPOXIA WORKUP**—oximetry, ABG, CO-hemoglobin
- **SOLID TUMOR WORKUP**—CT abd, MRI head (if tumors)
- **BONE MARROW BIOPSY**—rule out myelofibrosis and CML

DIAGNOSTIC ISSUES

CRITERIA FOR POLYCYTHEMIA RUBRA VERA (PRV)

- **ABSOLUTE**—↓ RBC mass, no secondary cause (normal PaO₂, EPO not elevated)
- **MAJOR**—splenomegaly, JAKV617F
- **MINOR**—WBC $>12 \times 10^3/\mu\text{L}$, platelet $>400 \times 10^3/\mu\text{L}$
- LAP $>100\text{U/L}$ and vitamin B12 $>650\text{pmol/L}$ [$>880\text{ pg/mL}$]
- **DIAGNOSIS**—need absolute criteria plus one major or two minor criteria for the diagnosis of polycythemia rubra vera. See myeloproliferative disorders (p. 165) for more details

MANAGEMENT

TREAT UNDERLYING CAUSE—**relative** (hydration), **CO hemoglobinemia** (smoking cessation. See p. 418), **sleep apnea** (CPAP. See p. 17), **polycythemia vera** (cytoreduction with hydroxyurea is preferable to phlebotomy to keep hematocrit <0.45 in ♂ and <0.42 in ♀, ASA 81 mg PO daily prevents thrombosis—but watch out for bleeding)

Microcytic Anemia

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DIFFERENTIAL DIAGNOSIS

★TAILS★

THALASSEMIA

ANEMIA OF CHRONIC DISEASE—infection, malignancy, inflammatory disorders

IRON DEFICIENCY—blood loss (GI, GU, vaginal, trauma), iron-deficient diet, celiac disease, atrophic gastritis, renal failure on EPO, pulmonary hemosiderosis, intravascular hemolysis

LEAD POISONING

SIDEROBLASTIC

PATHOPHYSIOLOGY

DEFINITION OF MICROCYTIC ANEMIA—Hb <135 g/L [<13.5 g/dL], MCV <80 fL

SEQUENCE OF IRON DEFICIENCY— \downarrow iron \rightarrow \uparrow TIBC \rightarrow \downarrow Hb \rightarrow \downarrow MCV \rightarrow hypochromia

ANEMIA OF CHRONIC DISEASE—chronic inflammatory states such as malignancy, infection and rheumatologic diseases \rightarrow \uparrow INF γ , TNF α , IL-1, IL-6, IL-10 \rightarrow \uparrow hepatic expression of hepcidin which inhibits duodenal absorption of iron, \uparrow uptake and storage of iron into monocytes and macrophages, \downarrow production of EPO \rightarrow \downarrow availability of iron for erythrocytes \rightarrow anemia (microcytic or normocytic)

CLINICAL FEATURES

HISTORY—shortness of breath, chest pain, dizziness, fatigue, bleeding (GI, menstrual), pica (ice, dirt), diet history, fever, night sweats, weight loss, past medical history (malignancy, chronic infections, rheumatologic disorders), medications (NSAIDs, ASA, anticoagulants), family history (thalassemia)

PHYSICAL—vitals, koilonychia (spoon nails), alopecia, blue sclerae, conjunctival pallor, angular chlorosis, atrophic glossitis, lymphadenopathy (anemia of chronic disease), rectal examination for occult blood and pelvic examination for blood loss

INVESTIGATIONS

BASIC

- **LABS**—CBCD, peripheral smear, reticulocyte count, serum iron, serum ferritin, TIBC (transferin), % sat, Hb electrophoresis, fecal occult blood (if suspect GI bleed)

SPECIAL

- **ENDOSCOPY**—gastroscopy and/or colonoscopy targeting symptoms in any man or post-menopausal woman with iron deficiency or in anyone with suspected GI bleeding
- **SOLUBLE TRANSFERRIN RECEPTOR (sTfR)**—helps to distinguish between iron deficiency and anemia of chronic disease

INVESTIGATIONS (CONT'D)

- **LIVER BIOPSY**
- **BONE MARROW ASPIRATE AND BIOPSY WITH IRON STAIN**

DIAGNOSTIC ISSUES

IRON INDICES

| | Ferritin | Iron | TIBC | % sat |
|---------------------------|---------------|-----------------|-----------------|-----------------|
| Iron deficiency | \downarrow | \downarrow | \uparrow | \downarrow |
| Anemia of chronic disease | \uparrow /N | \downarrow | N/ \downarrow | N/ \downarrow |
| Thalassemia | \uparrow /N | \uparrow | \downarrow | \uparrow |
| Sideroblastic | N/ \uparrow | N/ \downarrow | N/ \downarrow | N/ \downarrow |

DISTINGUISHING FEATURES BETWEEN IRON DEFICIENCY AND THALASSEMIA

- **RDW**—red cells in thalassemia tend to have a narrower distribution than in iron deficiency
- **MCV**—red cells in thalassemia tend to be smaller than in iron deficiency
- **RBC**—RBC high or normal if thalassemia but tend to decrease proportionally to Hb in iron deficiency
- **THALASSEMIA INDEX**—MCV/RBC. Suggests thalassemia if <13 and iron deficiency if >13
- **MORPHOLOGY**—thalassemia causes microcytic target cells

DISTINGUISHING FEATURES BETWEEN IRON DEFICIENCY AND ANEMIA OF CHRONIC DISEASE—ferritin is indicative of marrow iron stores and is key to the diagnosis of iron deficiency anemia as serum iron and TIBC levels may change with other diseases

- **<30 ng/ml**—iron deficiency anemia (PPV 92–98%)
- **30–100 ng/ml**—combination of anemia of chronic disease and true iron deficiency if (sTfR/log ferritin)>2. Anemia of chronic disease alone if (sTfR/log ferritin) <1
- **100 ng/ml**—anemia of chronic disease

MANAGEMENT

SYMPTOM CONTROL—transfusion 2 U PRBC IV over 2 h

TREAT UNDERLYING CAUSE—iron deficiency (*iron gluconate* 300 mg PO TID, *iron sulfate* 325 mg PO TID, *sodium ferric gluconate* complex in sucrose 125 mg IV, *ferumoxytol* 510 mg IV). It may take up to 6 weeks to correct anemia and 6 months to replete iron stores

SPECIFIC ENTITIES

PLUMMER–VINSON SYNDROME—iron deficiency anemia, atrophic glossitis and esophageal web. Increased risk of esophageal squamous cell carcinoma

Normocytic Anemia

DIFFERENTIAL DIAGNOSIS

ACUTE BLOOD LOSS—GI, GU, pelvis/abdomen, skin, CNS

↓ PRODUCTION

- **PRIMARY MARROW DISORDERS**—bone marrow suppression from drugs (esp. chemotherapy), multiple myeloma, myelodysplasia, myeloproliferative disorders, lymphoma, metastasis, infections (esp. TB)
- **DECREASED EPO**—renal failure
- **ANEMIA OF CHRONIC DISEASE**

SEQUESTRATION—splenomegaly

↑ DESTRUCTION

- **IMMUNE**—autoimmune hemolytic anemia (warm agglutinins, cold agglutinins)
- **NON-IMMUNE**
 - **RBC MEMBRANE**—spherocytosis
 - **RBC ENZYMES**—G6PD, pyruvate kinase deficiency
 - **RBC HEMOGLOBIN**—sickle cell anemia
 - **MICROANGIOPATHIC**—DIC, HUS/TTP, prosthetic valve, hypertensive crisis
 - **BLOOD**—toxins, infections (malaria), immune

MIXED PICTURE—combined microcytic and macrocytic anemia (e.g. malnutrition causing iron deficiency and vitamin B12 deficiency)

PATHOPHYSIOLOGY

DEFINITION OF NORMOCYTIC ANEMIA—Hb < 135 g/L (>13.5 g/dL), MCV 80–100 fL

CLINICAL FEATURES

HISTORY—shortness of breath, chest pain, dizziness, fatigue, bleeding, fever, night sweats, weight loss, diet history, past medical history (malignancy, chronic infections, rheumatologic disorders, liver disease, renal disease, alcohol, hypothyroidism, myelodysplasia), medications (NSAIDs, ASA, chemotherapy, anti-biotics, antiepileptics), family history (thalassemia)

PHYSICAL—vitals, jaundice, conjunctival pallor, cardiac examination, liver examination. Check for macroglossia, subacute combined degeneration and peripheral neuropathy. Rectal examination for occult blood

INVESTIGATIONS

BASIC

- **LABS**—CBCD, peripheral smear, reticulocyte count, iron, ferritin, TIBC, % sat, Cr, TSH, AST, ALT, ALP, bilirubin, INR, PTT, haptoglobin, LDH, direct and indirect Coombs test, serum protein electrophoresis, fecal occult blood (if suspect GI bleed)

INVESTIGATIONS (CONT'D)

SPECIAL

- **URINE TESTS**—urinalysis (hemoglobinuria)
- **BONE MARROW BIOPSY**

DIAGNOSTIC ISSUES

MCHC—↑ MCHC suggests spherocytosis

MCV—a rise in MCV suggests reticulocytosis; ↑↑↑ MCV indicates the presence of cold agglutinins causing agglutination in the laboratory specimen before blood is run through the analyzer

COOMBS TEST

• **DIRECT COOMBS TEST (DAT)**—patient's washed RBC incubated with anti-IgG and anti-C3. A positive result (i.e. agglutination) indicates that IgG and/or C3 have bound to RBC surface in vivo. DAT positivity suggests immune rather than non-immune causes of hemolysis

- **IMMUNE HEMOLYTIC ANEMIA (DAT positive)**—autoimmune hemolytic anemia, drug-induced hemolytic anemia, alloimmune hemolytic anemia (acute hemolytic reaction)
- **NON-IMMUNE HEMOLYTIC ANEMIA (DAT negative)**—TTP/HUS, DIC, hemoglobinopathies, hereditary spherocytosis

• **INDIRECT COOMBS TEST**—normal RBC incubated with patient's serum. It is mainly used to detect low concentrations of antibodies in a patient's serum prior to blood transfusion

RETICULOCYTE PRODUCTION INDEX (RPI, corrected reticulocyte count)—more accurate than raw reticulocyte count to evaluate if bone marrow response to anemia is appropriate or hypoproliferative

- **RPI** = [retic count × (hematocrit in %/45)]/maturation factor

| Maturation factor | Hematocrit |
|-------------------|------------|
| 1.0% | 45% |
| 1.5% | 35% |
| 2.0% | 25% |
| 2.5% | 20% |

- **INTERPRETATION**—RPI >2% suggests adequate marrow response, < 2% suggests hypoproliferative (i.e. ↓ production)

MANAGEMENT

TREAT UNDERLYING CAUSE

SYMPTOM CONTROL—**transfusion** 2 U PRBC IV over 2 h. **Erythropoietin** (*epoetin alfa* 50–200 U/kg/week SC/IV div 2–3×/week, *darbepoetin alfa* 20–40 µg SC weekly) for anemia of chronic kidney disease or selected patients on active chemotherapy

SPECIFIC ENTITIES

AUTOIMMUNE HEMOLYTIC ANEMIA: WARM AGGLUTININS—IgG

- **CAUSES**—**neoplasia** (CLL, especially with fludarabine, pentostatin, cladribine), **autoimmune** (SLE), **infections** (viral), **drugs** (penicillins, fludarabine, methyl dopa)
- **CLINICAL FEATURES**—anemia, jaundice, splenomegaly, anemia, smear (microspherocytosis), ↑ reticulocytes, ↑ bilirubin, ↑ LDH, ↓ haptoglobin, direct Coombs test (IgG±, C3±)
- **TREATMENTS**—**symptom control** (transfusion with caution, difficult to cross-match due to autoantibodies reacting with antigens present on cells of almost all individuals). **Steroids** (prednisone 1 mg/kg PO daily, taper after stable). Reduce effectiveness of antibodies (IVIg, splenectomy). **Immunosuppression** (azathioprine 100–150 mg PO daily, cyclophosphamide 100 mg PO daily). **Biological**

SPECIFIC ENTITIES (CONT'D)

agents (rituximab, alemtuzumab). **Treat underlying disease** (CLL, SLE, drugs)

AUTOIMMUNE HEMOLYTIC ANEMIA: COLD AGGLUTININS—IgM

- **CAUSES**—**neoplasia** (CLL, lymphoma, Waldenström's macroglobulinemia, adenocarcinoma), **infections** (mycoplasma pneumonia, infectious mononucleosis, CMV, VZV)
- **CLINICAL FEATURES**—anemia, agglutination, jaundice, splenomegaly. Anemia, smear (spherocytosis), ↑ reticulocytes, ↑ bilirubin, ↑ LDH, ↓ haptoglobin, direct Coombs test (IgG–, C3+), cold agglutinin screen
- **TREATMENTS**—**symptom control** (avoidance of cold). **Chemotherapy** (cyclophosphamide, chlorambucil). **Biological agents** (rituximab, INFα). Plasmapheresis

Macrocytic Anemia

DIFFERENTIAL DIAGNOSIS

LIVER DISEASE

ALCOHOL

DRUGS—**chemotherapy** (hydroxyurea, cytosine arabinoside, methotrexate, azathioprine, cladribine, capecitabine), **antiepileptics** (phenytoin, phenobarbital), **antibiotics/antivirals** (trimethoprim-sulfamethoxazole, zidovudine)

VITAMIN B12 DEFICIENCY FROM PERNICIOUS ANEMIA

DIETARY FOLATE DEFICIENCY

MYELODYSPLASTIC SYNDROME

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

HYPOTHYROIDISM

RETICULOCYTOSIS

PATHOPHYSIOLOGY

DEFINITION OF MACROCYTIC ANEMIA—

Hb <135 g/L [>13.5 g/dL], MCV >100 fL

Related Topics

Alcoholism (p. 105)

Chronic Liver Disease (p. 132)

Myelodysplastic Syndrome (p. 166)

Vitamin B12 Deficiency (p. 405)

CLINICAL FEATURES (CONT'D)

alcohol, hypothyroidism, myelodysplasia), medications (chemotherapy, antibiotics, antiepileptics)

PHYSICAL—look for signs of hypothyroidism, vitamin B12 deficiency and liver disease. Vitals (bradycardia, hypoventilation, hypotension), leukonychia, clubbing, Dupuytren's contractures, palmar erythema, asterixis, cool and dry skin, vitiligo, hair thinning, alopecia areata, periorbital edema, scleral icterus, conjunctival pallor, altered mental status, anemia, macroglossia, parotid enlargement, fetor hepaticus, goiter, lymphadenopathy, spider angiomas, gynecomastia, pericardial effusion, ascites, splenomegaly, caput medusa, hemorrhoids, testicular atrophy, proximal muscle weakness, hyporeflexia, edema (non-pitting), petechiae, subacute combined degeneration of the cord (B12 deficiency affecting dorsal columns and lateral corticospinal tracts), peripheral neuropathy

INVESTIGATIONS

BASIC

- **LABS**—CBCD, peripheral smear, reticulocyte count, vitamin B12, RBC folate, TSH, AST, ALT, ALP, bilirubin, INR, PTT

SPECIAL

- **SCHILLING'S TEST** for poor vitamin B12 absorption from intrinsic factor deficiency
- **BONE MARROW BIOPSY**

CLINICAL FEATURES

HISTORY—shortness of breath, chest pain, dizziness, fatigue, bleeding, fever, night sweats, weight loss, diet history, past medical history (liver disease,

MANAGEMENT

SYMPTOM CONTROL—**transfusion** 2 U PRBC IV over 2 h in everyone except those with pernicious

MANAGEMENT (CONT'D)

anemia. For patients with pernicious anemia, transfuse fewer units and transfuse each unit slowly over 3 h since an expanded intravascular volume puts patients at risk for transfusion-induced pulmonary edema

MANAGEMENT (CONT'D)

TREAT UNDERLYING CAUSE—folate deficiency (folate 0.4 mg PO/SC/IM daily \times 4–5 d). **Vitamin B12 deficiency** (vitamin B12 1000 μ g SC/IM daily \times 5–10 days, then 1000 μ g SC/IM qweek \times 4 weeks, then every month). **Hypothyroidism** (*L-thyroxine* start 12.5–50 μ g PO daily, adjust every 2 weeks)

Sickle Cell Disease

PATHOPHYSIOLOGY

β -CHAIN MUTATION—leads to formation of hemoglobin S (α 2 β S2) \rightarrow polymerization of hemoglobin S \rightarrow elongated fibers that distort shape of RBC \rightarrow vasoocclusive phenomena (infarctions, ischemia) and hemolysis. Subtypes include **sickle cell disease** (homozygous HbS, most severe), **hemoglobin SC disease** (heterozygous HbS and HbC, moderately severe) and **sickle cell trait** (heterozygous HbS, mild)

CLINICAL FEATURES

★ ABCDEFGH PAIN ★

ANEMIA

- **CHRONIC HEMOLYSIS**—normo or macrocytic due to reticulocytosis, elevated bilirubin, LDH, low haptoglobin). There may be associated folate/iron deficiency from increased utilization
- **ACUTE ANEMIA**—may be due to splenic sequestration crisis (venoocclusion of spleen leading to RBC pooling), aplastic crisis (transient arrest of erythropoiesis), and hyperhemolytic crisis (sudden onset of severe hemolysis). All of these may be triggered by viral infections such as parvovirus B19

BONES—bone infarction (pancytopenia), avascular necrosis, fat embolism, orbital compression syndrome

CARDIAC—myocardial infarction (due to increased oxygen demand from cardiac output)

DERMATOLOGIC—leg ulcers

EYES—proliferative retinopathy, retinal artery occlusion, retinal detachment and hemorrhage

FAIRLY BAD PAIN—back, chest, extremities, and abdomen. May be associated with fever, swelling, tenderness, tachypnea, hypertension, nausea, and vomiting. May be precipitated by weather changes, dehydration, infection, stress, menses, and alcohol. Multi-organ failure may develop in severe pain episodes

GENITAL—priapism

HEPATOSPLENIC—splenic infarction, acute hepatic ischemia, hepatic sequestration crisis, iron overload (transfusions)

PULMONARY—restrictive lung disease (chronic interstitial fibrosis), obstructive lung disease, hypoxemia, pulmonary hypertension, fat embolism

CLINICAL FEATURES (CONT'D)

ANEMIA—remember that sickle cell disease is associated with both acute and chronic anemia

INFECTIONS—sepsis (particularly asplenic patients), meningitis, pneumonia, osteomyelitis

NEUROLOGIC—ischemic stroke, intracerebral hemorrhage, septic emboli, spinal cord infarction or compression, vestibular dysfunction, sensory hearing loss, cognitive failure

INVESTIGATIONS

BASIC

- **LABS**—CBC/D, lytes, urea, Cr, AST, ALT, ALP, bilirubin, LDH, haptoglobin, smear (sickled red cells, polychromasia from reticulocytosis, Howell–Jolly bodies from hyposplenia), reticulocytes, RBC folate, Fe, ferritin, % saturation, transferrin, hemoglobin electrophoresis (identify subtypes), urinalysis
- **MICROBIOLOGY**—blood C&S, sputum Gram stain/AFB/C&S, urine C&S, stool C&S, O&P, C. diff toxin A/B

MANAGEMENT

ACUTE—ABC, O₂, IV

- **VASOOCCLUSIVE PAIN CRISIS**—fluids, pain control (morphine, ketorolac)
- **APLASTIC CRISIS**—transfusions. Avoid GCSF
- **SEQUESTRATION CRISIS**—younger patients
- **HEMOLYTIC CRISIS**
- **ACUTE CHEST SYNDROME** (chest pain, pulmonary infiltrates, cough, progressive anemia, hypoxemia, with or without fever)—treat precipitating factor, fluids, pain control, transfusions (simple or exchange)
- **PRIAPISM**—hydration, analgesics, transfusions, urology consultation
- **PREOPERATIVELY**—transfuse to Hb 100 g/L [10 g/dL]

CHRONIC—interprofessional team, **immunizations** (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Nisseria meningitidis*, hepatitis B virus, and influenza), **exchange transfusion** (goal HbS < 30%), **hydroxyurea** (increase levels of fetal Hb, decrease incidence of vasoocclusive pain), **folic acid** 1 mg PO daily

SPECIFIC ENTITIES

ASPLENIC PATIENTS—particularly susceptible to encapsulated bacteria (*S. pneumoniae*, *H. influenzae*, and *N. meningitidis*), *Capnocytophaga canimorsus*, Gram-negative enteric organisms, and babesiosis

- **VACCINATIONS**—all patients should receive vaccinations against *H. influenzae*, pneumococcus, and meningococcus. Flu shot should be given annually and other immunizations repeated every 5 years

SPECIFIC ENTITIES (CONT'D)

- **ANTIBIOTICS WITH FEVER**—any fever in an asplenic patient should prompt self-administration of pre-prescribed antibiotics (*levofloxacin* 750 mg PO daily, *moxifloxacin* 400 mg PO daily, or *cefuroxime* 1 g PO daily). Patients should then seek medical advice urgently
- **MEDICAL ALERT BRACELET**

Neutropenia

DIFFERENTIAL DIAGNOSIS

★PANIC★

POST-INFECTIONOUS—sepsis

AUTOIMMUNE—drug induced, SLE

NEOPLASTIC—lymphoproliferative disorders, myelodysplasia, leukemias, myelophthisis

INFECTIONS—sepsis, HIV

INSUFFICIENCY—folate, vitamin B12

IATROGENIC—chemotherapy, chloramphenicol, trimethoprim-sulfamethoxazole, synthetic penicillins, phenytoin, carbamazepine, NSAIDs, gold, antithyroid medications, phenothiazines, clozapine

CONSUMPTION—hypersplenism

Related Topic

Febrile Neutropenia (p. 236)

PATHOPHYSIOLOGY

DEFINITION OF NEUTROPENIA—neutrophils $< 1.5 \times 10^3/\mu\text{L}$

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, peripheral smear, PTT, INR, AST, ALT, ALP

INVESTIGATIONS (CONT'D)

SPECIAL

- **FURTHER WORKUP**—bilirubin, fibrinogen, LDH, ANA, vitamin B12, RBC folate
- **BONE MARROW BIOPSY**

MANAGEMENT

TREAT UNDERLYING CAUSE

GROWTH FACTORS—in some cases, the use of myeloid growth factors such as G-CSF or GM-CSF is appropriate

TREATMENT ISSUES

FEBRILE VS. NON-FEBRILE NEUTROPENIA—the presence of fever ($>38^\circ\text{C}$ [$>100.4^\circ\text{F}$]) in a neutropenic patient is considered an emergency, as overwhelming sepsis can develop quickly. Patients with febrile neutropenia (see p. 236 for definition) require early evaluation, initiation of antibiotics, and potentially hospitalization. However, neutropenia alone without fever can usually be monitored on an outpatient basis. Isolation is usually not required, although patients should avoid being in contact with people with active infections

SPECIFIC ENTITIES

ETHNIC NEUTROPENIA—neutrophil counts in blacks are generally lower. Neutrophil count may be down to $1.5 \times 10^3/\mu\text{L}$ and still be considered normal

Eosinophilia

DIFFERENTIAL DIAGNOSIS

★PAIN★

PRIMARYLY ORGAN-SPECIFIC DISORDERS

- **PULMONARY**—interstitial lung disease, AIDS-related pneumonia, idiopathic eosinophilic pneumonia, drug-induced lung disease

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **GASTROINTESTINAL**—eosinophilic gastroenteritis, eosinophilic esophagitis, primary biliary cirrhosis, primary sclerosing cholangitis

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **GENITOURINARY**—acute interstitial nephritis, acute post-streptococcal glomerulonephritis, eosinophilic cystitis, eosinophilic prostatitis
- **RHEUMATOLOGIC**—eosinophilia–myalgia syndrome and idiopathic eosinophilic synovitis, Churg–Strauss syndrome
- **DERMATOLOGIC**—eosinophilic panniculitis, episodic angioedema with eosinophilia, Kimura disease and angiolymphoid hyperplasia with eosinophilia, eosinophilic fasciitis, eosinophilic cellulitis, eosinophilic pustular folliculitis, recurrent cutaneous necrotizing eosinophilic vasculitis, eosinophilic ulcers of the oral mucosa

ALLERGIES

- **NASAL**—allergic rhinitis, asthma, nasal polyposis
- MEDICATIONS**—**cytokine mediated** (GM-CSF, IL-2), **pulmonary** (NSAIDs), **gastroenteritis** (NSAIDs), **interstitial nephritis** (penicillins, cephalosporins), **necrotizing myocarditis** (ranitidine), **vasculitis** (phenytoin, allopurinol), **asymptomatic** (ampicillin, penicillins, cephalosporins)

ADRENAL—adrenal insufficiency**ATHEROEMBOLIC**—cholesterol emboli**INFECTIONS**

- **PARASITIC**—angiostrongyliasis costaricensis, ascariasis, hookworm, strongyloidiasis, trichinosis
- **FUNGAL**—aspergillosis, coccidioidomycosis
- **OTHERS**—chronic TB, scarlet fever, HIV related

NEOPLASTIC

- **HEMATOLOGIC**—hypereosinophilic syndrome, Hodgkin's lymphoma, non-Hodgkin's lymphoma, mastocytosis
- **SOLID TUMOR**—**large cell carcinoma** (lung), **squamous cell carcinoma** (vagina, penis, skin, nasopharynx), **adenocarcinoma** (stomach, large bowel, uterine body), **transitional cell carcinoma**

PATHOPHYSIOLOGY**DEFINITION OF EOSINOPHILIA**—eosinophils >600/ μ L**EOSINOPHIL FUNCTION**—eosinophils play an important role in both combating infections (especially parasitic) and allergic response, through the release of cytotoxic molecules, reactive oxygen species, and cytokines. Thus, common causes of eosinophilia include infections and allergies**CLINICAL FEATURES****HISTORY**—dyspnea, chest pain, cough, sputum, diarrhea, rash, fever, lymphadenopathy, weight loss, night sweats, infectious contact, travel history, past medical history (allergic rhinitis,**CLINICAL FEATURES (CONT'D)**

asthma), medications (NSAIDs, antibiotics, phenytoin, allopurinol), allergies

PHYSICAL—vitals (hypotension, fever), rash, weight loss, nasal, lymphadenopathy, respiratory examination, abdominal examination**INVESTIGATIONS****BASIC**

- **LABS**—CBCD, peripheral smear, AST, ALT, ALP, bilirubin, CK, ESR, C3, C4, ANCA, serology for parasites
- **MICROBIOLOGY**—blood C&S, urine C&S, stool C&S, stool O&P
- **IMAGING**—CXR, CT chest

SPECIAL

- **BRONCHOSCOPY**—if pulmonary eosinophilia

DIAGNOSTIC ISSUES**PERIPHERAL EOSINOPHIL COUNTS**—as eosinophils are primarily tissue dwelling, they are likely several hundred-fold more abundant in affected tissues than represented in peripheral blood. Furthermore, the development of an intercurrent bacterial or viral infection may lead to suppression of blood eosinophilia until the superimposed acute infection has resolved. Thus, elevated or even normal blood eosinophil counts in a febrile patient should prompt investigations for eosinophilia (e.g. adrenal insufficiency)**MANAGEMENT****SYMPTOM CONTROL****TREAT UNDERLYING CAUSE**—**deworm** (if parasites), **stop offending drugs** (if suspect medication induced), **prednisone** (if unknown cause), **hydroxyurea**, or **imatinib** (for idiopathic hypereosinophilic syndrome)**SPECIFIC ENTITIES****PULMONARY EOSINOPHILIA**

- **PATHOPHYSIOLOGY**—defined as \uparrow eosinophils in blood with evidence of lung involvement, radiologically, through bronchoalveolar lavage or lung biopsy
- **CAUSES**—**infectious** (Loeffler's syndrome [*Ascaris*, hookworms, strongyloides], *Paragonimus* lung flukes, tropical pulmonary eosinophilia [*Wuchereria bancrofti*, *Brugia malayi*], coccidioidal), **medications** (NSAIDs, nitrofurantoin, ampicillin, minocycline, phenytoin, ranitidine), **idiopathic** (acute eosinophilic pneumonia, chronic eosinophilic pneumonia), **others** (Churg–Strauss, allergic bronchopulmonary aspergillosis)

Thrombocytosis

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DIFFERENTIAL DIAGNOSIS

PRIMARY (clonal thrombocytosis)—essential thrombocythemia, chronic myelogenous leukemia, polycythemia rubra vera, myeloid metaplasia with or without myelofibrosis, prefibrotic myelofibrosis

SECONDARY (reactive)

- **MALIGNANCY**
- **INFECTIONS**
- **CONNECTIVE TISSUE DISEASE**
- **DRUG REACTIONS**—vincristine, all-trans-retinoic acid, cytokines, growth factors
- **OTHERS**—iron deficiency, acute blood loss, hemolytic anemia, rebound from thrombocytopenia, splenectomy

PATHOPHYSIOLOGY

DEFINITION—platelets $>450 \times 10^3/\mu\text{L}$

Related Topic

Myeloproliferative Disorders (p. 165)

CLINICAL FEATURES

DISTINGUISHING FEATURES BETWEEN PRIMARY AND SECONDARY THROMBOCYTOSIS

| | Primary | Secondary |
|----------------------|-----------------|------------------|
| Underlying disease | N | Y |
| Digital ischemia/CVA | Y | N |
| Thrombosis | Y | N |
| Bleeding | Y | N |
| Splenomegaly | Y (40%) | N |
| Peripheral smear | Giant platelets | Normal platelets |
| Platelet function | Abnormal | Normal |
| BM megakaryocytes | ↑, giant | ↑, normal |

INVESTIGATIONS

BASIC

- **LABS**—CBCD, peripheral smear, PTT, INR, Fe, ferritin, TIBC, % sat, ESR (secondary cause), CRP (secondary cause)

SPECIAL

- **BONE MARROW BIOPSY**

DIAGNOSTIC ISSUES

IMPORTANT PEARL—remember that essential thrombocythemia is a diagnosis of exclusion. Thus, it is important to consider and rule out iron deficiency, occult malignancy, and another myeloproliferative disorder before making this diagnosis

MANAGEMENT

ESSENTIAL THROMBOCYTHEMIA—observation if asymptomatic and low risk of thrombosis, defined as age < 60 and no cardiovascular risk factors. For all others with platelet counts $>450 \times 10^3/\mu\text{L}$, use **ASA** 81 mg PO daily (low dose) plus **hydroxyurea** (or **anagrelide**) targeting normalization of the platelet count. When the platelets are $>1500 \times 10^3/\mu\text{L}$, **plateletpheresis** must be started for active ischemia and can be considered for use in asymptomatic patients at risk for coronary and/or cerebral ischemic events

SECONDARY CAUSES—treat underlying cause

Thrombocytopenia

DIFFERENTIAL DIAGNOSIS

PSEUDOTHROMBOCYTOPENIA—platelet clumping (usually due to EDTA-induced platelet activation)

DILUTIONAL—PRBC transfusion (at least 15–20 units), pregnancy

↓ PRODUCTION

- **INFILTRATIVE**—leukemia, MDS, bone marrow metastasis
- **INFECTIONS**—HIV, rubella, mumps, varicella, parvovirus, HCV, EBV
- **APLASIA**—aplastic anemia, Fanconi anemia
- **TOXINS**—chemotherapy, radiation, alcohol
- **B12/FOLATE DEFICIENCY**

HYPERSPLENISM—congestive, reactive, infiltrative (see SPLENOMEGALY p. 164)

↑ DESTRUCTION

- **IMMUNE THROMBOCYTOPENIC PURPURA**—primary, secondary (lymphoma, CLL, HIV, SLE, Evans syndrome)
- **ALLOIMMUNE**—post-transfusion, post-transplantation
- **MICROANGIOPATHIC HEMOLYTIC ANEMIA**—disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), HELLP syndrome, anti-phospholipid antibody syndrome
- **INFECTIONS**—HIV, EBV, CMV
- **MEDICATIONS**—heparin, GPIIb/IIIa inhibitors, quinine, quinidine, valproic acid, thiazides, sulfonamides, rifampin, indomethacin, vancomycin, linezolid

PATHOPHYSIOLOGY

DEFINITION—platelets $< 150 \times 10^3/\mu\text{L}$. However, an acute drop of 50%, even if the platelet count remains in the normal range, requires close monitoring and potential investigations

LIFE CYCLE—half-life of platelets is 8–10 days. One-third of the total body platelets is found in the spleen

BLEEDING RISK IN UNDER-PRODUCTION THROMBOCYTOPENIA

| Platelet count ($\times 10^3/\mu\text{L}$) | Bleeding risk |
|--|--|
| > 100 | Minimal symptoms |
| 50–100 | Minor symptoms |
| 10–50 | Prone to bruises |
| < 10 | Risk of spontaneous bleed (intracranial bleed) |

NOTE: in destruction or sequestration thrombocytopenia, bleeding does not correlate with the magnitude of thrombocytopenia

CLINICAL FEATURES

HISTORY—mucocutaneous bleeding (epistaxis, petechiae, easy bruising), abdominal pain, bloody diarrhea, recent infections, fever, weight loss, past medical history (malignancy, HIV, ITP, alcohol), medications (heparin, GPIIb/IIIa inhibitors, quinine, ASA, NSAIDs)

PHYSICAL—vitals. Look for intracranial bleed (fundoscopy), petechiae, and purpura. Check for lymphadenopathy and hepatosplenomegaly

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, peripheral smear, PTT, INR, AST, ALT, ALP, bilirubin, fibrinogen, LDH, ANA, vitamin B12, RBC folate, D-dimer, HIV serology, hepatitis serology, Coombs test

SPECIAL

- **HITT ASSAY**—heparin-induced platelet aggregation assay, heparin–PF4 solid phase immunoassay, serotonin release assay
- **BONE MARROW BIOPSY**

DIAGNOSTIC ISSUES

SMEAR

- **LARGE PLATELETS**—destruction (ITP)
- **SCHISTOCYTES/FRAGMENTS**—microangiopathic hemolytic anemia (DIC, TTP)

BONE MARROW BIOPSY

- **DECREASED MEGAKARYOCYTES**—underproduction
- **INCREASED MEGAKARYOCYTES**—destruction/sequestration/MDS

MANAGEMENT

SYMPTOM CONTROL—in under-production thrombocytopenia, **transfuse** 5 U platelets if platelets $< 50 \times 10^3/\mu\text{L}$ and severe bleeding, platelets $< 10 \times 10^3/\mu\text{L}$ in afebrile non-bleeding patient, $< 20 \times 10^3/\mu\text{L}$ in febrile non-bleeding patient, and prior to certain procedures (expect platelet rise of ~ 5 /unit). Note that platelet transfusions are not effective in ITP and may worsen TTP/HUS and HITT

TREAT UNDERLYING CAUSE—**discontinue medications** that may cause thrombocytopenia (platelets may return to normal in 14–21 days). Please refer to specific disorders below for details regarding treatment of each disease

SPECIFIC ENTITIES

MICROANGIOPATHIC HEMOLYTIC ANEMIA (MAHA)—also called fragmentation hemolysis. Characterized by non-immune hemolytic anemia and schistocytes. Causes include DIC, HELLP, TTP, HUS, malignancy, malignant hypertension, artificial heart valve, insertion of foreign bodies, and medications

SPECIFIC ENTITIES (CONT'D)

DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

- **PATHOPHYSIOLOGY**—damage to endothelium → release of tissue factor → massive activation of coagulation cascade → intravascular coagulation and depletion of clotting factors
- **CAUSES**—trauma, shock, sepsis (*Escherichia coli*, *N. meningitidis*, malaria), neoplasm (lung, prostate, pancreatic), obstetrical (abruptio placentae, pre-eclampsia, amniotic fluid embolus)
- **CLINICAL FEATURES**—microangiopathic hemolytic anemia, thrombocytopenia, bleeding, thrombosis, ischemia. ↑ INR, ↑ PTT, ↓ fibrinogen (although it can be normal or even elevated), ↓ factor VIII (in contrast to liver diseases, which have normal factor VIII). Schistocytes on peripheral smear
- **TREATMENTS**—**treat underlying cause and complications** (hypoxia, dehydration, acidosis, acute renal failure). **Replete coagulation factors if bleeding** (FFP 2 U, cryoprecipitate 10 U). **Anticoagulation if thrombosis** (consider IV heparin)

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

- **PATHOPHYSIOLOGY**—↓ ADAMTS13 activity → failure to degrade unusually large multimers of vWF → agglutination of platelets → arteriolar thrombi → systemic but CNS predominates
- **CAUSES**—idiopathic, vasculitis, malignancy, drug induced, pregnancy (second term)
- **CLINICAL FEATURES**—microangiopathic hemolytic anemia (100%), thrombocytopenia (90%), renal dysfunction, fever (90–100%), neurologic abnormalities (90%) with delirium, focal neurological deficit, seizure, coma. Schistocytes on peripheral smear
- **TREATMENTS**—full volume plasma exchange (plasmapheresis + FFP infusions), steroids, and splenectomy if not resolving. Avoid platelet transfusion, ASA and antimotility agents

NEJM 2006 354:18

HEMOLYTIC UREMIC SYNDROME (HUS)

- **PATHOPHYSIOLOGY**—exposure to Shiga toxin or defect in plasma factor H → arteriolar thrombi → predominantly renal involvement
- **CAUSES**—*E. coli* O157:H7
- **CLINICAL FEATURES**—microangiopathic hemolytic anemia (100%), thrombocytopenia (90%), renal dysfunction (90%). Schistocytes on peripheral smear
- **TREATMENTS**—supportive care only. Does not respond to plasma exchange

Related Topics

Anticoagulation Therapy (p. 160)
 Antiphospholipid Antibody Syndrome (p. 156)
 Thrombocytopenia in Pregnancy (p. 414)

SPECIFIC ENTITIES (CONT'D)

HEPARIN-INDUCED THROMBOCYTOPENIA AND THROMBOSIS (HITT)

- **PATHOPHYSIOLOGY**—**type I** (non-immune) happens within 2 days, mild drop in platelets, and return to normal by itself. **Type 2** (immune) starts between days 4 and 14. It is usually more severe (platelet drop >50%) and has great clinical significance. The pathogenesis is as follows: heparin complexes with PF4 (from platelets) → IgG against heparin–PF4 complex → these megacomplexes bind to platelets and activate them, producing more PF4 → platelet aggregation → thrombosis
- **CAUSES**—heparin, LMWH (much less likely)
- **CLINICAL FEATURES** (type II)—thrombocytopenia, thrombosis, ischemia
- **TREATMENTS** (type II)—**stop heparin**. If patient has indication for anticoagulation (acute thrombosis, atrial fibrillation), consider **danaparoid, lepirudin, argatroban**. Since the risk of thrombosis due to HITT approaches 50%, one should also consider primary prophylaxis with these agents until platelets return to normal. If both HITT and DVT, avoid warfarin until platelets >150 × 10³/μL and overlap warfarin with the alternative anticoagulant for 5 days (this reduces risk of venous limb gangrene). Avoid future heparin exposure except during CABG (performed at least 3 months after heparin exposure)

IDIOPATHIC/IMMUNE THROMBOCYTOPENIC PURPURA (ITP)

- **PATHOPHYSIOLOGY**—autoantibodies against platelets → isolated thrombocytopenia
- **ASSOCIATIONS**—neoplasm (CLL, lymphoma), infections (HIV), autoimmune (SLE)
- **DIAGNOSIS**—isolated thrombocytopenia with an otherwise normal CBC and no obvious causes
- **TREATMENTS**—should be started if patient symptomatic and/or platelets <20 × 10³/μL. The goal of treatment is to support platelet counts until spontaneous remission occurs
 - **FIRST LINE**—**prednisone** 1–2 mg/kg PO daily until platelet count returns to normal. Platelet recovery occurs within 3 weeks in 2/3 of patients. If platelet count did not increase after 4 weeks of treatment, consider splenectomy
 - **URGENT SUPPORT**—given to patients with active bleeding or extremely low platelets before steroid effect takes place. **IVIg** 1 g/kg IV daily × 1–2 days, which may increase the platelet count within days and lasts for a few weeks. **Methylprednisolone** 1 g IV daily × 3 days. **Platelet transfusions** may also provide temporary support for actively bleeding patients
 - **SECOND LINE**—**splenectomy**, with platelet recovery within 2 weeks in 2/3 of patients. See p. 147 for details on counseling of patients undergoing splenectomy

SPECIFIC ENTITIES (CONT'D)

- **THIRD LINE**—for patients with chronic refractory ITP (platelets $< 50 \times 10^3/\mu\text{L}$ after 3 months) who failed or refused splenectomy, consider observation if no bleeding and platelets $> 20 \times 10^3/\mu\text{L}$. Otherwise, treat with romiplostim or eltrombopag
- **OTHER OPTIONS**—rituximab, chemotherapy (CVP), danazol. HAART for HIV-associated ITP

NEJM 2002 346:13

SPECIFIC ENTITIES (CONT'D)

DRUG-INDUCED IMMUNE THROMBOCYTOPENIA—patients usually present with severe thrombocytopenia (platelets $< 20 \times 10^3/\mu\text{L}$). With the exception of platelet inhibitors, there is usually 5–7 days between initiation of drug therapy and platelet drop if patient is receiving the medication for the first time. Treatment consists of discontinuation of offending (or all) drugs and platelet transfusions

NEJM 2007 357:6

EVANS SYNDROME—ITP and autoimmune hemolytic anemia

Pancytopenia

DIFFERENTIAL DIAGNOSIS

★ PANIC ★

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)—↑ complement-mediated red cell lysis
APLASTIC ANEMIA

- **IDIOPATHIC** (50%)
 - **INFECTIONS**—EBV, CMV, parvovirus, hepatitis
 - **FANCONI'S ANEMIA**
 - **DRUG INDUCED**—chemotherapy, gold
 - **TOXINS**—alcohol
- NEOPLASTIC**—leukemia (AML, CLL), MDS, bone marrow metastasis

INFECTIONS—sepsis, TB, *Parvovirus*, fungal**INSUFFICIENCY**—folate, vitamin B12**IATROGENIC**—chemotherapy**CONSUMPTION**—hypersplenism, immune-mediated destruction

INVESTIGATIONS

BASIC

- **LABS**—CBCD, peripheral smear, B12, RBC folate, HIV test, Coombs test

SPECIAL

- **BONE MARROW BIOPSY**—if suspect aplastic anemia or malignancy
- **FLOW CYTOMETRY**—if suspect PNH. Historically, sucrose hemolysis test used for screening, followed by Ham acid hemolysis test for diagnosis. Currently flow cytometry is used to measure the

INVESTIGATIONS (CONT'D)

expression of the complement regulatory proteins CD55 and CD59, which are deficient on all blood cells among persons with PNH

DIAGNOSTIC ISSUES

PRE-MEDS FOR BONE MARROW BIOPSY—*morphine* 2.5–5 mg IV, *lorazepam* 1 mg SL, Elma cream

MANAGEMENT

TREAT UNDERLYING CAUSE

SPECIFIC ENTITIES

APLASTIC ANEMIA

- **PATHOPHYSIOLOGY**—precipitants (e.g. *Parvovirus*, drugs) → T-cell subsets produce local concentrations of $\text{INF}\gamma$ → ↑ Fas on CD34+ cells (maturing stem cells) → apoptosis → severe pancytopenia and hypocellular marrow. Complications include paroxysmal nocturnal hemoglobinuria, acute leukemia, and MDS
 - **TREATMENTS**—antithymocyte globulin, cyclosporine, allogeneic stem cell transplant (if age < 50)
- FANCONI'S ANEMIA**—hereditary form of aplastic anemia that usually affects children but occasionally presents in adults. The main features include pancytopenia, hyperpigmentation, skeletal malformation, small stature, and hypogonadism

Bleeding Diathesis

DIFFERENTIAL DIAGNOSIS

- **★ PVC ★** platelets, vessels, coagulopathy
- **EXTRINSIC PATHWAY** (isolated PT ↑)
- **FACTOR DEFICIENCY OR INHIBITOR**—Vllr

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **VITAMIN K DEFICIENCY**—malnutrition, pancreatic insufficiency, recent antibiotic use, warfarin use (early stage)

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **LIVER DISEASE**
- **EARLY DIC**

INTRINSIC PATHWAY (isolated PTT ↑)

- **FACTOR DEFICIENCY**—X-linked deficiency of factor VIII (hemophilia A) or factor IX (hemophilia B). Autosomal deficiency of factor XI, especially among Ashkenazi Jews (8% are carriers)
- **VON WILLEBRAND DISEASE**
- **FACTOR INHIBITORS**—lupus anticoagulant due to APA; acquired hemophilia due to an inhibitor to factor VIII
- **HEPARIN USE**

COMMON PATHWAY (PT ↑, PTT ↑)

- **FACTOR DEFICIENCY**—X, V, II, I
- **SEVERE VITAMIN K DEFICIENCY**—malnutrition, pancreatic insufficiency, recent antibiotic use, long term warfarin use
- **SEVERE LIVER DISEASE**
- **SEVERE DIC**

PLATELET DYSFUNCTION (normal PT and PTT, platelet $>90 \times 10^3/\mu\text{L}$, bleeding time ↑)

- **INHERITED**—Bernard-Soulier syndrome, Glanzmann's thrombasthenia, storage pool disease
- **ACQUIRED**—renal failure, liver failure, myeloproliferative disorders, paraproteinemias, autoantibodies, DIC, acquired storage pool disease

VESSELS—collagen vascular disease, scurvy

NOTE: INR=international normalized ratio, helps to standardize interpretation of PT

PATHOPHYSIOLOGY

HEMOSTASIS

- **PRIMARY HEMOSTASIS**—endothelium, platelets
- **SECONDARY HEMOSTASIS**—clotting factors, clotting cascade

PLATELET ACTIVATION PATHWAY

1. Collagen binds to GPIa/IIa on platelet membrane, also binds to GPIb/IX via vWF
2. Platelet becomes activated by agonist binding (thrombin, adenosine diphosphate, epinephrine, collagen)
3. Secretion of δ granules (serotonin, ADP) and α granules (vWF, growth factors, factor V, factor X, fibrinogen)
4. Conformational change \rightarrow phospholipids become available for factors V and VIII binding
5. Platelet aggregation (unstable) by vWF and fibrinogen binding to the activated GPIIb/IIIa complex
6. Platelet fibrin clot formation—fibrin—fibrin cross-linked by factor XIII and platelet-fibrin via GPIIb/IIIa

ANTICOAGULATION PATHWAYS

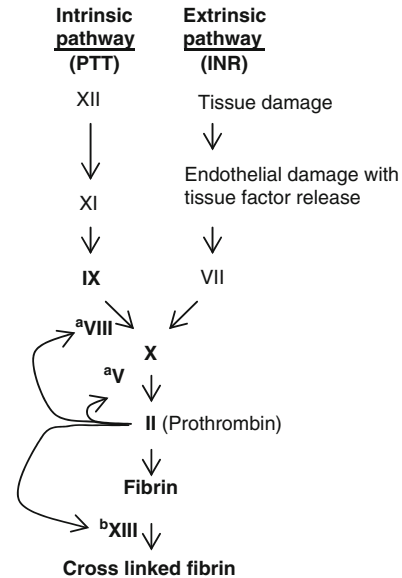
1. Antithrombin binds to thrombin and inhibits it
2. Thrombin binds to thrombomodulin which activates protein C and S to cleave factors Va and VIIIa

PATHOPHYSIOLOGY (CONT'D)

3. Factor Xa \rightarrow tPA (by endothelial cells) \rightarrow plasmin \rightarrow fibrinolysis

COAGULATION FACTOR PEARLS

- **SYNTHESIZED IN LIVER**—factors I, II, V, VII, VIII, IX, X, XI, XII, protein C, S, AT-III, plasminogen
- **VITAMIN K DEPENDENT**—factors II, VII, IX, X, protein C, S, Z
- **SYNTHESIZED IN ENDOTHELIAL CELLS AND MEGAKARYOCYTES**—vWF

COAGULATION PATHWAY

^aNon-enzymatic cofactors; ^bFactor XIII is called "fibrin-stabilizing factor" because it covalently cross-links fibrin polymers and strengthens the clot

FACTORS VII AND VIII ARE SPECIAL

- **FACTOR VII**—shortest half-life (5–7 h). Decreased factor VII results in INR ↑. Thus, INR can help to detect *early* stages of liver failure, DIC, vitamin K deficiency, and warfarin use
- **FACTOR VIII**—part of coagulation cascade and has von Willebrand factor (vWF, synthesized by endothelial cells) as carrier in plasma. Thus, von Willebrand disease (vWD) leads to ↓ factor VIII

CLINICAL FEATURES

BLEEDING SYNDROMES

- **PLATELET DYSFUNCTION**—skin/mucous membrane (petechiae, purpura, small/superficial ecchymosis, epistaxis, gingival bleed, menorrhagia), immediate bleed

CLINICAL FEATURES (CONT'D)

- **COAGULATION FACTORS**—joints/muscles (hemarthroses, muscle hematomas, large/palpable ecchymosis), delayed bleed

INVESTIGATIONS

BASIC

- **LABS**—CBCD, peripheral smear, AST, ALT, ALP, bilirubin, albumin, INR, PTT, D-dimer, fibrinogen

SPECIAL

- **HEPZYME STUDY**—to remove heparin from blood samples to distinguish if isolated elevation of PTT is spurious
- **50:50 MIXING STUDY**—to distinguish between factor deficiency (hemophilia) vs. inhibitors
- **HEMOPHILIA WORKUP**—factor VII, factors VIII, IX, XI, factors X, V, II, I
- **ANTIPHOSPHOLIPID ANTIBODY SYNDROME WORKUP**—lupus anticoagulant, anticardiolipin antibody, Russell's viper venom time
- **VON WILLEBRAND DISEASE WORKUP**—von Willebrand factor (vWF) antigen levels, factor VIII level,

INVESTIGATIONS (CONT'D)

- ristocetin cofactor activity, ristocetin-induced platelet aggregation
- **PLATELET DISORDER WORKUP**—bleeding time
- **MYELOMA WORKUP**—serum protein electrophoresis

MANAGEMENT

ACUTE—ABC, O₂, IV, **transfusion 2 U PRBC IV** over 2 h, transfusion **platelets 6 U**, **FFP 15 mL/kg**, **cryo-precipitate 10–15 U q48h** for fibrinogen deficiency
TREAT UNDERLYING CAUSE—**avoid** heparin, LMWH, warfarin. **Vitamin K deficiency** (vitamin K 10 mg PO/SC daily ×3 days). **vWD type I (DDAVP 0.3 µg/kg SC, intermediate purity factor VIII)**

SPECIFIC ENTITIES

VON WILLEBRAND DISEASE (VWD)

- **PATHOPHYSIOLOGY**—vWF acts as a linker between platelets and endothelium and also serves as carrier for factor VIII. Thus, vWD deficiency may lead to decrease in factor VIII levels

Inheritance

Pathophysiology

| | | |
|-----|------------------------------|--|
| I | Autosomal dominant | Mild to moderate quantitative ↓ of all multimers |
| IIA | Autosomal dominant/recessive | ↓ activity of vWF due to decrease in large multimers of vWF (synthesis of active forms in platelet adhesion) |
| IIB | Autosomal dominant | Same as IIA except decrease due to large multimer vWF adherence to platelets |
| IIN | Autosomal recessive | ↓ vWF affinity for factor VIII, similar to hemophilia |
| III | Autosomal recessive | Complete absence of vWF |

SPECIFIC ENTITIES (CONT'D)

- **CLINICAL FEATURES**—platelet disorder with bruising, skin or mucosal bleeding, and heavy menstrual cycles for most subtypes, except type IIN which manifests as hemophilia with soft tissue, joint, and urinary bleeding
- **DIAGNOSIS**—**Ristocetin cofactor activity** (RCo, assesses capacity of plasma vWF to support ristocetin-induced aggregation of control platelets),

SPECIFIC ENTITIES (CONT'D)

collagen binding activity (assesses vWF binding to collagen), **vWF antigen** (non-functional assay that quantifies vWF), **vWF multimer assay** (agarose gel to determine the size of multimers), **ristocetin-induced platelet aggregation** (assesses vWF binding to platelets in patients' platelet-rich plasma)

vWFAntigen vWF: RCo

vWF multimer

RIPA

| | | | |
|-----|--------|-------------------|--------|
| I | ↓ | ↓ all multimers | ↓ |
| IIA | ↓ or N | ↓ large multimers | ↓ or N |
| IIB | ↓ or N | ↓ large multimers | ↑ |
| IIN | Normal | Normal | Normal |
| III | ↓↓ | ↓↓ undetectable | ↓↓ |

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—**DDAVP 0.3 µg/kg** by IV infusion or 300 µg one spray each nasal for all type I and most type II patients. vWF concentrates containing all vWF multimers may be used for type III and for bleeding or surgical management of type II/I

SPECIFIC ENTITIES (CONT'D)

BERNARD-SOULIER SYNDROME—mutation of GPIIb/IX (platelet receptor for vWF)

GLANZMANN'S THROMBASTHENIA—mutation of GPIIb/IIIa (platelet receptor for fibrinogen)

STORAGE POOL DISEASE—defect in releasing platelet granules (especially ADP)

Hypercoagulable States

DIFFERENTIAL DIAGNOSIS

ANTICOAGULATION FACTORS

- **DEFICIENCY**—protein S, protein C, antithrombin III, plasminogen. Secondary causes of clotting factor deficiencies include HITT, DIC, TTP, HUS, PNH, APA, and nephrotic syndrome (reduced protein S and protein C)
- **ALTERATION**—factor V Leiden, prothrombin G20210A
- **EXCESS**—fibrinogen, hyperhomocysteinemia

VASCULAR DAMAGE—**vasculitis, sepsis, trauma, surgery, cancer** (Trousseau's syndrome, lymphoproliferative disease)

STASIS—bed rest, pregnancy, air travel, leg cast

PATHOPHYSIOLOGY

RISK FACTORS FOR VENOUS THROMBOEMBOLISM

- **COAGULATION FACTORS**—excess, mutation (factor V Leiden, prothrombin), deficiency (protein S, protein C, antithrombin III, plasminogen, tissue plasminogen activator)
- **NEOPLASTIC**—solid tumors, myeloproliferative
- **OTHERS**—immobilization, surgery, congestive heart failure, oral contraceptives, hormone replacement therapy, pregnancy, nephrotic syndrome

RISK FACTORS FOR ARTERIAL

THROMBOEMBOLISM

- **ATHEROSCLEROSIS**—hypertension, diabetes, smoking
- **EMBOLIC**—AF, atrial myxoma, endocarditis, cholesterol emboli, MI with ventricular thrombosis, paradoxical embolism
- **OTHERS**—SLE

RISK FACTORS FOR ARTERIAL AND VENOUS

THROMBOEMBOLISM

- **FACTORS**—homocysteinemia, dysfibrinogenemia, plasminogen activator deficiency
- **PLATELET DEFECTS**—myeloproliferative disorders, HITT, PNH
- **HYPERVISCOSITY**—polycythemia rubra vera, Waldenstrom's macroglobulinemia, cryoglobulinemia, sickle cell disease
- **OTHERS**—antiphospholipid antibody syndrome, vasculitis, paradoxical embolism
- **BIOPROSTHETIC HEART VALVE**—low-level anticoagulation (INR 2–3) in first 3 months following valve replacement

NEJM 2002 346:10

FACTOR V LEIDEN—mutation that resists cleavage by activated protein C. Most common hereditary form of thrombophilia (3–4% general population)

THROMBOPHILIC MUTATIONS—antithrombin III, homozygous factor V Leiden >protein S, protein C > heterozygous factor V Leiden in terms of risk of clots

INVESTIGATIONS

BASIC

- **LABS**—CBCD, PT, INR, activated protein C resistance, factor V Leiden, prothrombin G20210A, anticardiolipin antibody, lupus anticoagulant, homocysteine, protein C, protein S, antithrombin III, fibrinogen, urinalysis

- **IMAGING**—CXR

SPECIAL

- **PREGNANCY TEST**—if female <50

Related Topics

Anticoagulation Therapy (p. 160)

DVT (p. 158)

Pulmonary Embolism (p. 8)

DIAGNOSTIC ISSUES

WARFARIN AND PROTEIN C—draw protein C and S prior to warfarin therapy as it reduces protein C before those of all other vitamin K-dependent factors

MANAGEMENT

ACUTE—ABC, O₂ to keep sat >94%, IV, consider thrombolysis

ANTICOAGULATION—**heparin** (unfractionated heparin 5000U IV bolus, then 1000U/h and adjust to 1.5–2.5 × normal PTT) or **LMWH** (enoxaparin 1 mg/kg SC BID or 1.5 mg/kg SC daily). Start **warfarin** 5 mg PO daily within 72 h and continue heparin/LMWH until INR is between 2 and 3 for two consecutive days

IVC FILTER—if anticoagulation contraindicated

TREATMENT ISSUES

WARFARIN USE AND PROTEIN C DEFICIENCY—patients with protein C deficiency given warfarin may be susceptible to transient hypercoagulable state (coumadin necrosis). This can be avoided by administering heparin along with warfarin

PRIMARY PROPHYLAXIS OF THROMBOEMBOLISM IN HOSPITALIZED MEDICAL PATIENTS

- **INDICATIONS**—patients on the medical service >40-year old have limited mobility for ≥3 days, and have at least 1 of following risk factors

- **CONDITIONS**—acute infectious disease, congestive heart failure, acute myocardial infarction, acute respiratory disease, stroke, rheumatic disease, inflammatory bowel disease, cancer

- **CLINICAL CHARACTERISTIC**—previous venous thromboembolism, older age (especially >75),

TREATMENT ISSUES (CONT'D)

recent surgery or trauma, immobility or paresis, BMI >30 kg/m², central venous catheterization, inherited or acquired thrombophilic states, varicose veins, estrogen therapy

- **INTERVENTIONS**—early ambulation and exercises involving foot extension for all patients. Specific prophylaxis regimens include *heparin* 5000 U SC q8h, *enoxaparin* 40 mg SC daily, *dalteparin* 5000 U SC daily, or *fondaparinux* 2.5 mg SC daily. For patients at high risk for bleeding, consider non-pharmacologic measures such as graduated compression stockings and pneumatic compression devices

NEJM 2007 365:14

RISK REDUCTION BY ANTICOAGULATION

- **ACUTE VTE EPISODE**—without anticoagulation, the risk for recurrent DVT is 50% and for PE is 50%. Warfarin ↓ risk to 8–10% by 1 month and 4–5% by 3 months
- **VTE WITH LONG-TERM RISK FACTORS**—recurrent DVT risk 15%/year. Warfarin ↓ risk to 3%
- **VTE IN PATIENTS WITH CANCER**—risk of recurrence at 6 months 17% with warfarin and 9% with *dalteparin* 200 IU/kg for 3 weeks, followed by 150 IU/kg for at least 6 months
- **AF WITH PREVIOUS STROKE**—recurrent stroke risk 12%/year. ASA ↓ risk to 10%/year. Warfarin ↓ risk to 4%/year
- **AF WITH OTHER RISK FACTORS**—recurrent stroke 8%/year. ASA ↓ risk to 4%/year. Warfarin ↓ risk to 2%/year
- **LONE AF**—recurrent stroke risk 1–2%/year. ASA or warfarin ↓ risk to < 1%/year

MECHANICAL HEART VALVE—recurrent arterial embolic risk 4%/year. ASA ↓ risk to 2%. Warfarin ↓ risk to 0.7–1%/year. Mitral valve prostheses 2× risk of aortic valve prostheses. INR 2–3 for bileaflet or tilting-disc mechanical valves and 2.5–3.5 for caged-ball or caged-disc valves

SPECIFIC ENTITIES

ANTIPHOSPHOLIPID ANTIBODY SYNDROME (APS)

- **PATHOPHYSIOLOGY**—antibody against phospholipids or cell surface proteins bound to anionic phospholipids. These include lupus anticoagulants, anticardiolipin antibody (false-positive VDRL), and anti-β2GP1 (β2-glycoprotein 1) antibody → may lead to hypercoagulable state and may rarely inhibit coagulation
- **CAUSES**—primary APS, secondary APS (various rheumatic diseases such as SLE and infections such as HIV and drugs)
- **CLINICAL FEATURES**—venous and arterial thrombosis and rarely hemorrhage affecting the lungs, heart, CNS, GI, kidneys, skin, and eyes. Also recurrent fetal

SPECIFIC ENTITIES (CONT'D)

losses (recurrent first trimester or single late term), thrombocytopenia, and livedo reticularis

- **DIAGNOSIS—clinical criteria** include thrombosis (≥1 arterial, venous, or small-vessel thrombosis in any organ) or pregnancy complications (≥1 unexplained deaths of morphologically normal fetus at or after the 10th week of gestation, ≥1 premature births of morphologically normal neonate at or before the 34th week of gestation, or ≥3 unexplained consecutive spontaneous abortions before the 10th week of gestation). **Laboratory criteria** include anticardiolipin antibodies (IgG or IgM at moderate or high levels on ≥2 occasions at least 6 weeks apart) or the presence of a lupus anticoagulant (≥2 occasions at least 6 weeks apart). Diagnosis requires at least one clinical and one laboratory criteria (sens 70%, spec 98%)
- **CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME**—acute and devastating syndrome with multiple simultaneous vascular occlusions throughout the body, affecting mainly small vessels of kidney, lungs, CNS, heart, and skin. May be associated with DIC, ARDS, cerebral and myocardial microinfarctions. May be precipitated by infections, surgery, and withdrawal of anticoagulation. Treatment consists of a combination of anticoagulation, steroids, plasmapheresis, and/or IVIG. Mortality rate is 50%
- **TREATMENTS**—primary prophylaxis for thrombosis is not indicated in persons with incidentally discovered antiphospholipid antibodies or lupus anticoagulants. Treatment of thromboses (both venous and arterial) is indefinite warfarin anticoagulation targeting an INR of 2–3. See p. 414 for management of APS in pregnancy

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

- **PATHOPHYSIOLOGY**—mutation in PIG-A gene coding for GPI anchor → ↓ GPI-linked proteins such as CD59 (membrane attack complex inhibitory factor) and CD55 (decay accelerating factor) → complement-mediated lysis of RBC → acute renal failure due to hemoglobulinuria, chronic renal failure due to iron deposits. Also ↑ platelet activation due to complements, tissue damage with ↑ tissue factor, ↓ fibrinolysis → ↑ thrombosis
- **CLINICAL FEATURES**—hemolysis, thrombosis (hepatic vein, portal vein, splenic vein, renal vein), marrow aplasia, MDS, leukemia, infections, esophageal spasm, sexual dysfunction
- **DIAGNOSIS**—flow cytometry, historically, Ham's test (RBC sensitivity to acidity)
- **TREATMENTS**—steroids, allogeneic stem cell transplant

Deep Vein Thrombosis

NEJM 2004 351:3

DIFFERENTIAL DIAGNOSIS OF UNILATERAL LEG SWELLING/DEEP VEIN THROMBOSIS

VASCULAR—DVT, venous insufficiency, superficial thrombophlebitis (chronic)

LYMPHATIC—lymphedema (chronic)

DRUGS—drug-induced edema (calcium channel blockers)

OTHER—cellulitis, necrotizing fasciitis, knee injury, calf muscle tear, Baker cyst rupture

PATHOPHYSIOLOGY

LOCATION—DVT typically originates in the venous sinuses of the calf muscles and occasionally the proximal veins. While most calf vein thrombi lyse spontaneously, ~25% extend into proximal veins within a week

COMPLICATIONS—clot extension, pulmonary embolism, recurrent thrombosis, post-thrombotic syndrome, chronic pulmonary hypertension

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, PTT, INR, D-dimer, fibrinogen, AST, ALT, ALP, bili
- **IMAGING**—CXR, compression U/S (sens 95%, spec 95%), impedance plethysmography

INVESTIGATIONS (CONT'D)

SPECIAL

- **THROMBOPHILIA WORKUP**—if there is a family history of thrombosis, consider activated protein C resistance, factor V Leiden, prothrombin G20210A, antithrombin III, protein C, and protein S; check antiphospholipid antibodies if the VTE was unprovoked
- **PREGNANCY TEST**—in female <50
- **VENOGRAM**—gold standard

DIAGNOSTIC ISSUES

COMPRESSION U/S—high sensitivity (95%) and specificity (95%) for DVT. U/S of calf veins is not routinely performed because of lower sensitivity (70%). Rather, U/S of thigh (deep veins) is usually repeated in 1 week after a normal test to detect the possible extension of DVT from calf into proximal veins

Related Topics

Anticoagulation Therapy (p. 160)
Hypercoagulable States (p. 156)
Pulmonary Embolism (p. 8)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE DEEP VEIN THROMBOSIS?

WELL'S CRITERIA FOR DVT—alternative diagnosis more or as likely (–2), recent paralysis/paresis/plaster immobilization (+1), recent bedridden >3 days or major surgery <4 weeks (+1), localized tenderness along deep venous system (+1), calf swelling by more than 3 cm at 10 cm below tibial tuberosity (+1), pitting edema greater in symptomatic leg (+1), collateral non-varicose superficial veins (+1), active cancer (+1)

D-DIMER UTILITY FOR DVT BASED ON WELL'S CRITERIA

| | Sens | Spc | LR+ | LR– |
|---------------|------|-----|-----|------|
| Low risk | 88% | 72% | 3.3 | 0.18 |
| Moderate risk | 90% | 58% | 2.1 | 0.19 |
| High risk | 92% | 45% | 1.6 | 0.16 |

- **LOW RISK** (0 or less points)—<5% chance of DVT. If D-dimer negative, can exclude DVT
- **MODERATE RISK** (1–2 points)—17% chance of DVT. Workup may or may not be needed
- **HIGH RISK** (3 or greater points)—53% chance of DVT. D-dimer testing not useful. Proceed to compression U/S or impedance plethysmography → serial studies → venogram

APPROACH—“diagnostic accuracy for DVT improves when clinical probability is estimated before diagnostic tests. Patients with low clinical probability on the predictive rule have prevalence of DVT of <5%. In low-probability patients with negative D-dimer results, diagnosis of DVT can be excluded without ultrasound; in patients with high clinical suspicion for DVT, results should not affect clinical decisions”

JAMA 2006 295:2

DISGNOSTIC ISSUES (CONT'D)

THROMBOPHILIA WORKUP—should be done if suspect a hereditary cause of thromboembolic disease. Alarm features include age <45, unprovoked situation, family history (1 or more first degree relative), or

DIAGNOSTIC ISSUES (CONT'D)

clot in unusual location (upper extremities, mesenteric vessels, brain)

MALIGNANCY WORKUP—debatable when this should be done. Basic screening includes physical exam, CXR, U/S abd, mammogram, PSA

DIAGNOSTIC ISSUES (CONT'D)

PROTEIN S AND PROTEIN C DEFICIENCY WHILE ANTICOAGULATED—when anticoagulated, usually levels decrease by similar proportion. If significant decrease of one compared to the other, may suggest a deficiency

MANAGEMENT

ANTICOAGULATION—**heparin** (*unfractionated heparin* 5000U IV bolus, then 1000U/h, and adjust to 1.5–2.5 × normal PTT) or **LMWH** (*enoxaparin* 1 mg/kg SC BID or 1.5 mg/kg SC daily). For long-term anticoagulation, continue **LMWH** in cancer patients or start **warfarin** 5 mg PO daily within 72 hours and continue heparin/LMWH until INR is between 2 and 3 for two consecutive days

IVC FILTER—if anticoagulation contraindicated

THROMBOLYSIS—may have a role in hemodynamically unstable pulmonary embolism or massive iliofemoral thrombosis

TREATMENT ISSUES**ANTICOAGULATION DURATION**

- **AT LEAST 6 MONTHS**—first DVT with reversible or time-limited risk factor removed (i.e. if DVT in second term of pregnancy, stop therapy 3 months post-partum)
- **AT LEAST 1 YEAR**—first DVT and idiopathic

TREATMENT ISSUES (CONT'D)

- **LIKELY LIFELONG**—recurrent idiopathic DVT or continuing major risk factor (malignancy, antithrombin III deficiency, homozygous factor V Leiden, homozygous prothrombin G20210A, heterozygous factor V Leiden plus prothrombin G20210A)

CONTRAINDICATIONS TO ANTICOAGULATION THERAPY

- **ABSOLUTE**—neurosurgery, ocular surgery, or intracranial bleeding within the past 10 days, active bleeding, severe bleeding diathesis, or platelet $< 20 \times 10^3/\mu\text{L}$
- **RELATIVE**—mild–moderate bleeding diathesis or thrombocytopenia ($20\text{--}100 \times 10^3/\mu\text{L}$), brain metastases from melanoma, renal cell carcinoma, choriocarcinoma and thyroid cancers, recent major trauma, major abdominal surgery < 2 days, GI or GU bleeding < 2 weeks, endocarditis, severe hypertension ($> 200/120$ mmHg)

SPECIFIC ENTITIES

SUPERFICIAL THROMBOPHLEBITIS—characterized by painful, erythematous, palpable cord along a superficial vein usually in the lower extremity, can be associated with hypercoagulable states. Extension to deep vein system rarely occurs through perforating veins and is most likely when the proximal greater saphenous vein or saphenous–femoral junction is involved

Notes

Approach to Anticoagulation Therapies

| Class/Drugs | Mechanism | Indications | Usual dose | Complications/ monitoring |
|--|--|---|--|---|
| Warfarin | Inhibition of gamma carboxylation by inhibition of the vitamin K-dependent epoxide reductase. Inhibits hepatic synthesis of vitamin K-dependent factors (II, VII, IX, X, protein S, protein C) | DVT/PE Atrial fibrillation Prosthetic valves | <i>Warfarin</i> 5 mg PO daily \times 3 days, then adjust based on INR | Complications—bleeding (may be reversed with vitamin K), coumadin-induced skin necrosis Monitor —INR |
| Unfractionated heparin | Indirect thrombin and factor Xa inhibitor (non-selective) . Binds to antithrombin (AT) and converts it from a slow form to fast-acting form, which binds and inactivates thrombin and factors Xa, IXa, Xla, XIIa Heparin resistance is usually due to AT deficiency and could be treated with AT concentrates | Acute DVT/PE Arterial embolism Prosthetic valves ACS DVT prophylaxis | For acute clot, <i>unfractionated heparin</i> 5000 U IV bolus, then 1000 U/h, and adjust to 1.5–2.5 \times normal PTT For DVT prophylaxis, <i>unfractionated heparin</i> 5000U SC 2 h before surgery, then 5000U SC BID | Complications —bleeding (may be reversed by protamine 1 mg/100 U UFH), HIT, osteoporosis Monitor —aPTT (1.5–2.5 \times normal) and platelets Narrow therapeutic window and highly variable dose–response curve |
| Low molecular weight heparin: <i>Enoxaparin</i> <i>Dalteparin</i> <i>Tinzaparin</i> | Indirect factor Xa inhibitor (relatively selective) . Binds to AT and converts it from a slow form to fast acting form, which binds and inactivates factor Xa, and to a smaller extent, thrombin Inactivation of thrombin specifically requires heparin binding to <i>both</i> AT and thrombin. This complex only forms with heparin chains \geq 18-saccharide long. Thus, LMWH is not as effective in inhibiting thrombin and does not prolong aPTT | Acute DVT/PE Maintenance DVT/PE in cancer patients Arterial embolism Prosthetic valves ACS DVT prophylaxis | For acute clots, <i>enoxaparin</i> 1 mg/kg SC BID or 1.5 mg/kg SC daily, <i>dalteparin</i> 200 U/kg SC daily, <i>tinzaparin</i> 175 U/kg SC daily For DVT prophylaxis, <i>enoxaparin</i> 40 mg SC daily \times 7–14 days starting 12 h pre-op, <i>dalteparin</i> 2500U SC 1 h pre-op, then 2500 U SC 6 h after, then 5000 U SC daily \times 5–14 days | Complications —bleeding (may be reversed partially with <i>protamine sulfate</i> 1 mg/100 anti-Xa U of LMWH), HIT, avoid in spinal surgery Monitor —anti-factor Xa activity and platelets. Anticoagulant response correlates well with body weight, allowing fixed dosing without monitoring usually. Less likely to induce HIT but still requires platelet monitoring |
| Heparinoids: <i>Danaparoid</i> (<i>organon</i>) | Indirect factor Xa inhibitors (selective) . Mixture of heparin sulfate, dermatan sulfate, and chondroitin sulfate. Inhibits thrombin via a combination of AT (heparin cofactor I), heparin cofactor II, and some undefined mechanism More selective factor Xa inhibitor than LMWH, with a ratio of antifactor Xa to AT activity of 28:1 compared to 3:1 with LMWH. aPTT not useful for monitoring | HITT Acute DVT | For HITT, <i>danaparoid</i> 2000 anti-factor Xa U IV bolus, then 150–200 U/h, titrate to plasma anti-Xa level of 0.5–0.8 U/mL | Complications —bleeding Monitor —anti-factor Xa activity. Particularly important in renal failure 10% cross-reactivity between danaparoid and the antibody responsible for HITT, but clinical significance is uncertain |

Approach to Anticoagulation Therapies (cont'd)

| Class/Drugs | Mechanism | Indications | Usual dose | Complications/ monitoring |
|--|---|--|--|---|
| Fondaparinux | Indirect factor Xa inhibitor (highly selective). Similar to LMWH, but only a pentasaccharide that binds strongly to AT and inactivates factor Xa. Complex does not bind thrombin due to short length | DVT prophylaxis Acute DVT/PE Acute coronary syndrome HITT (no cross reactivity with heparin-dependent anti-platelet antibodies) | For DVT prophylaxis, <i>fondaparinux</i> 2.5 mg SC daily (start 6–8 h after surgical hemostasis) For acute clots, <i>fondaparinux</i> 5 mg SC daily for weight < 50 kg, 7.5 mg SC daily for weight 50–100 kg, 10 mg SC daily for weight > 100 kg For UA/NSTEMI, <i>fondaparinux</i> 2.5 mg SC daily × 8 days or until discharge For STEMI, <i>fondaparinux</i> 2.5 mg IV × 1 then 2.5 mg SC daily × 8 days or until discharge | Complications—bleeding; avoid in spinal surgery Monitor— antifactor Xa activity |
| Rivaroxaban | Direct factor Xa inhibitors (highly selective). Similar to fondaparinux, but specifically inhibits factor Xa by binding to its active site without interacting with AT | DVT prophylaxis (phase II) | | Complications—bleeding Monitor— antifactor Xa activity |
| Direct thrombin inhibitors: <i>Dabigatran</i> <i>Desirudin</i> <i>Lepirudin</i> <i>Argatroban</i> <i>Ximelagatran</i> | Direct thrombin inhibitors (highly selective). AT independent. In contrast to heparin, LMWH, and heparinoid, direct thrombin inhibitors can inhibit clot-bound thrombin because their sites for binding (active site ± exosite I) are not masked by fibrin. Does not depend on AT for action and thus unaffected by AT deficiency | HITT (lepirudin, argatroban) ACS (hirudin, argatroban) DVT prophylaxis (hirudin, dabigatran) | For HITT, <i>lepirudin</i> 0.1–0.4 mg/kg IV bolus, then 0.1–0.15 mg/kg/h; <i>argatroban</i> 2 µg/kg/min infusion | Complications—bleeding Monitor— aPTT |

CONTRAINDICATIONS TO WARFARIN THERAPY

ABSOLUTE—neurosurgery, ocular surgery or intracranial bleeding within the past 10 days, active bleeding, severe bleeding diathesis, or platelet < 20 × 10³/µL

RELATIVE—mild to moderate bleeding diathesis or thrombocytopenia (20–100 × 10³/µL), brain metastases, recent major trauma, major abdominal surgery < 2 days, GI or GU bleeding < 2 weeks, endocarditis, severe hypertension (>200/120 mmHg)

Related Topics

DVT (p. 158)

Hypercoagulable States (p. 156)

Pulmonary Embolism (p. 8)

WARFARIN-INDUCED SKIN NECROSIS

CLINICAL FEATURES—usually within first few days of warfarin therapy (especially large loading doses) → significantly decreases protein C levels → transient hypercoagulable → erythematous macule → purpuric zone → necrotic lesion. Occurs over extremities, breast, trunk, and penis

TREATMENTS—immediately stop warfarin, give vitamin K, heparin IV, consider FFP or protein C concentrate. Lesion may continue to progress despite adequate anticoagulation

CORRECTION OF SUPRATHERAPEUTIC INR DUE TO WARFARIN USE

INR < 5—if no significant bleeding, rapid reversal is not indicated. Reduce warfarin dose or hold the next warfarin dose

CORRECTION OF SUPRATHERAPEUTIC INR DUE TO WARFARIN USE (CONT'D)

INR 5–9—if no significant bleeding, hold the next 1–2 doses of warfarin or omit the next dose of warfarin and administer *vitamin K1* 2.5 mg PO. If rapid reversal required (e.g. bleeding or urgent surgery), FFP 10–20 mL/kg + *vitamin K1* 2–4 mg PO (↓ INR within 24 h), if INR remains high at 24 h, give additional *vitamin K1* 1–2 mg PO. May also consider prothromin complex concentrate in selected cases

INR >9—if no significant bleeding, hold warfarin and administer *vitamin K1* 5–10 mg PO. Use additional

CORRECTION OF SUPRATHERAPEUTIC INR DUE TO WARFARIN USE (CONT'D)

vitamin K1 if indicated by frequent INR monitoring. If serious bleeding, hold warfarin, administer FFP 20–30 mL/kg + *vitamin K1* 10 mg by slow IV infusion. Also can use prothrombin complex concentrate or recombinant factor VIIa, depending on volume status and urgency. If life-threatening bleeding, hold warfarin therapy and administer recombinant factor VIIa, FFP, and *vitamin K1* 10 mg by slow IV infusion. Monitor INR and repeat as necessary. May also consider prothromin complex concentrate in selected cases

Transfusion Reactions**COMPLICATIONS OF TRANSFUSIONS**

| Adverse Effect | Pathophysiology | Onset and Symptoms | Treatments |
|--|--|--|---|
| ABO incompatibility | Recipient Ab against donor RBC major antigen, 1/40,000 | Immediate. Fever, ↓ BP, CP, lumbar pain, hemoglobinuria, and bleed | Stop transfusion and check blood. Fluids, diuretics, FFP, dialysis |
| Acute hemolytic reaction | Recipient Ab against donor RBC minor antigen, 1/600,000 | Acute/delay. Milder form of above | Stop transfusion and check blood. Fluids, diuretics, FFP, dialysis |
| Febrile reaction | Recipient Ab against donor WBC PRBC, 1/300; or platelets (5U), 1/10 | End of transfusion. Fever, chills | Antihistamine (<i>diphenhydramine</i> 50 mg IV × 1 dose), acetaminophen |
| Anaphylaxis | Recipient Ab against donor IgA, 1/40,000 | Immediate. ↓ BP, bronchospasm, no fever | Stop transfusion, epinephrine, corticosteroids |
| Urticaria | Recipient IgE against donor antigens, 1/100 plasma-containing products | Acute. Pruritic rash | Antihistamine (<i>diphenhydramine</i> 50 mg IV × 1 dose) |
| Post-transfusion purpura (PTP) | Recipient Ab against donor platelet | 7–10 days after. Consumptive thrombocytopenia and purpura | Steroids, plasmapheresis |
| Transfusion-associated circulatory overload (TACO) | Hypervolemia 1/700 | Acute/delay. Pulmonary edema | Epinephrine, corticosteroids |
| Septic transfusion | Platelets (5 U) 1/10,000 risk of symptomatic sepsis and 1/40,000 chance of death PRBC (1 U), 1/100,000 risk of symptomatic sepsis and 1/500,000 chance of death | Acute. Fever, ↓ BP | Stop transfusion, empiric antibiotics |
| Air embolism TRALI | Donor Ab against recipient WBC, 1/5000 plasma-containing products | Acute. SOB, ↓ BP Acute. Hypoxemic, pulmonary edema | Supportive measures Supportive measures |
| GVHD | Donor lymphocytes against recipient tissue | Delay. Rash, hepatitis, diarrhea | |
| Infection risk | HIV 1/10 million, HCV 1/3 million, HBV 1/72,000, HTLV1 1/2 million, West Nile virus < 1/1 million | | |

INVESTIGATIONS

BLOOD TESTS—CBC/D, peripheral smear, urea, Cr, PTT, INR, fibrinogen, blood C&S, send blood product for culture/typing

URINE TESTS—urinalysis

IMAGING—CXR

INDICATIONS FOR SPECIALLY PREPARED BLOOD PRODUCTS

WASHED TRANSFUSION PRODUCT (removes almost all serum proteins and most leukocytes)—IgA deficiency, previous anaphylactic transfusion reaction, febrile reactions not prevented by leukocyte reduction, severe urticarial reactions not prevented by the antihistamines

LEUKOCYTE-DEPLETED TRANSFUSION PRODUCT (removes most leukocytes)—prevention of febrile

INDICATIONS FOR SPECIALLY PREPARED BLOOD PRODUCTS (CONT'D)

reactions or TRALI, prevention of HLA alloimmunization (leukemia, aplastic anemia, chronic hemolytic anemia, MDS, MPS), transplant candidates, substitute for CMV-negative blood

IRRADIATED TRANSFUSION PRODUCTS (kills all leukocytes and prevents transfusion-associated GVHD)—stem cell transplant recipients (prevents GVHD), recipients of directed donor transfusions from blood relatives, Hodgkin's lymphoma

CMV-NEGATIVE TRANSFUSION PRODUCTS (screened)—CMV-negative transplant recipients (solid organ or bone marrow from CMV negative donors), antepartum transfusions for CMV-negative women

Approach to the Peripheral Blood Smear**TERMS**

ANISOCYTOSIS—varying sizes of RBC

POIKILOCYTOSIS—varying shapes of RBC

HYPOCHROMIA—present when the central pale area >1/3 diameter. Occurs in iron deficiency, thalassemia, and lead poisoning

ANISOCROMIA—two cell populations circulating simultaneously. One population is microcytic and hypochromic and the other is normocytic and normochromic. Causes include treated iron deficiency anemia, post-transfusion of a hypochromic patient, sideroblastic anemia

RBC INTRACELLULAR INCLUSIONS

BASOPHILIC STIPPLING— β -thalassemia, lead, or arsenic poisoning

HEINZ BODIES—G6PD deficiency, alpha thalassemia

PAPPENHEIMER BODIES—non-nucleated RBC containing such inclusions are called siderocytes, due to hyposplenism, thalassemia, and sideroblastic disorders. Nucleated RBC are termed sideroblasts

NUCLEATED RBC—acute systemic hypoxia, intense erythropoietin stimulation, infiltrative narrow processes, extramedullary erythropoiesis

HOWELL-JOLLY BODIES—asplenia, megaloblastic hematopoiesis

POLYCHROMASIA—RBC with diffuse bluish discoloration due to the presence of RNA. Increased number of cells showing polychromasia indicates reticulocytosis

TELLTALE MORPHOLOGIES

TARGET CELLS—liver disease (especially obstructive jaundice, hepatitis), thalassemia, post-splenectomy, hemoglobinopathies (hemoglobin C and E), lecithin-cholesterol acyltransferase deficiency

FRAGMENTED CELLS (schistocytes, helmet cells)—microangiopathic hemolytic anemia (DIC, TTP, HUS), aortic valve prosthesis

TEAR DROP CELLS—myelophthisis, myelofibrosis with myeloid metaplasia (MMM), severe iron deficiency, thalassemia major. Disappear after splenectomy

BURR CELLS (echinocytes)—uremia, artifact

SPUR CELLS (acanthocytes)—chronic liver disease, abetalipoproteinemia, malabsorption, anorexia nervosa

SPHEROCYTES—due to loss of membrane surface area. Associated with autoimmune hemolytic anemia (microspherocytes), hereditary spherocytosis, and *Clostridium* infections

ELLIPTOCYTOSIS (ovalocytosis)—hereditary elliptocytosis, megaloblastosis

STOMATOCYTES—acute alcoholism, chronic liver disease, artifact

ROULEAUX—stacking of RBC suggestive of high ESR or hypergammaglobulinemia. Causes include malignancies (myeloma), infections, and connective tissue disease

Splenomegaly

DIFFERENTIAL DIAGNOSIS

CONGESTIVE—right heart failure, constrictive pericarditis, tricuspid regurgitation, IVC obstruction, hepatic/splenic vein obstruction, cirrhosis with portal hypertension

INFILTRATIVE

- **MALIGNANCY**—lymphoma (Hodgkin's, non-Hodgkin's, hairy cell leukemia), leukemia (CLL, CML), myeloproliferative disorders (PRV, CML, ET, MF), splenic tumor, metastasis

- **AMYLOIDOSIS**

- **SARCOIDOSIS**

REACTIVE

- **INFECTIONS**—**bacterial** (endocarditis, sepsis, TB, MAC), **viral** (mononucleosis, hepatitis), **fungal** (*Histoplasma*), **parasitic** (malaria, *Leishmania*, trypanosomiasis)

- **INFLAMMATORY**—rheumatoid arthritis (Felty's syndrome), SLE, Still's disease

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **SICKLE CELL, HEMOGLOBIN C, THALASSEMIA, IgG-MEDIATED AUTOIMMUNE HEMOLYTIC ANEMIA**

CLINICAL FEATURES

SIX WAYS TO DISTINGUISH SPLEEN FROM LEFT KIDNEY

1. Spleen has no palpable upper border
2. Spleen has a notch
3. Spleen moves inferomedially on inspiration while the kidney moves inferiorly
4. Spleen is not usually ballotable unless gross ascites are present, but the kidney is because of its retroperitoneal position
5. The percussion note is dull over the spleen but is usually resonant over the kidney
6. A friction rub may occasionally be heard over the spleen, but never over the kidney because it is too posterior

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE SPLENOMEGALY?

NORMAL SPLEEN—< 250 g [< 0.55 lb] or 250 cm³, 12 cm by 7 cm [4.7 in. by 2.8 in.], anatomically, the spleen lies below the left diaphragm. It follows the curvature of left 10th rib and points anteriorly toward, the left colic flexure

| | Sens | Spc |
|--|------|-----|
| Inspection | | |
| Bulging mass over left costal margin | Low | — |
| Percussion | | |
| Castell's method (percuss lowest intercostal space in the left anterior axillary line during both expiration and full inspiration; dullness suggests splenomegaly) | 82% | 83% |
| Nixon's method (right lateral decubitus position; percuss from lower level of pulmonary resonance in posterior axillary line downward obliquely to lower midanterior costal margin; >8 cm suggests splenomegaly) | 59% | 94% |
| Traube's space (percuss space 6 th rib superiorly, mid-axillary line laterally and costal margin inferiorly; dullness suggests splenomegaly) | 62% | 72% |
| Palpation | | |
| Two-handed palpation with patient in right lateral decubitus position | 71% | 90% |
| One-handed palpation with patient supine | — | — |
| APPROACH —"given the low sensitivity of the clinical examination, routine examination for splenomegaly cannot definitively rule in or rule out splenomegaly in normal, asymptomatic patients where the prevalence is < 10% and additional imaging tests will be required. Rather, the examination for splenomegaly is most useful to rule in the diagnosis of splenomegaly among patients in whom there is a clinical suspicion of at least 10%. The examination should always start with percussion. If no dullness is detected on percussion, there is no need to palpate as the results of palpation will not effectively rule in or rule out splenic enlargement. If the possibility of missing splenic enlargement remains an important clinical concern, then ultrasound or scintigraphy is indicated. In the presence of percussion dullness, palpation should follow. If both tests are positive, the diagnosis of splenomegaly is established (providing the clinical suspicion of splenomegaly was at least 10% before examination). If palpation is negative, diagnostic imaging will be required to confidently rule in or rule out splenomegaly" | | |

JAMA 1993 270:18

INVESTIGATIONS

BASIC

- **LABS**—CBCD, peripheral smear, AST, ALT, ALP, bili
- **MICROBIOLOGY**—blood C&S
- **IMAGING**—U/S abd

SPECIAL

- **CT ABD**—weight = $0.43 \times \text{Length} \times \text{Width} \times \text{Thickness}$
- **SCINTIGRAPHY**
- **MALIGNANCY WORKUP**—bone marrow biopsy, lymph node biopsy, laparoscopy/laparotomy

MANAGEMENT

TREAT UNDERLYING CAUSE

SPLENECTOMY—see p. 147 for more details

SPECIFIC ENTITIES

CAUSES OF MASSIVE SPLENOMEGALY—lymphoma, hairy cell leukemia, CML, myelofibrosis, malaria, MAC in HIV, thalassemia major, sarcoidosis, Gaucher's disease

Myeloproliferative Disorders

NEJM 2007 357:3

DIFFERENTIAL DIAGNOSIS

ESSENTIAL THROMBOCYTOSIS (ET)

POLYCYTHEMIA RUBRA VERA (PRV)

CHRONIC MYELOGENOUS LEUKEMIA (CML)

MYELOFIBROSIS (MF)

OTHERS—chronic eosinophilic leukemia, chronic myelomonocytic leukemia (CMML), chronic neutrophilic leukemia, systemic mastocytosis

PATHOPHYSIOLOGY

MYELOPROLIFERATIVE DISORDERS—associated with increased red blood cells (especially PRV), white blood cells (especially CML), and/or platelets (especially ET). MPS should not be confused with myelodysplastic syndrome (MDS), which is associated with a decreased production of blood cells. Both MPS and MDS can eventually lead to AML

POLYCYTHEMIA RUBRA VERA—see POLYCYTHEMIA (p. 143)

CHRONIC MYELOGENOUS LEUKEMIA (CML)—a stem cell disease with Philadelphia chromosome t(9;22) leading to fusion gene *bcr-abl*, found in erythroblasts, megakaryocytes, granulocytes, monocytes, and most lymphocytes. ↓ LAP. Chronic phase → accelerated phase → blast crisis, 2/3 myeloid, 1/3 lymphoid

- **CHRONIC PHASE** (5–6 years)—<15% blasts, <20% basophils, and <30% blasts plus promyelocytes
- **ACCELERATED PHASE** (6–9 months)—15–29% blasts, ≥20% basophils, ≥30% blasts+ promyelocytes or platelets < $100 \times 10^3/\mu\text{L}$
- **BLAST CRISIS** (3–6 months)—≥30% blasts or extramedullary involvement (chloroma). Usually constitutional symptoms, worsening blood counts, and may have extra Ph chromosome, inv(17q), trisomy 8, and trisomy 19

CHRONIC MYELOMONOCYTIC LEUKEMIA (CMML)—also known as smoldering leukemia, with persistent unexplained monocytosis. Classified as "MDS/MPS." Clinical features include leukocytosis (monocytosis $>1.0 \times 10^3/\mu\text{L}$ for at least 6 months), anemia, thrombocytopenia, and splenomegaly

PATHOPHYSIOLOGY (CONT'D)

ESSENTIAL THROMBOCYTOSIS—see THROMBOCYTOSIS (p. 150)

MYELOFIBROSIS—↑ fibroblasts, marked ↑ spleen, teardrop RBC, nucleated RBC, large platelets

Related Topics

Polycythemia (p. 143)

Thrombocytosis (p. 150)

CLINICAL FEATURES

HISTORY—B symptoms (fever, night sweats, weight loss, pruritus), hyperviscosity symptoms (facial plethora, headache, visual or mental status changes, stroke, or another ischemic/thrombotic event)

PHYSICAL—splenomegaly

INVESTIGATIONS

BASIC

- **LABS**—CBCD, peripheral smear, reticulocyte count, uric acid
- **BONE MARROW BIOPSY**—not useful for PRV. Consider cytogenetic studies of blood/bone marrow (FISH) or quantitative PCR to look for Ph chromosome

SPECIAL

- **GENETIC TESTING**—JAK2 mutation (sensitivity ~100% for PRV and highly specific for other myeloproliferative disorders), *bcr-abl* testing (CML)
- **LEUKOCYTE ALKALINE PHOSPHATASE (LAP)**—↑ in PRV, MF, ET, and leukemoid reactions; can be ↓ in CML and CMML
- **VITAMIN B12**—↑ in CML due to granulocyte transcobalamin I levels
- **EPO**—↓ in PRV

DIAGNOSTIC AND PROGNOSTIC ISSUES

LEUKOCYTE ALKALINE PHOSPHATASE—elevated in PRV, MF, and ET, but decreased in CML and CMML

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

POLYCYTHEMIA RUBRA VERA—median survival 10–15 years, ~1/100 transforms to CML, MF, AML

CHRONIC MYELOGENOUS LEUKEMIA—median survival 3–4 years, ~1/2 transforms to AML

ESSENTIAL THROMBOCYTOSIS—median survival 10–15 years, ~1/1000 transforms to AML

MYELOFIBROSIS—median survival 5 years, ~1/10 transforms to AML

MANAGEMENT

POLYCYTHEMIA RUBRA VERA—phlebotomy 1–2/week, aspirin, hydroxyurea

CHRONIC MYELOGENOUS LEUKEMIA

• **CHRONIC PHASE**—*imatinib mesylate* 400–800 mg PO daily with cytogenetic response rate 63%, dasatinib and nilotinib may be used for imatinib-resistant disease. Allogeneic stem cell transplant is associated with 60–70% cure rate

• **ACCELERATED PHASE**—*imatinib mesylate* 600–800 mg PO daily. Allogeneic stem cell transplant is associated with 30–45% cure rate

• **BLAST CRISIS**—*imatinib mesylate* 800 mg PO daily, plasmapheresis. Allogeneic stem cell transplant is associated with 10–15% cure rate

• **IMATINIB-RESISTANT CML**—dasatinib, nilotinib, and stem cell transplantation

ESSENTIAL THROMBOCYTOSIS—aspirin, anagrelide (↓ platelet via stabilizing membrane), hydroxyurea, alkylating agents,^{32p}

MYELOFIBROSIS—splenectomy, interferon α , thalidomide

TREATMENT ISSUES

RESPONSE CRITERIA FOR CML

• HEMATOLOGICAL RESPONSE

- **COMPLETE RESPONSE**—WBC $<10 \times 10^3/\mu\text{L}$ with no immature granulocytes and $<5\%$ basophils, platelet $<450 \times 10^3/\mu\text{L}$, and non-palpable spleen

TREATMENT ISSUES (CONT'D)

- **PARTIAL RESPONSE**—persistence of immature cells in peripheral blood, platelets $>450 \times 10^3/\mu\text{L}$ but $<50\%$ of pre-treatment levels, or persistent splenomegaly but $<50\%$ of pre-treatment size
- **CYTOGENETIC RESPONSE** (FISH detection of the Philadelphia chromosome)
 - **COMPLETE**—0% Ph+ cells
 - **PARTIAL**—1–35% Ph+ cells
 - **MAJOR**—complete and partial cytogenetic response
 - **MINOR**—36–65% Ph+ cells
 - **MINIMAL**—66–95% Ph+ cells
- **MOLECULAR RESPONSE** (bcr-abl transcript detection by RT-PCR)
 - **COMPLETE**—negative
 - **MAJOR**—bcr-abl to control gene ratio <0.1 (3 log decrease in bcr-abl transcript in peripheral blood)

DEFINITION OF TREATMENT FAILURE FOR CML PATIENTS ON IMATINIB THERAPY

| Months | Suboptimal | Failure |
|---------|------------------|---------------------|
| 3 | < CHR | No HR |
| 6 | < PCGR | < CHR, no CGR |
| 12 | < CCGR | < PCGR |
| 18 | < MMR | < CCGR |
| Anytime | ACA, loss of MMR | Loss of CHR or CCGR |

where HR=hematologic response, CHR=complete hematologic response, CGR=cytogenetic response, PCGR=partial cytogenetic response, CCGR=complete cytogenetic response, MMR=major molecular response, ACA=additional chromosomal abnormality

MONITORING FOR CHRONIC MYELOGENOUS LEUKEMIA—bone marrow annually, quantitative PCR every 3 months (repeat test in 4 weeks if >0.5 log increase)

IMATINIB RESISTANCE—bcr-abl mutations, overexpression or amplification of bcr-abl

Acute Myelogenous Leukemia

NEJM 1999 341:14

HEMATOLOGIC MALIGNANCIES OVERVIEW

MYELO—bone marrow. Myeloproliferative disorders (PRV, CML, ET, and MF) involve cell accumulation, while myelodysplastic disorders involve abnormal bone marrow cell growth. Both disorders have risk of transformation to acute myeloid leukemia

MYELOID—neutrophils, monocytes, macrophages, eosinophils, basophils, mast cells, erythrocytes, platelets, and their precursors. Myeloid malignancies include AML and CML

HEMATOLOGIC MALIGNANCIES OVERVIEW (CONT'D)

LYMPHOID—B cells, T cells, natural killer cells. Lymphoid malignancies include ALL, CLL, and all lymphomas

LEUKEMIA—malignant cells in blood and/or bone marrow. May be myeloid (AML, CML) or lymphoid* (LL/ALL, SLL/CLL) in origin. Myeloid leukemia seldom presents in lymph nodes

- **ACUTE LEUKEMIA**—involves immature blast cells. More aggressive course

HEMATOLOGIC MALIGNANCIES OVERVIEW (CONT'D)

- **CHRONIC LEUKEMIA**—involves mature differentiated cells. More indolent course
- LYMPHOMA**—malignancy of lymphoid origin and presents more in lymphoid organs
- **HODGKIN'S LYMPHOMA**—B cell (Reed–Sternberg cell)
- **NON-HODGKIN'S LYMPHOMA**—B, T, or NK cells
- *lymphoblastic lymphoma (LL) = acute lymphoblastic leukemia (ALL). Small lymphocytic lymphoma (SLL) = chronic lymphocytic leukemia (CLL)

PATHOPHYSIOLOGY**EPIDEMIOLOGY**

- **INCIDENCE**—1–2% of all cancers, 90% of all acute leukemias in adulthood, mean age 65
- **MORTALITY**—1.5% of all cancers

RISK FACTORS FOR AML

- **FAMILY HISTORY**—family history (3×), Down's, Klinefelter, Fanconi syndrome, Bloom's, ataxia telangiectasia, neurofibromatosis
- **ENVIRONMENTAL**—previous chemotherapy (alkylating agents [melphalan, cyclophosphamide, chlorambucil, temozolomide], topoisomerase II inhibitors [anthracyclines, etoposide]), radiation, benzene
- **DISEASES**—MDS, MPS (PRV, CML, ET, MF), PNH, aplastic anemia

DISTINGUISHING FEATURES BETWEEN TREATMENT-INDUCED AMLS

| | Alkylating agents | Topoisomerase II inhibitors |
|-------------|--------------------------|------------------------------------|
| Latency | 5–7 years | 2–3 years |
| MDS pre-AML | Yes | No |
| AML types | All, M1–2 | M4–5 |
| Karyotype | –5, –7 | 11q23, 21q22, inv16 |
| Prognosis | Worse | Poor except for Inv16 karyotype |

CLINICAL FEATURES

PANCYTOPENIA—weakness, fatigue, infections, gingival bleed, ecchymosis, epistaxis, menorrhagia

BONE PAIN—ribs, sternum, long bones

CUTANEOUS LESIONS—leukemic cutis (especially M4, M5), chloromas (skin local collection of blasts, granulocytic sarcoma especially M2), gum hypertrophy (M5)

CNS LEUKEMIA (especially M4, M4EO, and M5)

DIC—associated with M3 subtype

NOTE: lymphadenopathy, hepatosplenomegaly not common

INVESTIGATIONS**BASIC**

- **LABS**—CBCD, smear (Auer rods), lytes, urea, Cr, Ca, PO₄, Mg, uric acid, albumin, urinalysis, LDH, INR, PTT, fibrinogen

INVESTIGATIONS (CONT'D)

- **BONE MARROW BIOPSY (>20% BLASTS) WITH CYTOGENETIC ANALYSIS**

SPECIAL

- **IMAGING**—MUGA scan
- **LUMBAR PUNCTURE**—CSF for cytology (risk of CNS involvement greatest with high circulating blasts, elevated LDH, and monocytic variants of AML)
- **HLA TESTING**—to assist in obtaining HLA-matched platelets if needed during treatment and to find HLA-matched allogeneic bone marrow

DIAGNOSTIC AND PROGNOSTIC ISSUES

DIAGNOSTIC CRITERIA—>20% blasts in bone marrow

HISTOLOGIC TYPE

- **FAB M0**—AML, minimally differentiated
- **FAB M1**—AML, without maturation (19%)
- **FAB M2**—AML, with maturation (32%)
- **FAB M3**—acute promyelocytic leukemia (PML), with both hypergranular and variant microgranular subtypes (M3v)
- **FAB M4**—acute myelomonocytic leukemia (AMML), including the variant AMML with abnormal eosinophils (M4EO) (17%)
- **FAB M5**—acute monoblastic leukemia, including poorly differentiated (M5a) and differentiated (M5b)
- **FAB M6**—acute erythroleukemia
- **FAB M7**—acute megakaryoblastic leukemia

PROGNOSTIC FACTORS

- **GOOD RISK** (70% 5-year survival, 33% relapse)—favorable karyotypes t(8;21), t(15;17), inv(16)/t(16;16)/del(16q), FAB M3
- **INTERMEDIATE RISK** (48% 5 year survival, 50% relapse)—neither good nor bad; normal cytogenetics or trisomy 8
- **POOR RISK** (15% 5-year survival, 78% relapse)—adverse karyotypes include monosomy chromosome 5 or chromosome 7, del(5q), abn(3q26), t(6;9), 11q23 aberrations except for t(9;11), or multiple chromosomal changes, resistant disease after first course of chemotherapy (>15% blasts)
- **ADDITIONAL POOR PROGNOSTIC FACTORS**—age >60, Karnofsky score <60%, CD34+, MDR1+, FLT3 mutation, prior MDS, MPS, chemotherapy, radiation, trisomy 8, t(6;9), LDH >2.9× UNL

MANAGEMENT**AGE <60**

- **INDUCTION CHEMOTHERAPY**—IDAC (also known as the 7+3 regimen, cytarabine ×7 days + one of daunorubicin/idarubicin/mitoxantrone ×3 days), HDAC (same except higher dose of cytarabine q12h ×12 doses leads to longer disease free survival) or NOVE (mitoxantrone plus etoposide)

MANAGEMENT (CONT'D)

- **CONSOLIDATION TREATMENT**
 - **COMPLETE REMISSION POST-INDUCTION**
 - **GOOD RISK**—chemotherapy IDAC or HDAC $\times 3$
 - **INTERMEDIATE RISK**—sibling-donor allogeneic stem cell transplant (SCT) if available; otherwise, consolidation chemotherapy
 - **POOR RISK**—allogeneic SCT if matched donor available; otherwise, consolidation chemotherapy
 - **LACK OF COMPLETE REMISSION POST-INDUCTION**—repeat induction or give cyclophosphamide plus etoposide. Proceed to consolidation as in poor risk disease if complete remission. Otherwise, palliation only
 - **RELAPSE**—allogeneic SCT if matched donor available (preferred); otherwise, salvage chemotherapy with cytarabine/carboplatin, clinical trials, or palliation

AGE >60—individualized treatment. If unable to tolerate aggressive therapy, consider IDAC with attenuated doses or palliation with hydroxyurea cyto reduction

Related Topics

Febrile Neutropenia (p. 236)
Tumor Lysis Syndrome (p. 228)

TREATMENT ISSUES

COMPLETE REMISSION—normal BM cellularity, <5% blasts in BM, none with leukemic phenotype or abnormal cytogenetics. Lumbar puncture after complete remission with induction chemotherapy, especially those with monoblastic phenotype. After induction, the remission rate in younger patients (<55 years) is 70–85%, but only 40–50% in older patients

ALLOGENEIC SCT—if HLA matched, may opt for consolidation chemotherapy while waiting for match donor. Allogeneic SCT has resulted in cure rates of 50–60% for recipients in 1st remission

SPECIFIC ENTITIES

MYELODYSPLASTIC SYNDROME (MDS)—opposite of myeloproliferative disorders, decreased cell counts

- **SUBTYPES**—refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory anemia with multilineage dysplasia, refractory anemia with multilineage dysplasia and ringed sideroblasts, refractory anemia with excess blasts (RAEB) 5–10% blasts, refractory anemia with excess blasts in transformation (RAEB-t) 10–19% blasts, MDS unclassified. RA and RARS are at low risk of transforming to AML (i.e. >20% blasts), while the rest are at high risk

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—peripheral blood smear (RBC with abnormal morphologic features, dysgranulopoiesis with Pelger-Huët deformity, nuclear atypia and hypogranulation, relative monocytosis), bone marrow biopsy

INTERNATIONAL PROGNOSTIC SCORING SYSTEM FOR MYELODYSPLASTIC SYNDROMES

| Score | 0 | 0.5 | 1 | 1.5 | 2 |
|----------------|------|------|------|-------|-------|
| % blasts in BM | <5 | 5–10 | – | 11–20 | 21–30 |
| Karyotype | Good | Med. | Poor | – | – |
| Cytopenia | 0/1 | 2/3 | – | – | – |

For karyotype, good = $-y$, del(5q), del(20q); medium = neither good nor poor; poor = chromosome 7 or complex abnormalities

| Risk group | Score | Median survival |
|----------------|------------|-----------------|
| Low | 0 | 5.7 years |
| Intermediate 1 | 0.5–1.0 | 3.5 years |
| Intermediate 2 | 1.5–2.0 | 1.2 years |
| High | ≥ 2.5 | 0.4 year |

- **TREATMENTS**—transfusions, EPO, treat infections early, 5-azacytidine, lenalidomide, decitabine, allogeneic stem cell transplant (IPSS ≥ 1.5)

ACUTE PROMYELOCYTIC LEUKEMIA (M3, APL, PML)

- **PATHOPHYSIOLOGY**—associated with t(15;17) (q22;q21), which results in fusion of PML gene and retinoic acid receptor α gene. This gene product plays a key role in leukemogenesis. Other combinations include t(11;17) with fusion of PLZF gene, t(5;17) with fusion of NPM gene, or t(11;17) with fusion of NuMA gene. Note that all except PLZF-RARA are susceptible to retinoic acid treatment
- **CLINICAL FEATURES**—similar to AML. DIC commonly occurs in PML and should be monitored closely
- **TREATMENTS—induction** with all-*trans*-retinoic acid plus idarubicin, then **consolidation** with anthracycline and cytarabine, and then **maintenance** with all-*trans*-retinoic acid for 1 year. Retinoic acid exerts its effect via (1) degradation of PML-RAR protein, (2) transformation of PML-RAR from transcription repressor to activator, and (3) differentiation. Retinoic acid syndrome may occur with fever, respiratory distress, interstitial pulmonary infiltrates, pleural and pericardial effusion, episodic hypotension, acute renal failure, and weight gain. Arsenic trioxide can be used for **recurrent disease** but is associated with QT prolongation and sudden death

Acute Lymphoblastic Leukemia

NEJM 2006 354:2

PATHOPHYSIOLOGY

HISTOLOGIC TYPE

- **FAB L1**—small, uniform lymphoblasts with indistinct nucleoli
- **FAB L2**—larger, pleomorphic lymphoblasts with low nucleus to cytoplasm ratio and clear nucleoli
- **FAB L3**—large, pleomorphic lymphoblasts with basophilic cytoplasm, large nucleoli, vacuoles

WHO CLASSIFICATION

- **PRECURSOR B CELL** (L1, L2)
 - **PRO-B ALL**—resembles an early stage of B cell
 - **PRE-B-CELL ALL**—intracytoplasmic immunoglobulin
 - **B-CELL ALL**—express surface immunoglobulin
- **PRECURSOR T CELL** (L1, L2)
- **BURKITT-LIKE ALL** (L3)

RISK FACTORS FOR ALL—old age, previous chemotherapy or radiation, Down's syndrome

CLINICAL FEATURES

PANCYTOPENIA—weakness, fatigue, infections, gingival bleed, ecchymosis, petechiae, epistaxis, menorrhagia

ORGAN INVOLVEMENT—lymphadenopathy, hepatomegaly, splenomegaly, bone pain, cranial nerve palsies, headaches

NOTE: precursor B lymphoblastic lymphoma is associated with lymphadenopathy/extranodal involvement and < 25% blasts, while precursor T LBL is associated mediastinal mass and < 25% blasts

DISTINGUISHING FEATURES BETWEEN AML AND ALL

| | AML | Precursor ALL |
|-----------|--------|---------------|
| Blasts | Larger | Small |
| Auer rods | + | - |
| TdT | - | + |
| MPO | + | - |

INVESTIGATIONS

BASIC

- **LABS**—CBCD, smear, lytes, urea, Cr, Ca, PO₄, Mg, uric acid, albumin, urinalysis, LDH, INR, PTT, fibrinogen, flow cytometry of peripheral blood (immunophenotyping)
- **BONE MARROW BIOPSY**—>25% blast, flow cytometry for immunophenotyping, cytogenetic analysis (detection of BCR-ABL fusion and chromosomal abnormalities with pulsed-field gel electrophoresis and/or RT-PCR)
- **LUMBAR PUNCTURE**—CSF for cytology
- **TISSUE BIOPSY**—lymph node, skin, mediastinal mass

INVESTIGATIONS (CONT'D)

SPECIAL

- **IMAGING**—MUGA scan
- **HLA TESTING**—to assist in obtaining HLA-matched platelets if needed during treatment and to find HLA-matched allogeneic bone marrow

PROGNOSTIC ISSUES

PROGNOSTIC FACTORS—while childhood ALL is curable in 85% of cases, adult ALL has a worse prognosis, with a 5-year survival of 35%. Factors associated with poorer survival include the following:

- **CLINICAL**—lack of response to induction therapy (most important), old age, leukocyte count, CNS involvement
- **CYTOGENETICS**—BCR-ABL fusion or t(9;22) (also known as the Philadelphia chromosome, in 20–50% of adults), MLL-AF4 fusion or t(4;11) (in 5–6% of adults), t(8;14), t(1;19), hypodiploidy (< 45 chromosomes/cell), del(7), trisomy
- **FAVORABLE PROGNOSIS**—hyperdiploidy, del(9), TEL-AML1 fusion or t(12;21) (in 10% of adults)

RISK CATEGORIES

- **HIGH RISK**—any of age >60, t(9;22) or bcr-abl, t(4;11), t(1;19); WBC >30×10³/μL in B-ALL or >100×10³/μL in T-ALL or pro-B ALL
- **STANDARD RISK**—none of high-risk features

RISK FACTORS FOR CNS RELAPSE—high-risk genetic features, T-ALL, large tumor burden, CSF positivity

MANAGEMENT

REMISSION INDUCTION THERAPY—combination chemotherapy with prednisone, vincristine, an anthracycline ± asparaginase, and cyclophosphamide. Complete response 80–90%. Management of specific subgroups include

- **PH+ ALL**—add imatinib
- **B-CELL ALL**—treat as aggressive non-Hodgkin's lymphoma
- **T-CELL ALL**—treat with cyclophosphamide-containing regimens

CNS PROPHYLAXIS—to start after remission with intrathecal methotrexate with high-dose systemic methotrexate. Consider cranial radiation for patients at high risk of CNS relapse

INTENSIFICATION/CONSOLIDATION THERAPY

- **STANDARD RISK**—consolidation chemotherapy with various combinations of cyclophosphamide, 6-mercaptopurine, cytarabine, vincristine, and doxorubicin

MANAGEMENT (CONT'D)

- **HIGH RISK**—allogeneic SCT if HLA-matched donor available and eligible for transplant; otherwise, consolidation chemotherapy

MAINTENANCE THERAPY—POMP (6-mercaptopurine daily, methotrexate weekly, vincristine and prednisone monthly) or dexamethasone for 2–3 years, except for patients who received allogeneic SCT

TREATMENT ISSUES

SURVIVORSHIP ISSUES—risk of secondary malignancies, neurologic sequelae, cardiotoxicity, infertility, depression, anxiety, and fatigue

Related Topics

Febrile Neutropenia (p. 236)
Tumor Lysis Syndrome (p. 228)

Chronic Lymphocytic Leukemia

NEJM 2005 352:8

DIFFERENTIAL DIAGNOSIS OF LYMPHOCYTOSIS**NEOPLASTIC**

- **CHRONIC LYMPHOCYTIC LEUKEMIA (CLL, most common cause)**
- **PROLYMPHOCYTIC LEUKEMIA**
- **LEUKEMIC PHASE OF LYMPHOMAS**—mantle cell lymphoma, lymphoplasmacytic lymphoma, follicular lymphoma, marginal zone lymphoma, hairy cell leukemia
- **LARGE GRANULAR CELL LYMPHOCYTE LEUKEMIA**

INFECTIONS—pertussis, infectious mononucleosis, hepatitis, toxoplasmosis

PATHOPHYSIOLOGY

WHO CLASSIFICATION—CLL is identical to small lymphocytic lymphoma (SLL, mature B-cell non-Hodgkin's lymphoma). Traditionally, CLL diagnosis is made from peripheral blood, while SLL diagnosis is made from lymph node biopsy

TRANSFORMATION OF CLL—prolymphocytic leukemia 10%, diffuse large B-cell lymphoma (Richter's transformation) 3–10%, Hodgkin's disease 0.5%, multiple myeloma 0.1%

CLINICAL FEATURES

ORGAN INFILTRATION—lymphadenopathy (80%), splenomegaly (50%), hepatomegaly, skin and lung infiltration, gastric erosions

PERIPHERAL BLOOD—lymphocytosis with smudge cells, anemia, thrombocytopenia

CONSTITUTIONAL—weight loss, fever, night sweats, fatigue, anorexia

ASSOCIATED SYNDROMES—ITP, hemolytic anemia, pure red cell aplasia, cryoglobulinemia, MPGN, hypogammaglobulinemia, monoclonal gammopathy

SECOND MALIGNANCIES—non-melanoma skin cancer 4.7%, sarcomas 3.3%, kidney 2.8%, lung 2%, prostate 1.5%

INVESTIGATIONS**BASIC**

- **LABS**—CBCD, smear (smudge cells), lytes, urea, Cr, Ca, PO₄, Mg, uric acid, LDH, β₂ microglobulin, albumin, quantitative immunoglobulin, serum protein electrophoresis, urinary protein electrophoresis
- **PERIPHERAL BLOOD FLOW CYTOMETRY FOR SURFACE MARKERS**

SPECIAL

- **BONE MARROW BIOPSY**
- **LYMPH NODE BIOPSY**
- **MICROBIOLOGY**—monospot test, hepatitis serology if need to rule out other causes

DIAGNOSTIC AND PROGNOSTIC ISSUES**NCI WORKING GROUP DIAGNOSTIC CRITERIA**

- **PERIPHERAL BLOOD**—absolute lymphocyte count in the $>5 \times 10^3/\mu\text{L}$, with ≥ 1 B-cell marker (CD19, CD20, CD23) and CD5; $>55\%$ atypical cells
- **BONE MARROW**—a normocellular to hypercellular marrow with $>30\%$ lymphocytes. Interstitial/nodular pattern (70%) has a better prognosis than diffuse/extensive pattern (30%)
- **IMMUNOPHENOTYPE**—CD5+, CD19+, CD20+, CD23+, CD43+, CD10–, Slg+
- **NOTE**—for patients with lymphocyte count $5–10 \times 10^3/\mu\text{L}$, lymphocyte phenotyping is required

RAI STAGING

- 0** lymphocytosis in blood or bone marrow. Median survival >150 months
- I** lymphocytosis + lymphadenopathy. Median survival 101 months
- II** lymphocytosis + organomegaly. Median survival 71 months
- III** lymphocytosis + anemia (<110 g/L [<11 g/dL]). Median survival 19 months
- IV** lymphocytosis + thrombocytopenia ($<100 \times 10^3/\text{mL}$). Median survival 19 months

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

BINET STAGING

- A** <3 lymphoid-bearing sites enlarged. Median survival >10 years
- B** ≥3 lymphoid-bearing sites enlarged. Median survival 5 years
- C** anemia (<100 g/L [10 g/dL]) or thrombocytopenia (<100×10³/μL). Median survival 2 years

ADVERSE PROGNOSTIC FACTORS OF CLL—higher Rai stage, high Binet stage, diffuse pattern on bone marrow biopsy, lymphocyte doubling time <1 year (5-year survival vs. 12-year survival), CD38+, unmutated IgV_H genes, ZAP70 positive, P2X7 receptor, p53 mutation, gene 1513A/A genotype, 17p deletion, 11q deletion, trisomy 12

FEATURES SUGGESTIVE OF TRANSFORMATION—*new onset* localized lymph node enlargement, B symptoms (without obvious increase in tumor burden), hypercalcemia, elevation in LDH, or extranodal disease other than bone marrow and liver, rapid increase of splenomegaly, rapid elevation of lymphocytosis

MANAGEMENT

AGE <65 AND OTHERWISE HEALTHY (potentially curative)—consider high-dose chemotherapy + allogeneic stem cell transplant

AGE >65 OR COMORBIDITIES (palliative)—first-line regimens include **FR** (fludarabine, rituximab) or **FCR** (fludarabine, cyclophosphamide, rituximab). Second-line therapy includes mainly **alkylating agents** (chlorambucil, cyclophosphamide, CVP). **Alemtuzumab** (anti-CD52 antibody) is useful for fludarabine-refractory disease (i.e. lack of CR/PR, or response but <6 months).

Indications for treatment include symptoms (weakness, painful lymphadenopathy, B symptoms, symptomatic splenomegaly), anemia (Hb <110 g/L [<11 g/dL]), thrombocytopenia (platelets <100×10³/μL), autoimmune hemolytic anemia/thrombocytopenia that failed steroids, progressive disease (increasing lymphocytosis with doubling time <6 months ± rapidly enlarging lymph nodes, spleen, and liver). If evidence of

MANAGEMENT (CONT'D)

Richter's transformation, treat as aggressive lymphoma with CHOPR

NOTE—while traditionally SLL has been managed as a low-grade non-Hodgkin's lymphoma, it is identical to CLL and should be treated as such

TREATMENT ISSUES

NCI WORKING GROUP DIAGNOSTIC CRITERIA FOR TREATMENT RESPONSE

- **COMPLETE RESPONSE**—normal physical examination and no symptoms. Lymphocytes ≤4 ×10³/μL, neutrophils ≥1.5×10³/μL, platelets >100×10³/μL, Hb >110 g/L [>11 g/dL], and bone marrow lymphocytes <30% with no nodules. Duration of at least 2 months
- **PARTIAL RESPONSE**—nodes/liver/spleen ≥50% decrease PLUS one of neutrophils ≥1.5×10³/μL, platelets >100×10³/μL, or Hb >110 g/L [>11 g/dL] or 50% improvement. Duration of at least 2 months
- **STABLE DISEASE**—between PR and PD
- **PROGRESSIVE DISEASE**—any one of nodes/liver/spleen ≥50% increase or new lesions, lymphocytes ≥50% increase, or Richter's syndrome

SPECIFIC ENTITIES

HAIRY CELL LEUKEMIA

- **PATHOPHYSIOLOGY**—rare indolent non-Hodgkin's lymphoma with mononuclear cells displaying cytoplasmic projections giving a hairy appearance. Secretes fibronectin, cytokines, and TNF-causing bone marrow fibrosis
- **CLINICAL FEATURES**—splenomegaly (90%), cytopenia (fatigue, recurrent infections, thrombocytopenia), and leukocytosis. Lymphadenopathy is uncommon
- **TREATMENTS**—treat only if symptomatic (cytopenia, splenomegaly, B symptoms). Cladribine (2CdA) is first-line treatment and may be repeated. Other treatments include pentostatin, interferon, splenectomy, rituximab, and BL22 (CD22 antibodies)

Hodgkin's Lymphoma

PATHOPHYSIOLOGY

HISTOLOGIC TYPE

- **CLASSICAL HODGKIN'S LYMPHOMA** (95%)—B-cell lymphoma characterized by the presence of Reed–Sternberg cells. CD15 and CD30 positive. Spreads in orderly fashion to contiguous nodal regions

PATHOPHYSIOLOGY (CONT'D)

- **NODULAR SCLEROSIS** (70%)—more common in females, above diaphragm involvement (mediastinal mass). Three grades include lymphocyte predominant (G1), mixed (G2), and syncytial (G3)

PATHOPHYSIOLOGY (CONT'D)

- **MIXED CELLULARITY** (20–25%)—more common in men. Tend to be EBV+. Retroperitoneal disease. Worse prognosis
- **LYMPHOCYTE RICH** (5%)—more common in older males, peripheral lymph nodes. Excellent prognosis
- **LYMPHOCYTE DEPLETED** (2%)—liver and marrow involvement with relative sparing of lymph nodes. Worse prognosis
- **NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN'S LYMPHOMA** (5%)—males, upper neck involvement. Characterized by popcorn cells. Slow progression, excellent prognosis. CD20 positive

RISK FACTORS

- **FAMILY HISTORY**
- **ENVIRONMENTAL**—wood workers, farmers, meat workers
- **DISEASES**—mononucleosis (EBV infection 3×), AIDS, bone marrow transplant

CLINICAL FEATURES

SYMPTOMS

- **MASS EFFECT**—lymphadenopathy, hepatosplenomegaly, mediastinal/abdominal/pelvic masses may cause local destruction, obstruction, and compression
- **HEMATOLOGIC**—anemia, thrombocytopenia, lymphocytosis, eosinophilia
- **CONSTITUTIONAL**—B-symptoms specifically refer to weight loss >10% over 6 months, fever >38°C [>100.4°F], and drenching night sweats. Other constitutional symptoms include fatigue, anorexia, pruritus
- **PARANEOPLASTIC SYNDROMES**—**alcohol-induced pain, skin** (skin infiltration, erythema multiforme, erythema nodosum, necrotizing lesions, ichthyosis, acrokeratosis, urticaria), **neurologic** (paraneoplastic cerebellar degeneration, chorea, limbic encephalitis, subacute sensory neuropathy, subacute lower motor neuropathy, stiff man syndrome), **renal** (minimal change disease, FSGS), **hypercalcemia**

DISTINGUISHING FEATURES BETWEEN MALIGNANT AND NON-MALIGNANT LYMPHADENOPATHY

| | Malignancy | Benign |
|-------------|---------------|---------|
| Size | Larger, grows | Smaller |
| Consistency | Rubbery, firm | Soft |
| Mobility | Immobile | Mobile |
| Matted | Yes | No |
| Tenderness | No | Yes |

STAGING

COTSWOLDS STAGING (MODIFIED FROM ANN ARBOR STAGING)

- **I** Single node region or lymphoid structure (spleen, thymus, Waldeyer's ring)
- **II** Two or more node regions on the same side of diaphragm. All nodal disease within the mediastinum is considered to be a single lymph node region and hilar involvement constitutes an additional site of involvement. The number of anatomic regions should be indicated by a subscript (e.g. II-2)
- **III** Involvement on both sides of diaphragm. III-1 indicates involvement of the spleen or splenic hilar, celiac, or portal nodes. Stage III-2 indicates involvement of the paraaortic, iliac, inguinal, or mesenteric nodes
- **IV** Diffuse or disseminated foci of involvement of one or more extralymphatic sites (e.g. bone marrow, extranodal sites that cannot be included in one radiation field)

DESIGNATIONS

- **E**—extralymphatic site (i.e. involvement outside of lymph nodes, spleen, thymus, and Waldeyer's ring) or involvement by direct extension
- **X**—bulky disease defined as mediastinal mass >1/3 of internal transverse diameter of the thorax at the level of T5/6 interspace or >10 cm [>3.9 in.] maximum dimension of a nodal mass
- **A**—no B symptoms
- **B**—weight loss >10% over 6 months, fever >38°C [>100.4°F], drenching night sweats

INVESTIGATIONS

BASIC

- **LABS**—CBCD, peripheral smear, lytes, urea, Cr, AST, ALT, ALP, bilirubin, Ca, LDH, ESR, albumin, quantitative immunoglobulin, serum protein electrophoresis, HCV, HBV, and HIV serology
- **IMAGING**—CXR, CT chest/abdomen/pelvis, PET scan
- **LYMPH NODE BIOPSY**—referral to surgery

SPECIAL

- **BONE MARROW BIOPSY**—if B symptoms, Hb <120 g/L [<12 g/dL] in women, Hb <130 g/L [<13 g/dL] in men, WBC <4×10³/μL, platelets <125×10³/μL
- **ENT EXAMINATION**—stage IA or IIA with upper cervical lymph node involvement
- **MRI SPINE**—if suspect spinal cord compression
- **MUGA SCAN**—evaluate cardiac function prior to anthracycline therapy
- **GALLIUM SCAN**—stage IA or IIA without intrathoracic involvement

PROGNOSTIC ISSUES

PROGNOSTIC FACTORS FOR EARLY STAGE DISEASE—age >50, bulky disease, ESR >50 mm/h without B symptoms or ESR >30 mm/h with B symptoms, anemia

INTERNATIONAL PROGNOSTIC FACTOR PROJECT SCORE FOR ADVANCED HODGKIN'S LYMPHOMA (HASENLEVER SCORE)

- **FACTORS**—age >45, male gender, Ann Arbor clinical stage IV, albumin <40 g/L [<4 g/dL], hemoglobin <105 g/L [<10.5 g/dL], WBC $>15 \times 10^3/\mu\text{L}$, lymphocyte $<0.6 \times 10^3/\mu\text{L}$, or $<8\%$ of total WBC count
- **SCORING**—1 point per factor, with a score of 0–7
- **UTILITY**—the 5-year progression-free survival was 84, 77, 67, 60, 51, 42% for scores of 0, 1, 2, 3, 4, and 5–7, respectively

MANAGEMENT

LIMITED STAGE (stage IA, IIA, and IB in some institutions, 30%)—ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) $\times 2$ cycles. PET scan afterward, if complete remission, 2 more cycles; otherwise, give involved field radiation. If stage IA low bulk high neck (above hyoid) or epitrochlear nodular lymphocyte-predominant disease, involved field radiation only

ADVANCED STAGE (70%)—ABVD $\times 6$ cycles. Reassess with CT and/or PET scan. If residual disease, consider involved field irradiation. Alternative regimens

MANAGEMENT (CONT'D)

include BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) combined with involved field radiotherapy or Stanford V regimen (doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, prednisone) combined with involved field radiotherapy

REFRACTORY OR RELAPSED DISEASE—high-dose chemotherapy with CBV (cyclophosphamide, BCNU, etoposide) or BEAM (BCNU, etoposide, cytarabine, melphalan) and irradiation plus autologous stem cell transplant. Overall, 40–50% of refractory disease and 60–70% of first relapse can be cured

TREATMENT ISSUES

INDICATIONS FOR AUTOLOGOUS STEM CELL TRANSPLANT—progression during first-line chemotherapy, relapse <1 year after completion of chemotherapy, relapse with B symptoms or extranodal sites. Patients with relapse >1 year or only in previously unirradiated lymph nodes may or may not require transplant

FOLLOW-UP—every 3 months for the first 2 years, every 6 months for the next 3 years, then annually. Pay particular attention to relapse (10–30%), hypothyroidism (50%), dental caries, and second malignancies (breast, lung, esophageal, stomach, thyroid, melanoma, cervical, AML)

Non-Hodgkin's Lymphoma**DIFFERENTIAL DIAGNOSIS OF LYMPHADENOPATHY****INFECTIONS**

- **BACTERIAL**—local infections, brucellosis, leptospirosis, lymphogranuloma venereum, typhoid fever
- **ATYPICAL**—TB, syphilis, Lyme disease
- **VIRAL**—HIV, EBV, HSV, CMV, HBV, mumps, measles, rubella, dengue fever
- **FUNGAL**—histoplasmosis, coccidioidomycosis, cryptococcosis
- **PARASITIC**—toxoplasmosis

NEOPLASTIC

- **LYMPHOMA**—Hodgkin's, non-Hodgkin's
- **LEUKEMIA**
- **METASTATIC CANCER**
- **LYMPHOPROLIFERATIVE**—Castleman's disease, angioimmunoblastic lymphadenopathy, autoimmune lymphoproliferative disease

INFLAMMATORY—RA, SLE, dermatomyositis, Still's disease, Churg–Strauss syndrome

INFILTRATIVE—sarcoidosis, amyloidosis, histiocytosis, chronic granulomatous disease

DIFFERENTIAL DIAGNOSIS OF LYMPHADENOPATHY (CONT'D)

OTHERS—**medications** (phenytoin), **endocrine** (hypothyroidism, Addison's disease), serum sickness

PATHOPHYSIOLOGY**HISTOLOGIC TYPE (WHO CLASSIFICATION)**

- **INDOLENT B-CELL LYMPHOMAS**
 - **FOLLICULAR LYMPHOMA** (FL, 25%)—grade I (0–5 centroblasts/high power field), II (6–15 centroblasts/high power field), IIIA (>15 centroblasts/high power field, centrocytes present)
 - **MARGINAL ZONE LYMPHOMA** (MZL, 5%)—MALT, nodal, splenic
 - **MANTLE CELL LYMPHOMA** (MCL, 7%)—mantle zone, nodular, diffuse, blastoid variant
 - **SMALL LYMPHOCYTIC LYMPHOMA** (SLL, 5–10%)—identical to chronic lymphocytic leukemia in pathologic characteristics, but treated as low-grade B-cell lymphoma

PATHOPHYSIOLOGY (CONT'D)

- **HAIRY CELL LEUKEMIA (HCL)**
- **LYMPHOPLASMACYTIC LYMPHOMA (LPL, 2–3%)**—previously Waldenstrom's macroglobulinemia
- **PLASMA CELL MYELOMA/PLASMACYTOMA (MM)**
- **AGGRESSIVE B-CELL LYMPHOMAS**
- **FOLLICULAR LYMPHOMA (FL)**—grade IIIB (sheets of centroblasts)
- **DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL, 30–40%)**—clinical subtypes include primary mediastinal B-cell lymphoma, primary effusion lymphoma (HHV8), and intravascular B-cell lymphoma. Pathologic subtypes include T-cell-rich B cell lymphoma, anaplastic large cell lymphoma, centroblastic, and immunoblastic
- **DOUBLE-HIT DLBCL** (both c-myc and bcl2 translocations)
- **LEUKEMIC B-CELL LYMPHOMAS**
- **BURKITT'S LYMPHOMA (BL)**
- **PRECURSOR B LYMPHOBLASTIC LYMPHOMA (ALL)**
- **INDOLENT T-CELL LYMPHOMAS**
- **MYCOSIS FUNGOIDES (mf)**
- **PRIMARY CUTANEOUS ANAPLASTIC LARGE CELL (PCALC)**
- **LYMPHOPROLIFERATIVE DISEASE OF LARGE GRANULAR LYMPHOCYTES (LGL)**
- **INDOLENT NATURAL KILLER CELL LYMPHOMAS**
- **NATURAL KILLER CELL LARGE GRANULAR LYMPHOCYTE LEUKEMIA (NK-LGL)**
- **AGGRESSIVE T-CELL LYMPHOMAS**
- **PERIPHERAL T-CELL LYMPHOMA, NOT OTHERWISE SPECIFIED (PTCL-NOS)**
- **PERIPHERAL T-CELL LYMPHOMA, SPECIFIED**—angioimmunoblastic (AILD++ type), nasal T/NK-cell type, subcutaneous panniculitic, intestinal enteropathy associated, hepatosplenic, anaplastic large cell including null cell
- **LEUKEMIC T-CELL LYMPHOMAS**
- **ADULT T-CELL LYMPHOMA/LEUKEMIA (HTLV)**
- **PRECURSOR T LYMPHOBLASTIC**
- **LEUKEMIA/LYMPHOMA**

RISK FACTORS

- **FAMILY HISTORY**
- **ENVIRONMENTAL**—previous immunosuppressive therapy, radiation, allogeneic stem cell transplant, pesticides, agricultural chemicals, smoking, hair dyes, geography (e.g. risk of Burkitt's lymphoma is 50× higher in Africa than in the USA)
- **DISEASES**—infections (HIV, EBV, HHV8, HCV, HTLV, *Helicobacter pylori*), inflammatory disorders (RA, SLE, Sjogren's syndrome, mixed cryoglobulinemia, inflammatory bowel disease), inherited immune defects

PATHOPHYSIOLOGY (CONT'D)

CLASSIC TRANSLOCATIONS IN LYMPHOMA

- **MANTLE CELL LYMPHOMA**—t(11;14) in 95%, cyclin D1 (bcl1)
- **FOLLICULAR LYMPHOMA**—t(14;18) in 85%, anti-apoptotic protein (bcl2)
- **DIFFUSE LARGE CELL LYMPHOMA**—t(3;14) in 40%, zinc finger transcription factor (bcl6)
- **MALT**—t(1;14) in < 5%, bcl10
- **BURKITT'S LYMPHOMA**—t(8;14), t(2;8), or t(8;22) in 100%, c-myc

INFECTIONS AND LYMPHOMA

- **EBV**—Hodgkin's lymphoma, Burkitt lymphoma, post-transplant lymphoproliferative disorders, primary CNS lymphoma
- **HCV**—splenic marginal zone lymphoma
- **HHV8**—Castleman disease, primary effusion lymphoma
- **HIV**—primary CNS lymphoma
- **HTLV**—adult T-cell leukemia/lymphoma
- **BORRELLIA BURGDORFERI**—cutaneous marginal zone lymphoma
- **CAMPYLOBACTER JEJUNI**—small bowel marginal zone lymphoma
- **CHLAMYDIA PSITACCI**—eye marginal zone lymphoma
- **H. PYLORI**—gastric MALT

TRANSFORMATION OF INDOLENT LYMPHOMA—

10% of SLL, MZL, and LPL and 60% of FL eventually transform into aggressive DLBCL. Features suggestive of transformation include rapid local progression, progression at unusual extranodal sites (CNS, lungs, soft tissue), acute rise in LDH, hypercalcemia, and new onset B symptoms

CLINICAL FEATURES

SYMPTOMS

- **MASS EFFECT**—lymphadenopathy (occipital, posterior auricular, preauricular, mandibular, submental, cervical, supra- and infraclavicular, Waldenstrom's ring (tonsils, base of tongue, nasopharynx), epitrochlear, axillary, inguinal, popliteal), hepatosplenomegaly, mediastinal/abdominal/pelvic/testicular/CNS masses may cause local destruction, obstruction, and compression
- **HEMATOLOGIC**—anemia, thrombocytopenia, lymphocytosis
- **CONSTITUTIONAL**—B-symptoms. Other constitutional symptoms include fatigue, anorexia, pruritus
- **PARANEOPLASTIC SYNDROMES**
NOTE: lymphoma can mimic many diseases. Always have a high index of suspicion for lymphoma, particularly if B symptoms or multisystem involvement

STAGING

TUMOR BURDEN—a combination of stage, bulkiness (>10 cm in greatest diameter), B symptoms

ANN ARBOR STAGE

- **I** Single node region
- **II** Two or more node regions on same side of diaphragm
- **III** Involvement on both sides of diaphragm
- **IV** Diffuse or disseminated foci of involvement of one or more extralymphatic sites (e.g. bone marrow, extranodal sites that cannot be included in one radiation field)

DESIGNATIONS

- **E**—single extralymphatic site (i.e. involvement outside of lymph nodes, spleen, thymus, and Waldeyer's ring) or involvement by direct extension
- **S**—splenic involvement
- **A**—no B symptoms
- **B**—weight loss >10% over 6 months, fever >38°C [100.4°F], drenching night sweats

INVESTIGATIONS**BASIC**

- **LABS**—CBCD, peripheral smear, lytes, urea, Cr, AST, ALT, ALP, bilirubin, Ca, PO₄, Mg, uric acid, LDH, albumin, quantitative immunoglobulin, serum protein electrophoresis, HBV, HCV, and HIV serology
- **IMAGING**—CXR, CT chest/abdomen/pelvis, PET scan
- **LYMPH NODE BIOPSY**
- **BONE MARROW BIOPSY WITH SURFACE MARKERS**

SPECIAL

- **MRI SPINE**—if suspect spinal cord compression
- **MUGA SCAN**—evaluate cardiac function prior to anthracycline therapy for patients with significant cardiac risk factors

DIAGNOSTIC AND PROGNOSTIC ISSUES**IMMUNOPHENOTYPE OF SELECTED LYMPHOMAS**

| | CLL | MCL | FL | MZL |
|------|-----|-----|----|-----|
| CD20 | + | + | + | + |
| CD5 | + | + | — | — |
| CD23 | + | — | — | — |
| CD43 | + | + | — | + |
| CD10 | — | — | + | — |

INTERNATIONAL PROGNOSTIC INDEX (IPI)

- **FACTORS**—age >60, serum LDH >normal, ECOG performance status ≥2, Ann Arbor clinical stage III or IV, extranodal disease sites ≥2 (defined as involvement of organs other than lymph nodes, spleen, thymus, and Waldeyer's ring)

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

- **SCORING**—1 point per factor, with a score of 0–5
- **UTILITY**—5-year overall survival approximately 73%, 51%, 43%, and 26% for IPI of 0–1, 2, 3, and 4–5. With the new revised IPI (post-rituximab era), 5-year overall survival 94%, 79%, and 55% for IPI of 0, 1–2, and 3–5, respectively

FOLLICULAR LYMPHOMA INTERNATIONAL PROGNOSTIC INDEX (FLIPI)

- **FACTORS**—age >60, serum LDH >normal, hemoglobin <120 g/L [<12 g/dL], Ann Arbor clinical stage III or IV, involved nodal sites >4
- **SCORING**—1 point per factor, with a score of 0–5
- **UTILITY**—for follicular lymphoma patients specifically; 5-year survival approximately 91%, 78%, and 52% for FLIPI of 0–1, 2 and 3–5, respectively

MANAGEMENT**INDOLENT LYMPHOMAS**

- **LIMITED STAGE** (IA or IIA, 10%)—radiation (10-year survival 50%)
- **ADVANCED STAGE** (IB, IIB, III, IV, or any bulky disease, 90%)—if asymptomatic (40%), watchful waiting. If symptomatic or threatening disease (60%), CVPR ×8 cycles (cyclophosphamide, vincristine, prednisone, and rituximab), followed by maintenance rituximab for 2 years if PR/CR (15% relapse with maintenance rituximab compared to 35% for CVPR alone or 70% for CVP alone). Second-line agents include fludarabine, cyclophosphamide, rituximab, I¹³¹-tositumomab, and Y⁹⁰-ibritumomab. Stem cell transplant in fit individuals

AGGRESSIVE LYMPHOMAS

- **LIMITED STAGE** (IA or IIA, 30%)—CHOPR (cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab) ×3 cycles. PET scan afterwards, if complete remission, one more cycle; otherwise, give involved field radiation
- **ADVANCED STAGE** (IB, IIB, III, IV, or any bulky disease, 70%)—CHOPR ×6. PET scan afterwards, if local residual disease, give involved field radiation; if diffuse residual disease, consider **salvage therapy** (see below). For patients with bone marrow/peripheral blood involvement, **intrathecal chemotherapy** may be considered as 5–20% chance of leptomeningeal disease otherwise
- **SALVAGE—GDPR** (gemcitabine, dexamethasone, cisplatin, rituximab) or **RICE** (rituximab, ifosfamide, carboplatin, etoposide), followed by **autologous stem cell transplant**

HIGHLY AGGRESSIVE LYMPHOMAS

- **BURKITT'S LYMPHOMA**—expedited staging (within 1–2 days). For **low-risk disease** (stage I or II, non-bulky <5 cm, no bone marrow/blood/CNS

MANAGEMENT (CONT'D)

- disease and normal LDH), give CODOX-MR (cyclophosphamide, doxorubicin, vincristine, methotrexate, rituximab) $\times 1$ then restage. If CR/PR, give IVAC-R (ifosfamide, etoposide, cytarabine) $\times 1$ then CODOX-MR $\times 1$; otherwise, give IVAC-R $\times 1$ then proceed to stem cell transplant. For **high-risk disease**, give CODOX-MR $\times 1$, IVAC-R $\times 1$ then restage. If CR/PR and no marrow infiltration at diagnosis, then autologous stem cell transplant; otherwise, individualized higher intensity treatment. Allogeneic transplant may be considered (balance between time to find allogeneic donor and use of contaminated stem cells). A total of 8 doses of intrathecal chemotherapy should be given during treatment course. All patients should receive tumor lysis syndrome prophylaxis (hydration, allopurinol). Cure rate $\sim 60\%$
- **ACUTE LYMPHOBLASTIC LYMPHOMA**—expedited staging (within 1–2 days). For most patients, allogeneic/autologous stem cell transplant plus intrathecal chemotherapy (allogeneic if leukemic, otherwise, autologous). Another option is the hyper-CVAD/methotrexate/cytarabine regimen. All patients should receive tumor lysis syndrome prophylaxis (hydration, allopurinol)

TREATMENT ISSUES

INTERNATIONAL WORKSHOP CRITERIA FOR TREATMENT RESPONSE FOR HODGKIN'S AND NON-HODGKIN'S LYMPHOMA

COMPLETE REMISSION (CR)—disappearance of all evidence of disease

- **Nodal masses:** if FDG-avid or PET positive prior to therapy, mass of any size permitted if PET negative. If variably FDG-avid or PET negative, regression to normal size on CT required
- **Liver and spleen:** not palpable, nodules disappeared
- **Bone marrow:** infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative

PARTIAL REMISSION (PR)—regression of measurable disease and no new sites

- **Nodal masses:** $\geq 50\%$ decrease in sum of the product of the diameter (SPD) of up to 6 largest dominant masses; no increase in size of other nodes. If FDG-avid or PET positive prior to therapy, one or more PET positive at previously involved site; or if variably FDG-avid or PET negative, regression on CT $\geq 50\%$ decrease in SPD of nodules (for single nodule in greatest transverse diameter)
- **Liver and spleen:** no increase in size

TREATMENT ISSUES (CONT'D)

- **Bone marrow:** irrelevant if positive prior to therapy; cell type should be specified
- STABLE DISEASE (SD)**—failure to attain CR/PR or PD
- **Nodal masses:** if FDG-avid or PET positive prior to therapy, PET positive at prior sites of disease and no new sites on CT or PET. If variably FDG-avid or PET negative, no change in size of previous lesions on CT
- RELAPSED DISEASE (RD) OR PROGRESSIVE DISEASE (PD)**—any new lesion or increase by $\geq 50\%$ of previously involved sites from nadir
- **Nodal masses:** appearance of a new lesion(s) >1.5 cm in any axis, $\geq 50\%$ increase in SPD of more than one node, or $\geq 50\%$ increase in longest diameter of a previously identified node >1 cm in short axis. Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy
 - **Liver and spleen:** $>50\%$ increase from nadir in the SPD of any previous lesions
 - **Bone marrow:** new or recurrent involvement
- JCO 2007 25:5**

SPECIFIC ENTITIES

EYE LYMPHOMA

- **PATHOPHYSIOLOGY**—periocular involvement (mostly MALT type) or intraocular involvement (usually DLBCL with more indolent course)
- **TREATMENTS**—for periocular MALT, involved field radiation if localized disease or CVP if widespread disease. For intraocular disease, steroids, and involved field radiation. High-dose methotrexate may be useful

PRIMARY CNS LYMPHOMA

- **PATHOPHYSIOLOGY**—usually multifocal but confined to CNS. May have leptomeningeal or intraocular involvement. Frequently aggressive B-cell lymphoma
- **CLINICAL FEATURES**—focal neurological deficit, personality change, mild dementia, persistent headache
- **DIAGNOSIS**—CT or MRI head, lumbar puncture, slit lamp examination. If CNS lymphoma in the differential, try to avoid giving steroids before biopsy
- **TREATMENTS**—high-dose corticosteroid with high-dose methotrexate is preferred. Whole brain radiation represents an alternative. Prognosis is 60% 2-year survival and 30% 5-year survival

LEPTOMENINGEAL MENINGITIS

- **RISK FACTORS**—aggressive lymphomas (lymphoblastic lymphoma, DLBCL, Burkitt's lymphoma, MCL), extranodal sites involvement (bone marrow, testicular, paranasal, retroperitoneal lymph nodes), any of the five IPI prognostic factors

SPECIFIC ENTITIES (CONT'D)

- **CLINICAL FEATURES**—jaw pain and numbness, radicular pain, back pain, neck pain/rigidity, confusion, cranial nerve deficits (especially II, III, V, VI, VIII), focal weakness, sensory changes, headaches
- **DIAGNOSIS**—lumbar puncture with positive cytology (sens 60% with single attempt, 3 attempts for increased yield), gadolinium-enhanced MRI showing enhancement and enlargement of one or more cranial nerves due to tumor infiltration
- **TREATMENTS**—high-dose steroid (dexamethasone 12–20 mg PO/IV daily), radiation to the site of disease, intrathecal methotrexate, or cytarabine. Important to treat underlying systemic disease. Highly selected patients may benefit from high-dose chemotherapy with stem cell transplantation with better outcomes. Median survival after CNS recurrence is 3 months

LOCALIZED PARANASAL SINUS LYMPHOMA

- **PATHOPHYSIOLOGY**—usually DLBCL type. May involve CNS if invade through the base of skull
- **CLINICAL FEATURES**—local pain, rhinorrhea, nasal or upper airway obstruction, facial swelling, epistaxis, diplopia, visual loss
- **TREATMENTS**—CHOPR×3 + involved field radiation + intrathecal chemotherapy×6

MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT)

- **PATHOPHYSIOLOGY**—extranodal marginal zone B-cell lymphomas that present with localized disease involving the GI tract, salivary glands, thyroid, orbit, conjunctiva, breast, and lung. Note that diffuse large cell lymphoma and mantle cell lymphoma also commonly involve GI mucosa
- **ASSOCIATIONS**—*H. pylori*-associated chronic gastritis, celiac disease, crohn's disease, gastrointestinal nodular lymphoid hyperplasia
- **DIAGNOSIS**—for gastric MALT, need to determine presence of *H. pylori* by biopsy (gastroscopy) ± urea breath test
- **TREATMENTS**—for *H. pylori*-positive gastric MALT, triple therapy may be adequate. Need to confirm eradication of *H. pylori*. Follow closely with gastroscopy. If MALT persists for over 8–12 months, should consider single-agent chemotherapy (cyclophosphamide, chlorambucil) or involved-field radiation. Partial gastrectomy may be needed for hemorrhage or perforation

ACUTE LYMPHOBLASTIC LYMPHOMA

- **PATHOPHYSIOLOGY**—continuum of presentation with acute lymphoblastic leukemia. Considered lymphoma if < 5% blasts in bone marrow; otherwise, considered leukemia
- **CLINICAL FEATURES**—usually mediastinal mass in young males

SPECIFIC ENTITIES (CONT'D)**BURKITT'S LYMPHOMA**

- **PATHOPHYSIOLOGY**—t(8;14) leading to c-myc overexpression
- **CLINICAL FEATURES**—usually advanced stage (80–90%). Abdominal mass, CNS, breast/ovarian involvement, and nodal sites but mediastinum usually spared

TESTICULAR LYMPHOMA

- **PATHOPHYSIOLOGY**—60% primary testicular lymphoma, 40% spread from other sites. Frequently DLBCL or immunoblastic subtype
- **CLINICAL FEATURES**—painless testicular mass in older man. High risk for recurrence, particularly CNS relapse
- **DIAGNOSIS**—scrotal U/S
- **TREATMENTS**—unilateral orchiectomy + CHOPR + involved field radiation to scrotum + intrathecal chemotherapy if stage III/IV disease

POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS (PTLD)

- **PATHOPHYSIOLOGY**—mostly of host origin and usually EBV positive (LMP-1 oncogene). EBV-negative PTLD present later and are more aggressive than EBV-positive PTLD. Mostly B-cell non-Hodgkin's lymphoma and very rarely T-cell or NK cell lymphomas
- **RISK FACTORS**—high degree of immunosuppression, pre-transplant EBV negativity. Risk highest in the first year, then reduces by 80%
- **CLINICAL FEATURES**—clinical spectrum includes reactive plasmacytic hyperplasia (55%, infectious mononucleosis like illness with no malignant transformation), polymorphic B-cell hyperplasia (30%, polyclonal cytogenetic abnormalities, immunoglobulin gene rearrangements, and disruption of underlying tissue architecture), and B- or T-cell lymphomas (15%, monoclonal malignancy)
- **TREATMENTS**—reduction in immunosuppression (may be sufficient for hyperplasia without monoclonal component), rituximab, chemotherapy (CHOP), antiviral agents, IVIG, surgical resection, radiation, interferon α . Overall survival 25–35%. Prognostic factors include advanced age, performance status >1, involved site >1

MYCOSIS FUNGOIDES

- **PATHOPHYSIOLOGY**—indolent cutaneous T-cell lymphoma. Stages include premycotic, plaque, and tumor stage. Sezary syndrome is a variant of mycosis fungoides with a triad of erythroderma, lymphadenopathy, and leukemia
- **CLINICAL FEATURES**—localized patches or plaques evolving into nodules and diffuse exfoliative erythroderma associated with abnormal circulating cells. Poor prognostic factors include extensive

SPECIFIC ENTITIES (CONT'D)

cutaneous disease (erythroderma), nodal spread, and extracutaneous involvement (liver, spleen, lung, GI tract)

- **TREATMENTS**—topical corticosteroids, topical nitrogen mustard, psoralen with UVA/UVB, bexarotene, radiation. Systemic treatments include CHOP, pentostatin, cladribine, fludarabine, IL-2, IFN α , alemtuzumab, liposomal doxorubicin

SYSTEMIC ANAPLASTIC LARGE CELL LYMPHOMA

- **PATHOPHYSIOLOGY**—may be T-cell, B-cell, or null cell type. Uniform expression of CD4, CD30, clusterin and epithelial membrane antigen (EMA). Anaplastic lymphoma kinase (ALK) overexpression associated with t(2;5) is a key prognostic marker (ALK+ 65–90% 5-year survival vs. ALK– 30–40% 5 year survival)
- **CLINICAL FEATURES**—ALK+ cases usually present at younger age with early disease. ALK– cases usually

SPECIFIC ENTITIES (CONT'D)

present at older age with advanced stage, elevated LDH, B symptoms, and extranodal sites

- **TREATMENTS**—CHOP-based regimens, alternating with GDP for 6 cycles for advanced stage disease. Consider allogeneic stem cell transplant

CASTLEMAN'S DISEASE

- **PATHOPHYSIOLOGY**—lymphoid proliferation associated with POEMS syndrome, lymphomas (Hodgkin's, non-Hodgkin's), and Kaposi's sarcoma. HIV and HHV8 common in multicentric subtype
- **CLINICAL FEATURES**—unicentric (isolated lymphadenopathy, benign, HHV8 negative). Multicentric (fever, night sweats, fatigue, lymphadenopathy, pulmonary infiltrates, frequently HHV8 and HIV positive)
- **TREATMENTS**—unicentric (resection with high chance of cure, radiation, rituximab). Multicentric (steroid, antivirals, anti-IL-6, CHOP, rituximab. Survival 8–14 months)

Multiple Myeloma

NEJM 1997 336:23
NEJM 2004 351:18

TYPES OF PLASMA CELL DYSCRASIAS

MULTIPLE MYELOMA (75%)—malignant clone extends from pre-B-cell to plasma cell stage of differentiation. May produce IgG (60%), IgA (20%), or light chains (15%)

WALDENSTROM'S MACROGLOBULEMIA (20%)—proliferation of plasmacytoid lymphocytes (cell type that occurs earlier than plasma cell). Produces IgM. Now classified as lymphoplasmacytic lymphoma

HEAVY-CHAIN DEPOSITION DISEASE—IgA, IgG, or IgM heavy chain

LIGHT-CHAIN DEPOSITION DISEASE— κ or λ light chain

AL (PRIMARY) AMYLOIDOSIS— λ or κ light chain

PATHOPHYSIOLOGY

EPIDEMIOLOGY

- **INCIDENCE**—1%
- **MORTALITY**—1%

RISK FACTORS

- **PERSONAL**—old age, black race
- **DISEASES**—chronic polyclonal hypergammaglobulinemia
- **TREATMENT**—radiation

CLINICAL FEATURES

SYMPTOMS

- **PANCYTOPENIA**—weakness, fatigue, infections, gingival bleed, ecchymosis, epistaxis, menorrhagia

CLINICAL FEATURES (CONT'D)

- **INCREASED POLYCLONAL PROTEIN**—infections due to \downarrow normal Ig, hyperviscosity syndrome
- **LYTIC BONE LESIONS**—pain, fractures
- **HYPERCALCEMIA**—weakness, nausea, abdominal pain, polyuria, altered mental status
- **NEUROLOGIC**—peripheral neuropathy from amyloidosis, plasma cell infiltration of the meninges, cord compression, or radiculopathy from vertebral osteolytic lesions \pm plasmacytoma
- **RENAL FAILURE**
 - **PRE-RENAL**—N&V, renal vein thrombosis, Ca-induced vasospasm
 - **RENAL**—myeloma kidney (tubulointerstitial damage from increased light chain absorption at proximal tubule), plasma cell infiltration, Bence Jones/cast nephropathy, amyloidosis (λ), light-chain deposition disease (κ), hypercalcemia (nephrogenic DI), cryoglobulinemia, pyelonephritis, sepsis
 - **POST-RENAL**—renal stones (uric acid), neurogenic bladder
- **CONSTITUTIONAL**—anorexia, fatigue, weight loss

INVESTIGATIONS

BASIC

- **LABS**—CBCD, peripheral smear, lytes, urea, Cr, Ca, β_2 microglobulin, serum viscosity, quantitative immunoglobulin, albumin, serum protein electrophoresis (reciprocal depression), urinary

INVESTIGATIONS (CONT'D)

protein electrophoresis, 24 h urinary collection for Bence Jones protein

- **IMAGING**—skeletal survey
- **BONE MARROW BIOPSY**
- **NOTE:** light chain myeloma (20%) may have normal serum protein electrophoresis. Urinary Bence Jones protein (urine protein electrophoresis) is required to detect paraproteinemia; non-secretory myeloma (3%) requires bone marrow biopsy for diagnosis

Related Topics

Amyloidosis (p. 420)

Renal Failure (p. 68)

DIAGNOSTIC AND PROGNOSTIC ISSUES

INTERNATIONAL MYELOMA WORKING GROUP CRITERIA

- **MULTIPLE MYELOMA**
 - **BONE MARROW PLASMA CELLS/PLASMACYTOMA**—no percent specified, but usually >10%
 - **M-PROTEIN**—in serum and/or urine, no concentration specified, but >30 g/L [>3 g/dL] in serum if overt myeloma
 - **TISSUE IMPAIRMENT**—★**CRAB**★ increased calcium (>2.75 mmol/L [>11 mg/dL]), renal insufficiency (Cr >173 μmol/L [>1.9 mg/dL]), anemia (Hb <100 g/L [<10 g/dL] or drop by 20 g/L [2 g/dL]), bone lesions (lytic lesions, fractures). Other features include hyperviscosity, amyloidosis, or recurrent infections (>2 episodes in 12 months)
- **SMOLDERING MULTIPLE MYELOMA (SMM)**
 - **BONE MARROW PLASMA CELLS**—>10%
 - **M-PROTEIN**—>30 g/L [>3 g/dL] (but not necessary if bone marrow plasma cells>10%)
 - **TISSUE IMPAIRMENT**—no symptoms
- **MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS)**
 - **BONE MARROW PLASMA CELLS**—<10% (bone marrow biopsy is not required for suspected MGUS if M-protein ≤15 g/L [≤1.5 g/dL], IgG subtype, and patient asymptomatic)
 - **M-PROTEIN**—< 30 g/L [<3g/dL]
 - **TISSUE IMPAIRMENT**—no symptoms
 - **COURSE**—occurs in 2% of population over age 50 and 3% over age 70. Rate of transformation to malignant plasma cell disorder (multiple myeloma, Waldenstrom's macroglobulinemia, primary amyloidosis, B-cell lymphoma, or chronic lymphocytic leukemia) is about 1% per year

NEJM 2006 355:26

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

DIAGNOSTIC CLUES

- **SYMPTOMS**—the presence of tissue impairment suggests either multiple myeloma (usually high M-protein) or amyloidosis (usually low M-protein). AL amyloidosis is characterized by insoluble, toxic amyloid precursor (light chains) aggregates that deposit in tissues in antiparallel β-pleated sheet configuration. The absence of symptoms suggests MGUS or SMM
- **QUANTITATIVE IG**—typically decreased serum levels of normal polyclonal immunoglobulins in multiple myeloma. However, this may also occur in MGUS
- **BENCE JONES PROTEINURIA**—the presence of monoclonal light chains (especially >1 g/day) in the urine suggests multiple myeloma. However, small amounts (<50 mg/day) may also occur in MGUS
- **SERUM M PROTEIN LEVEL**—the higher the level, the higher the likelihood of multiple myeloma. Some define 35 g/L [3.5 g/dL] for IgG and 20 g/L [2 g/dL] for IgA as cutoff, others define 30 g/L [3 g/dL] regardless of Ig subtype as cutoff

DURIE-SALMON STAGING FOR MULTIPLE MYELOMA

- **STAGE I** (low tumor burden, $<0.6 \times 10^{12}/m^2$)—all of Hb >100 g/L [>10 g/dL], $Ca^{2+} \leq 2.6$ mmol/L [≤10.4 mg/dL], bones normal or solitary bone plasmacytoma only, IgG <50 g/L [<5 g/dL], IgA <30 g/L [<3 g/dL], and urinary λ or κ chains <4 g/day. Median survival ~60 months
- **STAGE II** (intermediate burden, $0.6-1.2 \times 10^{12}/m^2$)—between stages I and III. Median survival ~30 months
- **STAGE III** (high tumor burden, $>1.2 \times 10^{12}/m^2$)—any of Hb <85 g/L [<8.5 g/dL], $Ca^{2+} >2.6$ mmol/L [>10.4 mg/dL], >3 lytic lesions, plus one of IgG >70 g/L [>7 g/dL], IgA >50 g/L [>5 g/dL], or urinary λ or κ chains >12 g/day. Median survival ~15 months
- **SUBSTAGES**—A (Cr <175 μmol/L [<1.9 mg/dL]) and B (renal failure with Cr >175 μmol/L [>1.9 mg/dL])

PROGNOSTIC FACTORS FOR MULTIPLE MYELOMA—β2 microglobulin, albumin, platelet, creatinine, and age. The international staging system for multiple myeloma is particularly useful

- **STAGE I**—β2 microglobulin <3.5 mg/L, albumin ≥35 g/L [≥3.5 g/dL]. Median survival 62 months
- **STAGE II**—neither stage I nor III. Median survival 44 months
- **STAGE III**—β2 microglobulin ≥5.5 mg/L. Median survival 29 months

JCO 2005 23:15

MANAGEMENT

MULTIPLE MYELOMA

- **AGE <65 AND OTHERWISE HEALTHY** (curative)—**induction chemotherapy** with thalidomide plus dexamethasone (first choice), lenalidomide plus dexamethasone, pulse dexamethasone, or VAD (vincristine, doxorubicin, dexamethasone) \times 3–4 months. If good response, then proceed to **high-dose melphalan followed by autologous stem cell transplant**. This regimen prolongs survival by 12 months, but is not curative. Consider **tandem transplantation** if less than a good partial response (i.e. \leq 90% reduction of monoclonal protein)
- **AGE >65 OR COMORBIDITIES** (palliative)—**MP** (melphalan + prednisone) \pm thalidomide. Addition of interferon to MP provides small benefit. If bony disease, add **bisphosphonate** (alendronate, zoledronate). Second-line options include **thalidomide** (response \sim 30%) + **dexamethasone**, **lenalidomide** + **dexamethasone**, **bortezomib** (response \sim 30%), **dexamethasone** alone, and infusional VAD
- **SUPPORTIVE MEASURES**—**hydration** ($>$ 3 l/day), **hypercalcemia** (hydration, *prednisone* 25 mg PO QID, *pamidronate*), **renal insufficiency** (treat underlying cause), **infections** (antibiotics, consider IVIG as last resort if recurrent infections despite prophylactic antibiotics), **skeletal lesions** (*pamidronate* 90 mg IV over 2 h q3–4weeks, radiation, vertebroplasty), **anemia** Hb $<$ 90 g/L [$<$ 9 g/dL] (transfusions, usually respond to an erythropoiesis stimulating agent, although one should exercise great caution given the increased risk of thromboembolism and death), **hyperviscosity syndrome** (Ostwald viscosimeter $>$ 5, plasmapheresis), **anticoagulation** (if on thalidomide/lenalidomide and chemotherapy)

MANAGEMENT (CONT'D)

SMM—no treatment. Follow clinically
MGUS—no treatment. Follow clinically

TREATMENT ISSUES

INDICATIONS FOR TREATING MULTIPLE MYELOMA— \rightarrow stage I, increasing level of M-protein in serum or urine, significant hypercalcemia, anemia, renal insufficiency, lytic bone lesions, extramedullary plasmacytoma

SPECIFIC ENTITIES

SOLITARY PLASMACYTOMA OF BONE—single osteolytic bone lesion with limited amount of monoclonal protein in the serum or urine and absence of tissue impairment. Radiation is usually treatment of choice and may result in a cure. 80% chance of developing multiple myeloma

AMYLOIDOSIS—See p. 420 for more details. Workup include abdominal fat biopsy, abd U/S, and echocardiogram

POEMS SYNDROME—osteosclerotic myeloma with Polyneuropathy, Organomegaly, Endocrine (diabetes, hypothyroidism, parathyroid hypogonadism, HPA), Monoclonal protein, Skin changes (hyperpigmentation, hypertrichosis, acrocyanosis, plethora, hemangioma/telangiectasia). Polyneuropathy and monoclonal plasma cell disorder most important

HYPERVISCOSITY SYNDROME—IgG $>$ 70 g/L [$>$ 7 g/dL] or IgA $>$ 50 g/L [$>$ 5 g/dL]. Symptoms include fatigue, changes in mental status, focal or non-focal neurologic changes, visual changes along with retinopathy, angina pectoris, bleeding disorder, cryoglobulin, Raynaud's phenomenon, or purpuric eruptions on exposure to the cold

Febrile Neutropenia

See FEBRILE NEUTROPENIA (p. 236)

Hematopoietic Stem Cell Transplant

CMAJ 2004 170:10
 NEJM 2006 354:17

TERMINOLOGIES

ALLOGENEIC TRANSPLANTATION (40%)—stem cells from HLA-matched sibling donor (25%) or unrelated donor (75%). The main advantage is graft vs. leukemia effect (GVL), while the main disadvantage is graft vs. host effect (GVHD)

TERMINOLOGIES (CONT'D)

AUTOLOGOUS TRANSPLANTATION (60%)—stem cells from self. The main advantage is lesser toxicity compared to allogeneic transplant, while the main disadvantage is possible contamination of the graft with malignant cells

TERMINOLOGIES (CONT'D)

DONOR SOURCE—peripheral blood (10–20 L of blood, mobilization with GCSF, venipuncture, leukapheresis (up to 3 times for autologous stem cell transplant), faster engraftment, and improved overall survival (for autologous stem cell transplant and matched sibling allogeneic transplant), **bone marrow**, **umbilical cord blood** (unlimited supply of donors, although limited amount of cord blood. More tolerant for mismatches in allogeneic transplant)

COMMON INDICATIONS

DECIDING BETWEEN ALLOGENEIC AND AUTOLOGOUS STEM CELL SOURCE—dependent on age, underlying disease, donor availability, institutional preference. In general, allogeneic transplant is more suitable for younger, healthier adults as it is more toxic but potentially more effective than autologous transplant

ALLOGENEIC—acute leukemia (50–70% cure if first remission, 10–30% cure if relapse), myelodysplastic syndrome (40–50% cure rate), chronic myeloid leukemia (50–70% cure if chronic phase, 10–30% cure if blast phase), chronic lymphocytic leukemia, indolent lymphoma, severe immunodeficiency syndromes, hemoglobinopathies

AUTOLOGOUS—progressive Hodgkin's lymphoma (60–70% cure if relapse, 40–50% cure if refractory disease), multiple myeloma, progressive large cell lymphoma, relapsed germ cell cancer

ALLOGENEIC TRANSPLANTATION

HUMAN LEUKOCYTE ANTIGEN MOLECULES—responsible for displaying endogenous and exogenous peptides to T cells. Mismatch between host and donor HLA type could result in graft vs. host disease, graft failure, or death. Note that transplant is not affected by differences in ABO blood groups

- **HLA CLASS I**—HLA-A, HLA-B, HLA-C
- **HLA CLASS II**—HLA-DR, HLA-DQ, HLA-DP

MATCHING PROCESS—need to ensure good match of the following loci: HLA-A, HLA-B, HLA-C, DRB1, and DQB1. The chance of finding a sibling match is $1-0.75^n$, where n =number of siblings. The chance of finding a matched unrelated donor is >60%, higher for Caucasians and lower for other races. Search for a match typically takes 3–4 months

CONDITIONING—goal is to eradicate malignancy and suppress recipient's immune system to minimize rejection of donor's stem cells. Myeloablative regimens include cyclophosphamide plus total body irradiation (TBI) or high-dose busulfan. Reduced intensity regimens include fludarabine plus busulfan. Reduced intensity (also known as non-myeloablative or "mini" transplant) regimens use a milder conditioning regimen more tolerable for older patients (e.g.

ALLOGENEIC TRANSPLANTATION (CONT'D)

fludarabine plus cyclophosphamide, melphalan). Monitor toxicities closely during this time

- **HEMATOLOGIC**—pancytopenia, febrile neutropenia
- **EARLY NON-HEMATOLOGIC**—alopecia, N&V, oropharyngeal mucositis, diarrhea, sinusoidal obstruction syndrome (previously known as hepatic veno-occlusive disease with tender hepatomegaly, jaundice and ascites), seizures, parotitis, pericarditis, cardiomyopathy, interstitial pneumonitis, hemorrhagic cystitis, rash
- **LATE NON-HEMATOLOGIC**—hypothyroidism, sterility or premature menopause, growth impairment, dry eyes or mouth, cataracts, osteopenia, or osteoporosis
- **FERTILITY**—infertility is almost certain in both men and women after TBI regimens, but not definite with non-TBI regimens
- **SECOND MALIGNANCIES**—increased incidence of solid tumors (bone, oropharynx, connective tissue, CNS, thyroid, melanoma), myelodysplastic syndrome, acute myelogenous leukemia, and lymphoproliferative disorders. Highest risks in patients with TBI

TRANSPLANTATION—infusion of stem cells over 30 min to 2 h

ENGRAFTMENT—typically happens between days +10 and +20. Defined as ANC $>0.5 \times 10^3/\mu\text{L}$, with platelet and RBC engraftment following. GCSF may be used in non-leukemic patients to accelerate engraftment by up to 1 week. Patient is supported with blood products and antimicrobial prophylaxis (e.g. ciprofloxacin for Gram negatives, trimethoprim-sulfamethoxazole for PCP, acyclovir for HSV, fluconazole for fungal agents) until engraftment occurs. Failure to engraft (primary graft failure) and irreversible decline of blood counts (secondary graft failure) are serious complications (<5%). For non-myeloablative transplant, perform chimerism analysis and consider either donor leukocyte infusion (DLI) or reducing immunosuppression to improve disease control

IMMUNORECONSTITUTION—restoration of T-cell and B-cell immunity takes up to 12 months. Immunosuppressive treatment can usually be stopped within 1–3 years post-allogeneic transplant. Graft vs. host disease (GVHD) is a donor T-cell-mediated process. Overall transplant-related mortality is approximately 20–25%

GRAFT VS. HOST DISEASE

- **ACUTE GVHD** (<100 days)—occurs in 40% of matched sibling and 80% of unrelated donor transplant. Symptoms include rash, hepatic dysfunction, diarrhea, vomiting. Mortality up to 80% in grade III and IV acute GVHD. Prophylaxis consisting of methotrexate and cyclosporine is usually used for anyone other than identical twins. Treatments include corticosteroids, cyclosporine, mycophenolate mofetil, tacrolimus, and antithymocyte globulin

ALLOGENEIC TRANSPLANTATION (CONT'D)

- **CHRONIC GVHD** (>100 days)—an autoimmune syndrome occurs in up to 50% of matched sibling and >50% of unrelated donor transplant. Symptoms include oral and ocular changes (sicca), alopecia, cholestatic hepatic dysfunction, polyserositis, cutaneous scleroderma, and bronchiolitis obliterans. Treatments include corticosteroids and cyclosporine or tacrolimus for at least 6 months

INFECTIONS

- **PRE-GRAFTMENT** (<30 days)—HSV, Gram-negative bacteria, Gram-positive *Streptococcus*, fungal, central line infections (*S. epidermis*)
- **EARLY INFECTIONS** (30–100 days)—CMV, some fungal, PCP, central line infections (*S. epidermis*)
- **LATE INFECTIONS** (>100 days)—VZV, encapsulated bacteria, PCP, *Aspergillus*

AUTOLOGOUS TRANSPLANTATION

MATCHING PROCESS—not applicable

CONDITIONING—similar to allogeneic transplant. Regimens include CBV (cyclophosphamide, BCNU, etoposide), cyclophosphamide plus total body

AUTOLOGOUS TRANSPLANTATION (CONT'D)

irradiation, and BEAM (BCNU, etoposide, cytosine arabinoside, melphalan)

TRANSPLANTATION—similar to allogeneic transplant, except stem cells obtained from patient pre-transplant and cryopreserved

ENGRAFTMENT—similar to allogeneic transplant
IMMUNORECONSTITUTION—more rapid immune recovery and no GVHD. Overall transplant-related mortality is approximately 2%

LATE EFFECTS—MDS and AML in at least 10% of patients 5–10 years after autologous transplant

Related Topics

Acute Leukemia (p. 166)
 Chemotherapy-Induced Diarrhea (p. 231)
 Non-Hodgkin's Lymphoma (p. 173)
 Febrile Neutropenia (p. 236)
 Fungal Infections (p. 265)
 Multiple Myeloma (p. 178)
 Oral Mucositis (p. 230)
 Sepsis (p. 99)
 Tumor Lysis Syndrome (p. 228)

Notes

Notes