# 6
# HEMATOLOGY

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## Polycythemia

### DIFFERENTIAL DIAGNOSIS

**SPURIOUS**—stress (Gaisböck's syndrome), decreased 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. 102)
Myeloproliferative Disorders (p. 184)

### CLINICAL FEATURES

**HISTORY**—hyperviscosity (headache, blurred vision, epistaxis), dyspnea, epigastric pain, early satiety, 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, leukocyte alkaline phosphatase (LAP), vitamin B12, RBC mass (total blood volume × 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. JAK2 mutation >95% sensitive for primary PRV
- **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 $PaO_2$, EPO not elevated)
- **MAJOR**—splenomegaly, JAKV617F
- **MINOR**—WBC $>12 \times 10^3/\mu L$, platelet $>400 \times 10^3/\mu L$
- **DIAGNOSIS**—need absolute criteria plus one major or two minor criteria for the diagnosis of polycythemia rubra vera. See myeloproliferative disorders (p. 184) for more details

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## MANAGEMENT

**TREAT UNDERLYING CAUSE**—**relative** (hydration), **CO hemoglobinemia** (smoking cessation. See p. 480), **sleep apnea** (CPAP. See p. 20), **polycythemia vera** (cytoreduction with hydroxyurea

## MANAGEMENT (CONT'D)

is preferable to phlebotomy target to keep hematocrit <0.45 in ♂ and <0.42 in ♀, *ASA* 81 mg PO daily prevents thrombosis—but watch out for bleeding)

# Microcytic Anemia NEJM 2005 352:10

## 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**—↓ iron → ↑ TIBC → ↓ Hb → ↓ MCV → hypochromia

**ANEMIA OF CHRONIC DISEASE**—chronic inflammatory states such as malignancy, infection and rheumatologic diseases → ↑ INF$\gamma$, TNF$\alpha$, IL-1, IL-6, IL-10 → ↑ hepatic expression of hepcidin which inhibits duodenal absorption of iron, ↑ uptake and storage of iron into monocytes and macrophages, ↓ production of EPO → ↓ availability of iron for erythrocytes → 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 cheilitis, 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 (transferrin), % 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. Depleted iron stores is associated with increased sTfR levels
- **BONE MARROW ASPIRATE AND BIOPSY WITH IRON STAIN**

## DIAGNOSTIC ISSUES

**IRON INDICES**

| | Ferritin | Iron | TIBC | % sat |
|---|---|---|---|---|
| Iron deficiency | ↓ | ↓ | ↑ | ↓ |
| Anemia of chronic disease | ↑/N | ↓ | N/↓ | N/↓ |
| Thalassemia | ↑/N | ↑ | ↓ | ↑ |
| Sideroblastic | N/↑ | N/↓ | N/↓ | N/↓ |

**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

### DIAGNOSTIC ISSUES (CONT'D)

- **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. Ferritin may be elevated as acute phase reactant

- **<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** 1–2 U PRBC IV over 2 h for symptom control

**TREAT UNDERLYING CAUSE**—**iron deficiency** (*iron gluconate* 300 mg PO BID, *iron sulfate* 325 mg PO BID, *sodium ferric gluconate* complex in sucrose 125 mg IV, iron sucrose 200 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 IgG antibody, cold IgM 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, antibiotics, antiepileptics), family history (sickle cell)

**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

**SPECIAL**

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

### DIAGNOSTIC ISSUES

**MCHC**—↑ MCHC suggests spherocytosis

**MCV**—a rise in MCV suggests reticulocytosis; ↑↑↑ MCV indicates the presence of cold agglutinins

**DIAGNOSTIC ISSUES (CONT'D)**

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 nonimmune 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 (after ensuring iron stores replete)

**MANAGEMENT (CONT'D)**

**SPECIFIC ENTITIES**

**AUTOIMMUNE HEMOLYTIC ANEMIA: WARM ANTIBODY—IgG**

- **CAUSES**—**neoplasia** (CLL, especially with fludarabine, pentostatin, cladribine), **autoimmune** (SLE), **infections** (viral), **drugs** (penicillins, fludarabine, methyldopa)
- **CLINICAL FEATURES**—anemia, jaundice, splenomegaly, 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 antibody-mediated clearance** (IVIG, splenectomy). **Immunosuppression** (*azathioprine* 100–150 mg PO daily, *cyclophosphamide* 100 mg PO daily). **Biological agents** (rituximab, alemtuzumab). **Treat underlying disease** (CLL, SLE, drugs)

**AUTOIMMUNE HEMOLYTIC ANEMIA COLD AGGLUTININS—IgM**

- **CAUSES**—**neoplasia** (CLL, lymphoma, Waldenstrom's macroglobulinemia, adenocarcinoma), **infections** (mycoplasma pneumonia, infectious mononucleosis, CMV, VZV)
- **CLINICAL FEATURES**—anemia, agglutination, jaundice, splenomegaly, smear (spherocytosis), ↑ reticulocytes, ↑ bilirubin, ↑ LDH, ↓ haptoglobin, direct Coombs test (IgG–, C3+), cold agglutinin screen
- **TREATMENTS**—**symptom control** (avoidance of cold). **Steroids** (*prednisone* 1 mg/kg PO daily, taper after stable). **Chemotherapy** (cyclophosphamide, chlorambucil). **Biological agents** (rituximab, INF$\alpha$). **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**

**DIFFERENTIAL DIAGNOSIS (CONT'D)**

### DIFFERENTIAL DIAGNOSIS (CONT'D)

**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. 117)
Chronic Liver Disease (p. 149)
Myelodysplastic Syndrome (p. 187)
Vitamin B12 Deficiency (p. 459)

### CLINICAL FEATURES

**HISTORY**—shortness of breath, chest pain, dizziness, fatigue, bleeding, fever, night sweats, weight loss, diet history, past medical history (liver disease, alcohol, hypothyroidism, myelodysplasia), medications (chemotherapy, antibiotics, antiepileptics)
**PHYSICAL**—look for signs of hypothyroidism, vitamin B12 deficiency and chronic 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, 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, test for Romberg sign, vibration and proprioception), peripheral neuropathy

### INVESTIGATIONS

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

**SPECIAL**
- **UGI ENDOSCOPY**—to identify atrophic gastritis and survey for gastric cancer
- **BONE MARROW BIOPSY**

### MANAGEMENT

**SYMPTOM CONTROL**—**transfusion** 2 U PRBC IV over 2 h in everyone except those with pernicious 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
**TREAT UNDERLYING CAUSE**—**folate deficiency** (*folate* 0.4 mg PO/SC/IM daily × 4–5 days). **Vitamin B12 deficiency** (*vitamin B12* 1,000 µg PO/SC/IM daily × 5–10 days, then 1,000 µg PO/SC/IM qweek × 4 weeks, then every month). **Hypothyroidism** (*levothyroxine* start 12.5–50 µg PO daily, adjust every 2 weeks)

## Sickle Cell Disease

### PATHOPHYSIOLOGY

**β-CHAIN MUTATION**—leads to formation of hemoglobin S ($\alpha 2\beta S2$) → polymerization of hemoglobin S → elongated fibers that distort shape of RBC → 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)

### CLINICAL FEATURES (CONT'D)

**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 or splenic sequestration crisis, iron overload (transfusions)
**PULMONARY**—restrictive lung disease (chronic interstitial fibrosis), obstructive lung disease, hypoxemia, pulmonary hypertension, fat embolism
**ANEMIA**—remember that sickle cell disease is associated with both acute and chronic anemia
**INFECTIONS**—sepsis (particularly asplenic patients), meningitis, pneumonia, osteomyelitis (susceptible to Salmonella and gram negative osteomyelitis)
**NEUROLOGIC**—ischemic stroke, intracerebral hemorrhage, septic emboli, spinal cord infarction or compression, vestibular dysfunction, sensory hearing loss, cognitive failure

### INVESTIGATIONS

**BASIC**

- **LABS**—CBCD, 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, $O_2$, IV

- **VASOOCCLUSIVE PAIN CRISIS**—fluids, pain control (morphine, ketorolac)
- **APLASTIC CRISIS**—transfusions. Avoid GCSF
- **SEQUESTRATION CRISIS**—fluids, judicious transfusion if symptomatic anemia to avoid overload if trapped splenic blood re-enters circulation
- **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*, *Niesseria 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
- **ANTIBIOTICS WITH FEVER**—any fever in an asplenic patient should prompt self-administration of preprescribed 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-INFECTIOUS**—sepsis
**AUTOIMMUNE**—drug induced, SLE
**NEOPLASTIC**—lymphoproliferative disorders, myelodysplasia, leukemias, myelophthisis
**INFECTIONS**—sepsis, HIV
**INSUFFICIENCY**—folate, vitamin B12

### DIFFERENTIAL DIAGNOSIS (CONT'D)

**IATROGENIC**—chemotherapy, chloramphenicol, trimethoprim–sulfamethoxazole, synthetic penicillins, phenytoin, carbamazepine, NSAIDs, gold, antithyroid medications, phenothiazines, clozapine
**CONSUMPTION**—hypersplenism

**Related Topic**
Febrile Neutropenia (p. 263)

### PATHOPHYSIOLOGY

**DEFINITION OF NEUTROPENIA**—neutrophils $<1.5\times10^3/\mu L$, severe neutropenia if absolute neutrophil count (ANC) $<0.5\times10^3/\mu L$

### INVESTIGATIONS

**BASIC**

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

**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 (>38.3 °C [>101 °F] or >38 °C [>100.4 °F] sustained >1 h) in a neutropenic patient is considered an emergency, as overwhelming sepsis can develop quickly. Patients with febrile neutropenia (see p. 263 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 the following: (1) being in contact with people with active infections, (2) consumption of uncooked meat/vegetables and unpasteurized dairy products and (3) exposure to fresh flowers or plants

### SPECIFIC ENTITIES

**ETHNIC NEUTROPENIA**—neutrophil counts in blacks are generally lower. Neutrophil count may be down to $1.5\times10^3/\mu L$ and still be considered normal

## Eosinophilia

### DIFFERENTIAL DIAGNOSIS

**★PAIN★**

**PRIMARILY ORGAN-SPECIFIC DISORDERS**

- **PULMONARY**—interstitial lung disease, AIDS-related pneumonia, idiopathic eosinophilic pneumonia, drug-induced lung disease
- **GASTROINTESTINAL**—eosinophilic gastroenteritis, eosinophilic esophagitis, primary biliary cirrhosis, primary sclerosing cholangitits
- **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

### DIFFERENTIAL DIAGNOSIS (CONT'D)

- **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/μL

**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, 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 ↑ 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 NEJM 2004 350:12

## 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

## DIFFERENTIAL DIAGNOSIS (CONT'D)

- **OTHERS**—iron deficiency, acute blood loss, hemolytic anemia, rebound from thrombocytopenia, splenectomy

## PATHOPHYSIOLOGY

**DEFINITION**—platelets >450 × $10^3$/μL

**Related Topic**
Myeloproliferative Disorders (p. 184)

### 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 $>450\times10^3/\mu L$, use ***ASA*** 81 mg PO daily (low dose) plus **hydroxyurea** (or **anagrelide**) targeting normalization of the platelet count. When the platelets are $>1{,}500\times10^3/\mu L$, **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, recollect with citrate)

**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. 182)

**↑ DESTRUCTION**

- **IMMUNE THROMBOCYTOPENIC PURPURA**—primary, secondary (lymphoma, CLL, HIV, SLE, Evans syndrome)
- **ALLOIMMUNE**—neonatal, post-transfusion, post-transplantation

### DIFFERENTIAL DIAGNOSIS (CONT'D)

- **MICROANGIOPATHIC HEMOLYTIC ANEMIA**—disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), HELLP syndrome, antiphospholipid antibody syndrome
- **INFECTIONS**—HIV, EBV, CMV
- **MEDICATIONS**—heparin, GPIIb/IIIa inhibitors, quinine, quinidine, valproic acid, thiazides, sulfonamides, rifampin, indomethacin, vancomycin, linezolid

### PATHOPHYSIOLOGY

**DEFINITION**—platelets $<150\times10^3/\mu L$. 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

## PATHOPHYSIOLOGY (CONT'D)

**BLEEDING RISK IN UNDER-PRODUCTION THROMBOCYTOPENIA**

| Platelet count ($\times 10^3/\mu L$) | 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 retinal 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), sequestration
- **SCHISTOCYTES/FRAGMENTS**—microangiopathic hemolytic anemia (DIC, TTP)

**BONE MARROW BIOPSY**

- **DECREASED MEGAKARYOCYTES**—underproduction
- **INCREASED MEGAKARYOCYTES**—destruction/sequestration/MDS (5q- syndrome)

## MANAGEMENT

**SYMPTOM CONTROL**—in under-production thrombocytopenia, **transfuse** 5 U platelets if platelets $<50\times10^3/\mu L$ and severe bleeding, platelets $<10\times10^3/\mu L$ in non-bleeding patient, and prior to certain procedures (expect platelet rise of ~5/unit). 1-h post-transfusion platelet count can help differentiate under-production vs. destructive causes. 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 7–14 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 with schistocytosis. Causes include DIC, HELLP, TTP, HUS, malignancy, malignant hypertension, artificial heart valve, insertion of foreign bodies, and medications

**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, preeclampsia, amniotic fluid embolus)
- **CLINICAL FEATURES**—microangiopathic hemolytic anemia, thrombocytopenia, bleeding and/or thrombosis, ischemia. ↑ INR, ↑ PTT, ↓ fibrinogen (although it can be normal or even elevated in acute phase), ↑ D-dimers, ↓ 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** (FFP) **and fibrinogen** (cryoprecipitate) **if deficient and bleeding. Anticoagulation if thrombosis** (consider IV heparin 200–500 IU/h infusion)

**THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)**

- **PATHOPHYSIOLOGY**—↓ ADAMTS13 activity → failure to degrade unusually large multimers of vWF → agglutination of platelets → arteriolar

**SPECIFIC ENTITIES (CONT'D)**

thrombi → systemic ischemia of brain, kidneys, gut, and heart
- **CAUSE**—autoantibody to ADAMTS13
- **CLINICAL FEATURES**—MAHA (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 rituximab if not resolving. Avoid platelet transfusion, ASA and antimotility agents. High mortality without treatment

**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**—MAHA (100%), thrombocytopenia (90%), renal dysfunction (90%). Schistocytes on peripheral smear
- **TREATMENTS**—supportive care only. Does not respond to plasma exchange. Avoid antibiotics unless patient septic.

**Related Topics**
Anticoagulation Therapy (p. 178)
Antiphospholipid Antibody Syndrome (p. 175)
Thrombocytopenia in Pregnancy (p. 477)

**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 (can present earlier if recent heparin exposure in past 1–3 months). It is usually more severe (platelet drop >50%) and has great clinical significance. Pathogenesis: 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 immediately and treat with danaparoid**, **lepirudin**, **or argatroban** until platelets return to normal. Begin warfarin when platelets $>150\times10^3/\mu L$ 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)

**IMMUNE THROMBOCYTOPENIA (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 when platelets $<20\times10^3/\mu L$. The goal of treatment is to support platelet counts until spontaneous remission occurs
  - **URGENT SUPPORT**—given to patients with active bleeding. ***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
  - **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 second line therapies
  - **SECOND LINE**—**rituximab**, **thrombopoietic agents** (romiplostim, eltrombopag) **splenectomy**. See p. 163 for details on counseling of patients undergoing splenectomy
  - **OTHER OPTIONS**—chemotherapy (CVP), danazol. HAART for HIV-associated ITP

**NEJM 2002 346:13**

**EVANS SYNDROME**—ITP and autoimmune hemolytic anemia

**DRUG-INDUCED IMMUNE THROMBOCYTOPENIA**—patients usually present with severe thrombocytopenia (platelets $<20\times10^3/\mu L$). 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 as needed

**NEJM 2007 357:6**

# 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 expression of the complement regulatory proteins CD55 and CD59, which are deficient on blood cells in 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 INFγ → ↑ Fas on CD34+ cells (maturing stem cells) → apoptosis → severe pancytopenia and hypocellular marrow. Complications include paroxysmal nocturnal hemoglobinuria, acute leukemia, and MDS
- **TREATMENTS**—corticosteroids, antithymocyte globulin, cyclosporine, stem cell transplant

**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★ p**latelets, **v**essels, **c**oagulopathy

**EXTRINSIC PATHWAY** (isolated PT/INR ↑)

- **FACTOR DEFICIENCY OR INHIBITOR**—VII or X
- **VITAMIN K DEFICIENCY**—malnutrition, pancreatic insufficiency, recent antibiotic use, warfarin use (early stage)
- **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
- **VITAMIN K DEFICIENCY**—malnutrition, pancreatic insufficiency, recent antibiotic use
- **LIVER DISEASE**

## DIFFERENTIAL DIAGNOSIS (CONT'D)

- **DIC**

**PLATELET DYSFUNCTION** (normal PT and PTT, platelet >90 × $10^3$/μL, 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 from extracorporeal circulation

**VESSELS**—collagen vascular disease, scurvy

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

## PATHOPHYSIOLOGY

### HEMOSTASIS

- **PRIMARY HEMOSTASIS**—endothelium, platelets
- **SECONDARY HEMOSTASIS**—coagulation proteins

### 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 $\delta$ granules (serotonin, ADP) and $\alpha$ granules (vWF, growth factors, factor V, factor X, fibrinogen)
4. Conformational change → 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 crosslinked by factor XIII and platelet–fibrin via GPIIb/IIIa

### ANTICOAGULATION PATHWAYS

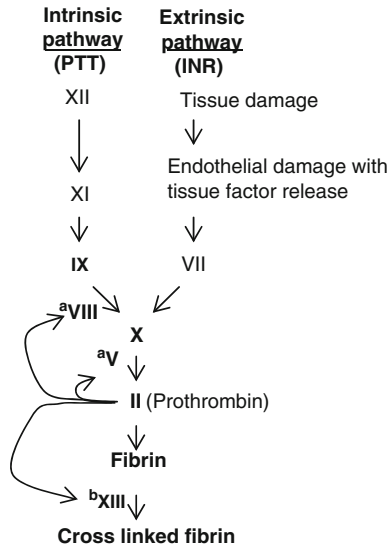
1. Antithrombin binds to thrombin and inhibits it
2. Thrombin binds to thrombomodulin which activates protein C and S to cleave factors Va and VIIIa
3. Factor Xa → tPA (by endothelial cells) → plasmin → fibrinolysis

### 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
- **SYNTHESIZED IN ENDOTHELIAL CELLS AND MEGAKARYOCYTES**—vWF

## PATHOPHYSIOLOGY (CONT'D)

### COAGULATION PATHWAY




[a]Non-enzymatic cofactors; [b]Factor 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 bleeding
- **COAGULATION FACTORS**—joints/muscles (hemarthroses, muscle hematomas, large/palpable ecchymosis), delayed bleeding

## INVESTIGATIONS

### BASIC

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

| VWD | Inheritance | Pathophysiology |
|---|---|---|
| I | Heterozygous mutations | 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 | Homozygous mutations | Complete absence of vWF |

## INVESTIGATIONS (CONT'D)

### 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 vs. inhibitors (factor deficiency corrects with mixing study)
- **HEMOPHILIA WORKUP**—factors VIII, IX, XI
- **ANTIPHOSPHOLIPID ANTIBODY SYNDROME WORKUP**—lupus anticoagulant screen, anticardiolipin antibody, dilute Russell's viper venom time, anti-β2 glycoprotein 1 antibody
- **VON WILLEBRAND DISEASE WORKUP**—von Willebrand factor (vWF) antigen levels, factor VIII level, ristocetin cofactor activity, ristocetin-induced platelet aggregation
- **PLATELET DISORDER WORKUP**—bleeding time, platelet aggregometry
- **MYELOMA WORKUP**—serum protein electrophoresis

## MANAGEMENT

**ACUTE**—ABC, $O_2$, IV, **transfusion** 2 U **PRBC** IV over 2 h, transfusion **platelets** 6 U, **FFP** 15 mL/kg, **cryoprecipitate** 10–15 U q48h for fibrinogen deficiency

**TREAT UNDERLYING CAUSE**—**avoid** heparin, LMWH, warfarin. **Vitamin K deficiency** (*vitamin K* 10 mg PO/IV daily × 3 days; IV vitamin K replacement has risk of anaphylaxis). **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
- **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), **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)
- **TREATMENTS**—*DDAVP* 0.3 μg/kg by IV infusion or 300 μg one spray each nasal for type I patients. vWF concentrates containing all vWF multimers may be used for type II and III and for bleeding and surgical management of type 1 patients

**BERNARD–SOULIER SYNDROME**—mutation of GPIb/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)

| VWD | vWF:Ag | 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 | ↓↓ |

# 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 antithrombin III)
- **ALTERATION**—factor V Leiden, prothrombin G20210A mutations
- **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, leukemia
- **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**—hyperhomocysteinemia, dysfibrinogenemia, plasminogen activator deficiency

## PATHOPHYSIOLOGY (CONT'D)

- **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 > prothrombin gene mutation in terms of risk of thrombosis

## 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. 178)
DVT (p. 176)
Pulmonary Embolism (p. 10)

## DIAGNOSTIC ISSUES

**INDICATIONS FOR HYPERCOAGULABILITY WORKUP**—testing for inherited thrombophilia is not routinely warranted in a patient with first episode unprovoked VTE. However, there may be benefit to investigating patients with a family history of VTE, unusual thrombosis (hepatic, portal, mesenteric, or cerebral veins), recurrent thromboembolism, or arterial thrombosis

**THROMBOPHILIA WORKUP AFTER ACUTE THROMBOSIS OR DURING ANTICOAGULATION**—acute VTE and anticoagulants can affect thrombophilia testing

| Hypercoagulable Disorder | Acute Thrombosis | Heparin Anticoagulation | Warfarin Anticoagulation |
|---|---|---|---|
| Anti-thrombin deficiency | ↓ | ↓ | – |
| APLA | – | – | – |
| Lupus anticoagulant | – | Cannot measure | False positive |
| Factor V Leiden | – | – | – |
| Protein C and S | ↓ | – | Cannot measure |
| Prothrombin gene mutation | – | – | – |

Draw protein C and S prior to warfarin therapy

## MANAGEMENT

**ACUTE**—ABC, $O_2$ to keep sat >94%, IV, consider thrombolysis for systolic BP <90 mmHg for >15 min

**ANTICOAGULATION**—see Approach to Anticoagulation Table. For cancer patients, extended anticoagulation beyond the first 6 months is generally considered and LMWH preferred anticoagulant

**IVC FILTER**—when anticoagulation is contraindicated; use a retrievable filter if the contraindication is temporary

## 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 overlapping heparin with warfarin for 5 days (with minimum 48 h therapeutic INR overlap)

**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), recent surgery or trauma, immobility or paresis, BMI >30 kg/m$^2$, 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* 5,000 U SC q8h, *enoxaparin* 40 mg SC daily, *dalteparin* 5,000 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**—without anticoagulation, the risk for recurrent VTE is 50% Anticoagulation ↓ risk to 8–10% by 1 month and 4–5% by 3 months
- **VTE WITH LONG-TERM RISK FACTORS**—recurrent DVT risk 10%/year. Anticoagulation ↓ risk to <3%/year

**TREATMENT ISSUES (CONT'D)**

- **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. LMWH is anticoagulant of choice in patients with malignancy
- **AF WITH PREVIOUS STROKE**—recurrent stroke risk 12%/year. Anticoagulation ↓ risk to < 4%/year
- **AF WITH OTHER RISK FACTORS**—recurrent stroke 8%/year. Anticoagulation ↓ risk to < 2%/year
- **LONE AF**—recurrent stroke risk 1–2%/year. Anticoagulation ↓ risk to < 1%/year

**MECHANICAL HEART VALVE**—recurrent arterial embolic risk 4%/year. Warfarin ↓ risk to < 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-β2-glycoprotein 1 antibody → may lead to hypercoagulable state
- **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 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 anti-

**SPECIFIC ENTITIES (CONT'D)**

cardiolipin or anti-β2-glycoprotein 1 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 criterion (sens 70%, spc 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. 478 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 and endothelial injury due to complement activation, ↑ tissue factor, ↓ fibrinolysis → ↑ thrombosis
- **CLINICAL FEATURES**—hemolysis, venous thrombosis (hepatic vein, portal vein, splenic vein, renal vein), arterial thrombosis (rarer), marrow aplasia, MDS, leukemia, infections, esophageal spasm, sexual dysfunction
- **DIAGNOSIS**—flow cytometry, historically, Ham's test (RBC sensitivity to acidity)
- **TREATMENTS**—steroids, eculizumab (anti-complement protein 5), 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, ~15% extend into proximal veins within 2 weeks
**COMPLICATIONS**—clot extension, pulmonary embolism, recurrent thrombosis, post-thrombotic syndrome, chronic thromboembolic pulmonary hypertension

## INVESTIGATIONS

### BASIC

- **LABS**—CBCD, lytes, urea, Cr, PTT, INR, D-dimer, fibrinogen, AST, ALT, ALP, bili
- **IMAGING**—doppler/compression US (sens 95%, spc 95%)

## 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
- **PREGNANCY TEST**—in female <50
- **VENOGRAM**—gold standard

## DIAGNOSTIC ISSUES

**COMPRESSION US**—high sensitivity (95%) and specificity (95%) for DVT. US of calf veins is not routinely performed because of lower sensitivity (70%). Rather, US of thigh (deep veins) is usually repeated in 2 weeks after a normal test to detect the possible extension of DVT from calf into proximal veins

**Related Topics**
Anticoagulation Therapy (p. 178)
Hypercoagulable States (p. 173)
Pulmonary Embolism (p. 10)

**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 |

***Post-test Probability of DVT Using High Sensitivity D-dimer Assay***
**LOW RISK** (0 or less points)—0.5% chance of DVT. If D-dimer negative, can exclude DVT
**MODERATE RISK** (1–2 points)—1% chance of DVT. Workup may or may not be needed
**HIGH RISK** (3 or greater points)—8.6% chance of DVT. D-dimer testing not useful. Proceed to compression US 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**
**The Rational Clinical Examination. McGraw-Hill, 2009**

## DIAGNOSTIC ISSUES (CONT'D)

**THROMBOPHILIA WORKUP**—should be done if suspect a hereditary cause of thromboembolic disease. Alarm features include age < 45, unprovoked VTE family history (1 or more first degree relatives), or clot in unusual location (mesenteric vessels, brain)

**MALIGNANCY WORKUP**—basic screening includes history and physical, CXR, CBC, LFTs, calcium, and U/A. Consider CT abdomen and pelvis for those >40 years. Consider mammography for women >40 years

**PROTEIN S AND PROTEIN C DEFICIENCY WHILE ANTICOAGULATED**—when anti-coagulated, these levels decrease by similar proportion to II, VII, IX and X

## MANAGEMENT

**ANTICOAGULATION**—see Approach to Anticoagulation Table

**IVC FILTER**—if anticoagulation contraindicated

**THROMBOLYSIS**—may have a role in hemodynamically unstable pulmonary embolism (systemic) or massive iliofemoral thrombosis (local)

## TREATMENT ISSUES

### ANTICOAGULATION DURATION

- **3–6 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**—idiopathic VTE
- **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
- **RELATIVE**—mild–moderate bleeding diathesis or thrombocytopenia ($<25 \times 10^3/\mu L$), 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)

## TREATMENT ISSUES (CONT'D)

## 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. 25% will have synchronous ipsilateral DVT and a new DVT develops within 3 months in 10%

### CATHETER RELATED THROMBOSIS

- **INCIDENCE**—approximately 40% (range 12-74%) of patients with long term central venous catheter develop DVT
- **RISK FACTORS**—in addition to traditional risk factors (e.g. cancer), left subclavian vein placement, positioning of catheter tip too high in the superior vena cava and previous catheter infections
- **CLINICAL FEATURES**—often asymptomatic. However, patients may experience arm swelling, erythema, pain, warmth, development of collateral vessels and fever. Acute PE, post thrombotic syndrome and persistent vascular compromise represent potential complications
- **DIAGNOSIS**—ultrasound (sens 78-100%, spc 86-100%), venogram is gold standard but rarely done
- **TREATMENTS**—if catheter is still needed (e.g. for chemotherapy administration), consider anticoagulation for at least 3 months with catheter in place, followed by prophylactic doses until catheter removed. Note that in serious cases in which the limb may be threatened or if anticoagulation is contraindicated, catheter may need to be removed regardless. If no need for catheter, consider anticoagulation for 3–5 days, then remove catheter, and then anticoagulation for up to 3 months. Primary prophylaxis is not indicated

## 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<br>Atrial fibrillation<br>Prosthetic valves | *Warfarin* 5 mg PO daily overlapping with heparin for 5 days, then adjust based on INR target of 2–3 | **Complications**—bleeding (may be reversed with vitamin K), coumadin-induced skin necrosis<br>**Monitor**—INR |
| Unfractionated heparin | **Indirect thrombin and factor Xa inhibitor** (**nonselective**). Binds to antithrombin (AT) and converts it from a slow form to fast-acting form, which binds and inactivates thrombin and factors Xa, IXa, XIa, XIIa<br>Heparin resistance is usually due to AT deficiency and could be treated with AT concentrates | Acute DVT/PE<br>Arterial embolism<br>Prosthetic valves<br>ACS<br>DVT prophylaxis | For acute clot, *unfractionated heparin* 80 U/kg or 5,000 U IV bolus, then 18 U/kg/h or 1,000 U/h, and adjust to 1.5–2.5× normal PTT<br>For DVT prophylaxis, *unfractionated heparin* 5,000U SC 2 h before surgery, then 5,000U SC TID | **Complications**—bleeding (may be reversed by protamine 1 mg/100 U UFH), HITT, osteoporosis<br>**Monitor**—aPTT (1.5–2.5× normal) and platelets<br>Narrow therapeutic window and highly variable dose–response curve |
| Low molecular weight heparin:<br>*Enoxaparin*<br>*Dalteparin*<br>*Tinzaparin* | **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<br>Inactivation of thrombin specifically requires heparin binding to *both* AT and thrombin. This complex only forms with heparin chains ≥18-saccharide long. Thus, LMWH is not as effective in inhibiting thrombin and does not prolong aPTT | Acute DVT/PE<br>Maintenance DVT/PE in cancer patients<br>Arterial embolism<br>Prosthetic valves<br>ACS<br>DVT prophylaxis | For acute clots, *enoxaparin* 1 mg/kg SC BID or 1.5 mg/kg SC daily, *dalteparin* 200 U/kg SC daily, tinzaparin 175 U/kg SC daily<br>For DVT prophylaxis, *enoxaparin* 40 mg SC daily × 7–14 days starting 12 h pre-op, *dalteparin* 2500 U SC 1 h pre-op, then 5000 U SC daily × 5–14 days | **Complications**—bleeding (may be reversed partially with protamine sulfate 1 mg/100 anti-Xa U of LMWH), HITT, avoid in spinal surgery<br>**Monitor**—anti-factor Xa activity and platelets. Anticoagulant response correlates well with body weight, allowing fixed dosing without monitoring usually. Less likely to induce HITT but still requires platelet monitoring |

## Approach to Anticoagulation Therapies (cont'd)

| Class/Drugs | Mechanism | Indications | Usual dose | Complications/monitoring |
|---|---|---|---|---|
| Heparinoids:<br>*Danaparoid* (*organon*) | **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. aPTT not useful for monitoring | HITT<br>Acute DVT | For HITT, *danaparoid* 2,000 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<br>**Monitor**—anti-factor Xa activity. Particularly important in renal failure<br>10% cross-reactivity between danaparoid and the antibody responsible for HITT, but clinical significance is uncertain |
| Fondaparinux | **Indirect factor Xa inhibitor** (**highly selective**).<br>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<br>Acute DVT/PE<br>Acute coronary syndrome<br>HITT (no cross reactivity with heparin-dependent anti-platelet antibodies) | For DVT prophylaxis, *fondaparinux* 2.5 mg SC daily (start 6–8 h after surgical hemostasis)<br>For acute clots, *fondaparinux* 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 | **Complications**—bleeding; avoid in spinal surgery<br>**Monitor**—antifactor Xa activity |
| Oral Direct Factor Xa inhibitor:<br>*Rivaroxaban*[a]<br>*Apixaban*[a] | **Direct factor Xa inhibitors** (**highly selective**). Inhibits factor Xa by binding to its active site without interacting with AT | DVT prophylaxis<br>VTE treatment (except if hemodynamically unstable or massive PE)<br>Atrial fibrillation | For DVT prophylaxis, *rivaroxiban* 10 mg PO daily or *apixaban* 2.5 mg PO BID<br>For acute VTE, *rivaroxaban* 15 mg PO BID for 3 weeks, *apixaban* 10 mg PO BID for 7 days<br>For atrial fibrillation, *rivaroxaban* 20 mg PO daily or *apixaban* 5 mg PO BID | **Complications**—bleeding<br>**Monitor**—no routine monitoring assay is available |
| Direct thrombin inhibitors:<br>*Desirudin*<br>*Bivalirudin*<br>*Argatroban*<br>*Dabigatran*[a] | **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.<br>Does not depend on AT for action and thus unaffected by AT deficiency | HITT (argatroban, bivalirudin)<br>ACS (bivalirudin)<br>DVT prophylaxis (desirudin)<br>VTE treatment (dabigatran)<br>Atrial fibrillation (dabigatran) | For HITT, *argatroban* 2 μg/kg/min infusion<br>For DVT prophylaxis, *desirudin* 15 mg SC BID<br>For VTE treatment, *dabigatran* 150 mg PO BID after 5 days heparin<br>For atrial fibrillation, *dabigatran* 150 mg PO BID | **Complications**—bleeding<br>**Monitor**—aPTT is unreliable<br>**Dose adjust dabigatran**—ClCr < 30 ml/min |

[a]Novel oral anticoagulants

**Related Topics**
DVT (p. 176)
Hypercoagulable States (p. 173)
Pulmonary Embolism (p. 10)

### 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 ± 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 prothrombin complex concentrate in selected cases

**INR > 9**—if no significant bleeding, hold warfarin and administer *vitamin K1* 2.5–5 mg PO. Use additional 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 prothrombin 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<br>PRBC, 1/300; or platelets (5U), 1/10 | End of transfusion. Fever, chills | Antihistamine (*diphenhydramine* 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 (*diphenhydramine* 50 mg IV × 1 dose) |

## Transfusion Reactions (cont'd)

| Adverse Effect | Pathophysiology | Onset and Symptoms | Treatments |
|---|---|---|---|
| Post-transfusion purpura (PTP) | Recipient Ab against donor platelet, rare | 7–10 days after. Consumptive thrombocytopenia and purpura | Steroids, plasmapheresis |
| Transfusion-associated circulatory overload (TACO) | Hypervolemia 1/700 | Acute/delay. Pulmonary edema | Diuresis, supportive measures |
| Septic transfusion | Platelets (5 U) 1/10,000 risk of symptomatic sepsis and 1/40,000 chance of death<br>PRBC (1 U), 1/100,000 risk of symptomatic sepsis and 1/500,000 chance of death | Acute. Fever, ↓ BP | Stop transfusion, empiric antibiotics (vancomycin + broad spectrum beta-lactam or aminoglycoside) |
| Air embolism | | Acute. SOB, ↓ BP | Supportive measures |
| TRALI | Donor Ab against recipient WBC, 1/5,000 plasma-containing products | Acute. Hypoxemic, pulmonary edema | 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**—CBCD, peripheral smear, urea, Cr, LDH, indirect bilirubin, serum hemoglobin, Coombs testing, 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 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** (inhibits lymphocyte proliferation and prevents transfusion-associated GVHD)—stem cell transplant recipients, 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

### 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** (dacrocytes)—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**
- **CONGENITAL STORAGE DISEASES**—Gaucher, Niemann-Pick disease

**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
- **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

## CLINICAL FEATURES (CONT'D)

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

## CLINICAL FEATURES (CONT'D)

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 $cm^3$, 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

| | LR+ | LR– |
|---|---|---|
| **Percussion** | | |
| Nixon's method (right lateral decubitus position; percuss from lower level of pulmonary resonance in posterior axillary line downward obliquely to lower mid-anterior costal margin; >8 cm suggests splenomegaly) | 3.6 | 0.41 |
| Traube's space (percuss space 6th rib superiorly, mid-axillary line laterally and costal margin inferiorly; dullness suggests splenomegaly | 2.3 | 0.48 |
| Castell's method (percuss lowest intercostal space in the left anterior axillary line during both expiration and full inspiration; dullness suggests splenomegaly | 1.2 | 0.45 |
| **Palpation** | | |
| One-handed palpation with patient supine | 8.2 | 0.41 |
| Middleton hooking maneuver | 6.5 | 0.16 |

**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**

***UPDATE***—palpation may have greater accuracy than percussion, especially in lean patients. Examiners should become proficient in one palpation and one percussion method, because the combination of both results may be better than either alone.

**The Rational Clinical Examination. McGraw-Hill, 2009**

## INVESTIGATIONS

**BASIC**

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

**SPECIAL**

- **CT ABD**—weight = 0.43 × Length × Width × Thickness
- **SCINTIGRAPHY**
- **MALIGNANCY WORKUP**—bone marrow biopsy, lymph node biopsy, laparoscopy/laparotomy

## MANAGEMENT

**TREAT UNDERLYING CAUSE**

**SPLENECTOMY**—see p. 163 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 dysplastic blood cells. Both MPS and MDS can eventually lead to AML

**POLYCYTHEMIA RUBRA VERA**—see POLYCYTHEMIA (p. 159)

**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 $<100\times10^3/\mu L$
- **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 $>1.0\times10^3/\mu L$ for at least 6 months), anemia, thrombocytopenia, and splenomegaly

**ESSENTIAL THROMBOCYTOSIS**—see THROMBOCYTOSIS (p. 166)

**MYELOFIBROSIS**—↑ fibroblasts, massive spleen, teardrop RBC, nucleated RBC, large platelets

**Related Topics**
Polycythemia (p. 159)
Thrombocytosis (p. 166)

## 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

**POLYCYTHEMIA RUBRA VERA**—median survival 20 years; ~14/100 transform to AML over 2 decades

**CHRONIC MYELOGENOUS LEUKEMIA**—median survival is now decades and risk of blast crisis is declining with *bcr-abl* tyrosine kinase inhibitors; ~1/2 transforms to AML

**ESSENTIAL THROMBOCYTOSIS**—median survival 20 years; ~25/1,000 transform to AML over 3 decades

**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

**MANAGEMENT (CONT'D)**

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**—dasitinib, nilotinib, and stem cell transplantation

**ESSENTIAL THROMBOCYTOSIS**—aspirin, hydroxyurea, anagrelide

**MYELOFIBROSIS**—hydroxyurea, ruxolitinib, splenectomy, interferon $\alpha$, thalidomide

**TREATMENT ISSUES**

**RESPONSE CRITERIA FOR CML**

- **HEMATOLOGICAL RESPONSE**
  - **COMPLETE RESPONSE**—WBC $<10\times10^3/\mu L$ with no immature granulocytes and <5% basophils, platelet $<450\times10^3/\mu L$, and non-palpable spleen
  - **PARTIAL RESPONSE**—persistence of immature cells in peripheral blood, platelets $>450\times10^3/\mu L$ but <50% of pre-treatment levels, or persistent splenomegaly but <50% of pre-treatment size
- **CYTOGENIC RESPONSE** (FISH detection of the Philadelphia chromosome)
  - **COMPLETE**—0% Ph + cells
  - **PARTIAL**—1–35% Ph + cells
  - **MAJOR**—complete and partial cytogenetic response

**TREATMENT ISSUES (CONT'D)**

  - **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) 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 (T315I mutation confers tyrosine kinase inhibitor resistance), overexpression or amplification of *bcr–abl*

**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 |

## 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

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

**HEMATOLOGIC MALIGNANCIES OVERVIEW (CONT'D)**

**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
- **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)

## HEMATOLOGIC MALIGNANCIES OVERVIEW (CONT'D)

- **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 OF AML

### 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

- **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, $PO_4$, Mg, uric acid, albumin, urinalysis, LDH, INR, PTT, fibrinogen
- **BONE MARROW BIOPSY** (>**20**% **BLASTS**) **WITH FLOW CYTOMETRY AND CYTOGENETIC/MOLECULAR ANALYSES**

### SPECIAL

- **LUMBAR PUNCTURE**—CSF for cytology (risk of CNS involvement greatest with high circulating blasts, elevated LDH, and monocytic variants of AML) and flow cytometry
- **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, t(6;9), LDH >2.9 × ULN

## 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)
- **CONSOLIDATION TREATMENT**
  - **COMPLETE REMISSION POST-INDUCTION**
    - **GOOD RISK**—chemotherapy IDAC induction followed by HDAC consolidation
    - **INTERMEDIATE RISK**—stem cell transplant (SCT) if available; otherwise, consolidation chemotherapy
    - **POOR RISK**—SCT if donor available; otherwise, consolidation chemotherapy
  - **LACK OF COMPLETE REMISSION POST-INDUCTION**—repeat induction. Proceed as in poor risk disease
- **RELAPSE**—SCT if donor available (preferred); otherwise, salvage chemotherapy

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

**Related Topics**
Febrile Neutropenia (p. 263)
Tumor Lysis Syndrome (p. 254)

## 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

**SCT**—may opt for consolidation chemotherapy while identifying donor. SCT is a potentially curative therapy

## 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
- **DIAGNOSIS**—peripheral blood smear (RBC with abnormal morphologic features, dysgranulopoiesis with Pelger-Huët deformity, nuclear atypia and hypogranulation, 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, erythropoietin/darbopoietin (for patients with serum EPO <500 ng/ml and low transfusion requirement), treat infections early, 5-azacytidine, lenalidomide, decitabine, 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 $\alpha$ 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

**SPECIFIC ENTITIES (CONT'D)**

- **TREATMENTS**—**induction** with all-*trans*-retinoic acid (ATRA) plus idarubicin, then **consolidation** with anthracycline and cytarabine, and then **maintenance** with ATRA 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 upfront (with ATRA) and 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**—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 | – | + |
| Myeloperoxidase | + | – |

## INVESTIGATIONS

**BASIC**

- **LABS**—CBCD, smear, lytes, urea, Cr, Ca, $PO_4$, Mg, uric acid, albumin, urinalysis, LDH, INR, PTT, fibrinogen, flow cytometry of peripheral blood (immunophenotyping)
- **BONE MARROW BIOPSY**—> 20% 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

**SPECIAL**

- **IMAGING**—MUGA scan to evaluate cardiac function prior to anthracycline therapy
- **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), TELAML1 fusion or t(12;21) (in 10% of adults)

### PROGNOSTIC ISSUES (CONT'D)

**RISK CATEGORIES**

- **HIGH RISK**—any of age >60, t(9;22) or *bcr–abl*, t(4;11), t(1;19); WBC $>30\times10^3/\mu L$ in B-ALL or $>100\times10^3/\mu L$ 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 high-dose cyclophosphamide, prednisone, vincristine, ananthracycline ± asparaginase. Complete response 80–90%. Management of specific subgroups include

- **PH + ALL**—add imatinib
- **L3 B-CELL ALL**—treat like Burkitt'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

### MANAGEMENT (CONT'D)

**INTENSIFICATION/CONSOLIDATION THERAPY**

- **STANDARD RISK**—consolidation chemotherapy with various combinations of cyclophosphamide, 6-mercaptopurine, cytarabine, vincristine, and doxorubicin
- **HIGH RISK**—SCT if 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. 263)
Tumor Lysis Syndrome (p. 254)

## 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, CMV, 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, $PO_4$, Mg, uric acid, LDH, β2 microglobulin, albumin, quantitative immunoglobulin, serum protein electrophoresis, urinary protein electrophoresis

## INVESTIGATIONS (CONT'D)

- **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 $>5\times10^3/\mu L$, with ≥1 B-cell marker (CD19, CD20, CD23) and CD5; >55% atypical cells
- **BONE MARROW**—a normocellular to hypercellular marrow with >20% clonal lymphocytes. Interstitial/nodular pattern (70%) has a better prognosis than diffuse/extensive pattern (30%)
- **IMMUNOPHENOTYPE**—CD5+, CD19+, CD20+ dim, CD23+, CD43+, CD10–, SIg+dim
- **NOTE**—for patients with lymphocyte count $5–10\times10^3/\mu L$, 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 ($<100\times10^3$/mL). Median survival 19 months

**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 ($<100\times10^3/\mu L$). 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, 17p deletion, 11q deletion, trisomy 12

## DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

**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), **bendamustine** or **ibrutininb** (bruton's tyrosine kinase inhibitor) are useful for fludarabine-refractory disease. **Indications for treatment** include symptoms (weakness, painful lymphadenopathy, B symptoms, symptomatic splenomegaly), anemia (Hb <110 g/L [<11 g/dL]), thrombocytopenia (platelets $<100\times10^3/\mu L$), 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 Richter's transformation, treat as aggressive lymphoma with R-CHOP

**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 $\leq4\times10^3/\mu L$, neutrophils $\geq1.5\times10^3/\mu L$, platelets $>100\times10^3/\mu L$, 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 $\geq1.5\times10^3/\mu L$, platelets $>100\times10^3/\mu L$, 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%), tricytopenia (fatigue, recurrent infections, thrombocytopenia), and lymphocytosis. 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 and rituximab

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

## CLINICAL FEATURES (CONT'D)

- **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 (<1 cm) |
| 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. $II_2$)

## STAGING (CONT'D)

**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 $<4\times10^3/\mu L$, platelets $<125\times10^3/\mu L$
- **ENT EXAMINATION**—stage IA or IIA with upper cervical lymph node involvement
- **MRI SPINE**—if suspect spinal cord compression
- **MUGA SCAN OR ECHOCARDIOGRAM**—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 (HASENCLEVER 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 $>15\times10^3/\mu L$, lymphocyte $<0.6\times10^3/\mu L$, 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) *x*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×6 cycles. Reassess with CT and/or PET scan. If residual disease, consider involved field irradiation. Alternative regimens 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**—brentuximab (anti-CD30 antibody conjugated to auristatin), 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- or second-line chemotherapy, relapse <1 year after

**TREATMENT ISSUES (CONT'D)**

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

**TREATMENT ISSUES (CONT'D)**

**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

**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

**PATHOPHYSIOLOGY (CONT'D)**

  - **SMALL LYMPHOCYTIC LYMPHOMA** (SLL, 5–10%)—identical to chronic lymphocytic leukemia in pathologic characteristics, but treated as low grade B-cell lymphoma
  - **HAIRY CELL LEUKEMIA** (HCL)
  - **LYMPHOPLASMACYTIC LYMPHOMA** (LPL, 2–3%)—also called 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)

## PATHOPHYSIOLOGY (CONT'D)

- **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

### 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 overexpression

### INFECTIONS AND LYMPHOMA

- **EBV**—Hodgkin's lymphoma, Burkitt lymphoma, post-transplant lymphoproliferative disorders, primary CNS lymphoma
- **HCV**—splenic marginal zone lymphoma
- **HHV8** (also known as Kaposi's Sarcoma Herpes Virus)—Castleman disease, primary effusion lymphoma
- **HIV**—primary CNS lymphoma
- **HTLV**—adult T-cell leukemia/lymphoma
- ***BORRELIA 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, Waldeyer'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, neutropenia, 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, $PO_4$, 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 FLOW CYTOMETRY FOR LYMPHOID SURFACE MARKERS**

### SPECIAL

- **MRI SPINE**—if suspect spinal cord compression
- **MUGA SCAN OR ECHOCARDIOGRAM**—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 | + dim | + | + | + |
| 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)
- **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

## DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

- **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%), R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) CVPR×8 cycles (cyclophosphamide, vincristine, prednisone, and rituximab), or R-bendamustine followed by maintenance rituximab for 2 years if PR. Other options include ibrutinib, fludarabine, cyclophosphamide, $I^{131}$-tositumomab, and $Y^{90}$-ibritumomab. Evaluation for SCT is appropriate

### AGGRESSIVE LYMPHOMAS

- **LIMITED STAGE** (IA or IIA, 30%)—R-CHOP× 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%)—R-CHOP×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 disease and normal LDH), give CODOX-MR (cyclophosphamide, doxorubicin, vincristine, methotrexate, rituximab)×1 then restage. If CR/PR, give IVAC-R (ifosfamide, etoposide, cytarabine)×1 then CODOX-MR×1; otherwise, give IVAC-R×1 then proceed to stem cell transplant. For **high-risk disease**, give CODOX-MR×1, IVAC-R×1 then restage. If CR/PR and no marrow infiltration at diagnosis, then autologous stem cell transplant;

## MANAGEMENT (CONT'D)

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, rasburicase). Cure rate ~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:** ≥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 ≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter)
- **Liver and spleen:** no increase in size
- **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 ≥50% of previously involved sites from nadir

- **Nodal masses:** appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥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

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## SPECIFIC ENTITIES

### EYE LYMPHOMA

- **PATHOPHYSIOLOGY**—periorbital involvement (mostly MALT type) or intraocular involvement (usually DLBCL with more indolent course)
- **TREATMENTS**—for periorbital 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. Always check HIV
- **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, VII), 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**—R-CHOP × 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

**BURKITT'S LYMPHOMA**

- **PATHOPHYSIOLOGY**—t(8;14, 2;8, 8;22) 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 US
- **TREATMENTS**—unilateral orchiectomy + R-CHOP + 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 $\alpha$, adoptive immunotherapy. 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,

**SPECIFIC ENTITIES (CONT'D)**

and tumor stage. Sezary syndrome is a systemic 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 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$\alpha$, 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 present at older age with advanced stage, elevated LDH, B symptoms, and extranodal sites
- **TREATMENTS**—CHOP-based regimens or brentuximab. 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 (rituximab, steroid, antivirals, anti-IL-6, CHOP)

## 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**—$\kappa$ or $\lambda$ light chain

**AL (PRIMARY) AMYLOIDOSIS**—$\lambda$ or $\kappa$ light chain

**PATHOPHYSIOLOGY**

**EPIDEMIOLOGY**

- **INCIDENCE**—1%
- **MORTALITY**—1%

**PATHOPHYSIOLOGY (CONT'D)**

**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
- **INCREASED POLYCLONAL PROTEIN**—infections due to ↓ 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 ± plasmacytoma

## CLINICAL FEATURES (CONT'D)

- **RENAL FAILURE**
  - **PRE-RENAL**—N&V, renal vein thrombosis
  - **RENAL**—myeloma kidney (tubulointerstitial damage from increased light chain absorption at proximal tubule), plasma cell infiltration, Bence Jones/cast nephropathy, amyloidosis ($\lambda$), light-chain deposition disease ($\kappa$), 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, $\beta$2 microglobulin, serum viscosity, quantitative immunoglobulin, albumin, serum protein electrophoresis (reciprocal depression), urinary protein electrophoresis, 24 h urinary collection for Bence Jones protein
- **IMAGING**—skeletal survey (NB: standard bone scan does NOT play a role in routine myeloma staging)
- **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; nonsecretory myeloma (3%) requires bone marrow biopsy for diagnosis

**Related Topics**
Amyloidosis (p. 483)
Renal Failure (p. 78)

## 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 **c**alcium (>2.75 mmol/L [>11 mg/dL]), **r**enal insufficiency (Cr >173 μmol/L [>1.9 mg/dL]), **a**nemia (Hb <100 g/L [<10 g/dL] or drop by 20 g/L [2 g/dL]), **b**one 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 [<3 g/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 $\beta$-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

## DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

[≤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 $\lambda$ or $\kappa$ 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 $\lambda$ or $\kappa$ 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 bortezomib plus dexamethasone (first choice), lenalidomide plus dexamethasone, or bortezomib plus thalidomide plus dexamethasone, or bortezomib plus doxorubicin plus dexamethasone, or bortezomib plus lenalidomide plus dexamethasone. If good response, then proceed to **high-dose melphalan followed by autologous stem cell transplant**. Post-SCT maintenance therapy with lenalidomide is recommended
- **AGE >65 OR COMORBIDITIES** (palliative)—melphalan plus prednisone plus thalidomide, melphalan plus prednisone plus lenalidomide, or melphalan plus prednisone plus bortezomib, lenalidomide plus low dose dexamethasone or bortezomib plus dexamethasone. Addition of interferon to MP provides small benefit. If bony disease, add **bisphosphonate** (alendronate, zoledronate)

## MANAGEMENT (CONT'D)

- **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 caution given the increased risk of thromboembolism and death), **hyperviscosity syndrome** (Ostwald viscosimeter >5, plasmapheresis), **prophylactic anticoagulation** (if on thalidomide/lenalidomide and chemotherapy)

**SMM**—no treatment. Follow clinically

**MGUS**—no treatment. Follow clinically

## TREATMENT ISSUES

**INDICATIONS FOR TREATING MULTIPLE MYELOMA**—>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. 483 for more details. Workup include abdominal fat biopsy, abd US, and echocardiogram

**POEMS SYNDROME**—osteosclerotic myeloma with **P**olyneuropathy, **O**rganomegaly, **E**ndocrine (diabetes, hypothyroidism, parathyroid hypogonadism, HPA), **M**onoclonal protein, **S**kin 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. 263)

## 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)

**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

**HAPLOIDENTICAL TRANSPLANTATION** (increasing use in adults)—stem cells from parent, child or sibling. Main advantage is the relative ease of identifying a donor, while the main disadvantage is graft rejection and GVHD

**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** (expands supply of donors, although limited amount of stem cells in cord blood can affect engraftments and directs frequent use of "dual cord" transplantation; less GVHD with mismatches)

### 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

### COMMON INDICATIONS (CONT'D)

**AUTOLOGOUS**—progressive Hodgkin's lymphoma (60–70% cure if relapse, 40–50% cure if refractory disease), multiple myeloma, relapsed and 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**—ensure good match of 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. 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 venoocclusive disease with tender hepatomegaly, jaundice and ascites), seizures, parotitis, pericarditis, cardiomyopathy, interstitial pneumonitis, hemorrhagic cystitis, rash

## ALLOGENEIC TRANSPLANTATION (CONT'D)

- **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. Consider oocyte/sperm/embryo cryopresevation
- **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 $>0.5 \times 10^3/\mu L$, 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 PJP, 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

**IMMUNE RECONSTITUTION**—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
- **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, PJP, central line infections (*S. epidermis*)
- **LATE INFECTIONS** (>100 days)—VZV, encapsulated bacteria, PJP, Aspergillus

## AUTOLOGOUS TRANSPLANTATION

**MATCHING PROCESS**—not applicable

**CONDITIONING**—similar to allogeneic transplant. Regimens include CBV (cyclophosphamide, BCNU, etoposide), cyclophosphamide plus total body irradiation, and BEAM (BCNU, etoposide, cytosine arabinoside, melphalan)

**TRANSPLANTATION**—similar to allogeneic transplant, except stem cells obtained from patient pretransplant 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. 185)
Chemotherapy-Induced Diarrhea (p. 257)
Non-Hodgkin's Lymphoma (p. 193)
Febrile Neutropenia (p. 263)
Fungal Infections (p. 298)
Multiple Myeloma (p. 198)
Oral Mucositis (p. 256)
Sepsis (p. 111)
Tumor Lysis Syndrome (p. 254)