## HEMATOLOGY

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Leora Horn, associate editor

### APPROACH TO THE BLOOD FILM

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- Hodgkin’s Disease
- Non-Hodgkin’s Lymphoma

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- Monoclonal Gammapathy of Unknown Significance (MGUS)
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- Coagulation Factors
  - Group and Reserve Serum
- Acute Complications of Blood Transfusions
- Delayed Complications in Transfusions

#### Medications Commonly Used in Hematology

### References
APPROACH TO THE BLOOD FILM

Size
- macrocytic
  - increased size
  - e.g. low B12, low folate
- microcytic
  - reduced size
  - e.g. iron deficiency, thalassemia

Colour
- hypochromatic
  - increase in the size of the central pallor (normal = less than half of the diameter of RBC)
  - increased polychromasia (blue cells) indicates increased RBC production by the marrow

Shape
- normal = discocyte (biconcave)
- spherocyte = spherical RBC
  - e.g. hereditary spherocytosis, immune hemolytic anemia
- fragmented cells (schistocytes) = split RBC
  - e.g. microangiopathic hemolytic anemia (TTP, DIC, vasculitis, glomerulonephritis), prosthetic heart valve
- elliptocyte (ovalocyte) = oval, elongated RBC
  - e.g. hereditary elliptocytosis, megaloblastic anemia
- sickle cell = sickle-shaped RBC
  - e.g. sickle cell disorders, HbSC, HbSS
- target cell = bell-shaped, looks like target on dried film
  - e.g. liver disease, hemoglobin S and C, thalassemia, Fe deficiency
- teardrop cell (darcocyte) = single pointed end, looks like a teardrop
  - e.g. myelofibrosis

Distribution
- rouleaux formation = aggregates of RBC resembling stacks of coins
  - e.g. artifact, paraprotein (multiple myeloma, macroglobulinemia)

Inclusion
- nuclei
  - immature RBC
  - indicates serious medical disease
  - e.g. severe anemia, leukemia, bone marrow metastases
- Heinz bodies
  - denatured hemoglobin
  - e.g. G6PD deficiency
- Howell-Jolly bodies
  - small nuclear remnant with the colour of a pyknotic nucleus
  - e.g. post-splenectomy, hyposplenism, hemolytic anemia, megaloblastic anemia
- basophilic stippling
  - deep blue granulations of variable size and number, pathologic aggregation of ribosomes
  - e.g. lead intoxication, thalassemia

Investigations (see Table 1)

Table 1. RDW (Red Cell Distribution Width)

<table>
<thead>
<tr>
<th>Normal</th>
<th>Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>anemia of chronic disease thalassemia</td>
<td>iron deficiency</td>
</tr>
<tr>
<td></td>
<td>dual deficiency (e.g. iron and folate)</td>
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<tr>
<td></td>
<td>myelodysplastic syndrome</td>
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<td></td>
<td>AIHA</td>
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<td></td>
<td>liver disease</td>
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<tr>
<td></td>
<td>pernicious anemia</td>
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<td>folate deficiency</td>
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</table>
ANEMIA

CLINICAL APPROACH TO ANEMIA
- acute vs chronic
- decreased production vs increased destruction
- anemia vs pancytopenia
- based on MCV
- rule out dilutional anemia (low Hb due to increased effective circulating volume)

<table>
<thead>
<tr>
<th>Table 2. Differential Diagnosis of Anemia Based on MCV</th>
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<tbody>
<tr>
<td><strong>Hypochromic microcytic</strong> (MCV&lt;80)</td>
</tr>
<tr>
<td>• Fe deficiency</td>
</tr>
<tr>
<td>• Thalassemia</td>
</tr>
<tr>
<td>• Lead Poisoning</td>
</tr>
<tr>
<td>• Sideroblastic</td>
</tr>
<tr>
<td>• Chronic disease (some cases)</td>
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Hematological History
- ID: background: Mediterranean, Asian, black (thalassemia), black (sick cell)
- presenting symptom & HPI: depend on how rapidly the anemia develops
  - fatigue, malaise, weakness, palpitations, syncope, dyspnea, headache, vertigo, tinnitus
- PMH: past anemias, therapies, past blood loss (GI/GU), blood donation history, menstrual history, signs/symptoms of renal, liver, endocrine disturbances, AIDS and other chronic diseases, malignancies
- family Hx: important in hereditary anemia; ask about anemia, jaundice, gallbladder disease, splenectomy
- medications: drugs may cause aplasia, macrocytic/megaloblastic states, hemolysis, blood loss
- diet: iron, folic acid, vitamin B12 supplementation: amount, frequency, duration, reason
- alcohol consumption: quantify amount and duration (toxic effect on bone marrow or anemia due to liver disease)

Physical Exam
- HEENT: pallor: mucous membranes, conjunctivae (Hb < 90 g/L), icterus, cervical lymphadenopathy, ocular bruits (Hb < 55 g/L), glossitis
- CVS: tachycardia, postural changes, systolic flow murmur, wide pulse pressure, CHF
- GI: hepatomegaly, splenomegaly, rectal (occult blood)
- skin: pallor, jaundice, skin creases (Hb < 75 g/L), telangiectasia as in hemolytic anemia, koilonychia (spoon-shaped nails) as in iron deficiency anemia

IRON METABOLISM

IRON INTAKE (Dietary)
- “average” Canadian adult diet = 10-20 mg Fe/day
- absorption = 5-10% (0.5-2 mg/day)
- males have a positive Fe balance
- menstruating females have a negative Fe balance

PHYSIOLOGIC CAUSES OF INCREASED FE REQUIREMENTS
- infancy-growth spurt
- puberty-growth spurt, menarche
- pregnancy-maternal RBC, fetus
- blood donation
- 500 mL blood = 250 mg Fe
- 4 donations/year = 1 g
Iron Absorption

- In duodenum, iron combines with apoferritin to form ferritin that is absorbed through villi.

<table>
<thead>
<tr>
<th>Table 3. Intraluminal Factors in Absorption of Non-Heme Iron</th>
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<tbody>
<tr>
<td><strong>Promoters</strong></td>
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<tr>
<td>Gastric HCl</td>
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<td>Reducing agents</td>
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<tr>
<td>• ascorbic acid</td>
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<tr>
<td>In Fe^{2+} form</td>
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<tr>
<td>Inorganic form</td>
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<tr>
<td>Soluble chelators</td>
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<tr>
<td>• amino acids</td>
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<td>• sugars</td>
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<td>• alcohol</td>
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Iron Transport

- Majority of non-heme Fe in plasma is bound to transferrin.
- Transferrin is a beta-globulin.
- Carries Fe from mucosal cell to RBC precursors in marrow.
- Carries Fe from storage pool in hepatocytes and macrophages to RBC precursors in marrow.

Iron Storage

- Fe is stored in two forms: ferritin and hemosiderin.
- Ferritin contains ferric Fe complexed to a protein called apoferritin.
- Hepatocytes are the main site of ferritin storage.
- Minute quantities are present in plasma in equilibrium with intracellular ferritin.
- Hemosiderin aggregates or crystals of ferritin with apoferritin partially removed.
- Macrophage-monocyte system is the main source of hemosiderin storage.

Iron Indices

- Bone marrow aspirate is the gold standard test for iron stores.
- Serum ferritin is the single most important blood test for iron stores.
- Serum iron is virtually all bound to transferrin but varies significantly daily.
- Total iron binding capacity (TIBC) is a measure of total amount of transferrin present in blood.
- Saturation is serum Fe divided by TIBC, expressed as a proportion or a %.

Interpreting Iron Indices

<table>
<thead>
<tr>
<th>Table 4. Interpreting Iron Indices</th>
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<tbody>
<tr>
<td><strong>Ferritin</strong></td>
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<tr>
<td>Iron Deficiency</td>
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<tr>
<td>Chronic Disease</td>
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<tr>
<td>Sideroblastic Anemia</td>
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<tr>
<td>Iron Overload</td>
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</table>
IRON METABOLISM . . . CONT.

LABORATORY FEATURES
- Fe stores diminished
  - decreased stainable iron in marrow
  - serum ferritin decreased
- Fe stores absent (in order of increasing Fe deficiency)
  - serum Fe falls
  - TIBC increases
  - hemoglobin falls
  - microcytosis (Hb levels of 100-110 g/L or 10-11 g/dL)
  - hypochromia (Hb 90-100 g/L or 9-10 g/dL)

IRON DEFICIENCY
- most common cause of anemia in Canada
- imbalance of intake vs. requirements or loss
- may indicate the presence of serious GI disease

PHYSIOLOGIC CAUSES
- increased need for iron in the body

PATHOLOGIC CAUSES
- in adult males and post-menopausal females, Fe deficiency is usually related to chronic blood loss
- dietary deficiencies (rarely the only etiology)
  - cow’s milk (infant diet)
  - “tea and toast” (elderly)
- absorption imbalances
  - post-gastrectomy
  - malabsorption
- hemorrhage
  - obvious causes - menorrhagia
  - occult - peptic ulcer disease, aspirin, GI tract cancer
- intravascular hemolysis
  - hemoglobinuria
  - hemosiderinuria
  - cardiac valve RBC fragmentation

CLINICAL PRESENTATION
- iron deficiency may cause fatigue before clinical anemia develops
- brittle hair
- dysphagia (esophageal web, Plummer-Vinson ring)
- nails
  - brittle
  - koilonychia
- glossitis
- angular stomatitis
- pica (appetite for bizarre substances e.g. ice, paint, dirt)

DIAGNOSIS
- major diagnostic difficulty is to distinguish from anemia of chronic disease
- serum
  - ferritin < 20 is diagnostic of iron deficiency anemia
  - iron deficiency anemia unlikely if ferritin > 22-322
  - platelet count may be elevated
- peripheral blood film (see Colour Atlas H3)
  - hypochromic microcytosis: RBCs are under hemoglobinized due to lack of Fe
  - pencil forms
  - target cells (thin)
- bone marrow
  - intermediate and late erythroblasts show micronormoblastic maturation
  - Fe stain (Prussian blue) shows decreased iron in macrophages
  - decreased normal sideroblasts

TREATMENT
- treat the underlying cause
- different preparations available: tablets, syrup, parenteral (if malabsorption)
- dose: ferrous sulphate 325 mg PO TID or ferrous gluconate 300 mg PO TID until anemia corrects and then for 3 months after
IRON DEFICIENCY . . . CONT.

**RECOVERY TIME**
- reticulocytes begin to increase after one week
- Hb normalizes by 10 grams per week
- if serum ferritin is normal then discontinue iron therapy

**ANEMIA REFRACTORY TO TREATMENT WITH ORAL IRON**
- medication
  - poor preparation (e.g. expired)
  - drug interactions
- patient
  - poor compliance
  - continued bleeding
  - malabsorption (rare)
- physician
  - misdiagnosis

**THE ANEMIA OF CHRONIC DISEASE**

**Etiology**
- infections
- cancer
- inflammatory and rheumatologic disease
- renal disease
- endocrine disorders (e.g. thyroid)

**Pathophysiology**
- a mild hemolytic component is often present
- red blood cell survival modestly decreased
- erythropoietin levels are normal or slightly elevated but are inappropriately low for the degree of anemia
- iron cannot be removed from its storage pool in hepatocytes and reticuloendothelial cells

**Diagnosis**
- a diagnosis of exclusion, biochemically rule out Fe deficiency
- serum
  - serum iron, TIBC, and % saturation all normal or slightly reduced
  - serum ferritin is normal or increased
- peripheral blood
  - usually normocytic and normochromic if the anemia is mild
  - may be microcytic and normochromic if the anemia is moderate
  - may be microcytic and hypochromic if the anemia is severe but rarely < 90 g/L
- bone marrow
  - normal or increased iron stores
  - decreased "normal" sideroblasts

**Management**
- resolves if underlying disease is treated
- erythropoietin may normalize the hemoglobin value
- dose of erythropoietin required higher than for patients with renal disease
- only treat patients who can benefit from a higher hemoglobin level

**LEAD POISONING**

L: Lead Lines on gingivae and epiphyses of long bones on X-ray
E: Encephalopathy and Erythrocyte basophilic stippling
A: Abdominal colic and microcytic Anemia
D: Drops: wrist and foot drop. Dimercaprol and EDTA as first line of treatment
SIDEROBLASTIC ANEMIA

- group of disorders with various defects in the porphyrin biosynthetic pathway leading to a reduction in heme synthesis resulting in an increase in cellular iron uptake
- characterized by presence of abnormal erythroid precursors in marrow

Types of Sideroblasts

- "normal" sideroblasts
  - aggregates of ferritin, diffusely spread throughout the red blood cell cytoplasm
  - small
  - found in normal individuals
- "ring" sideroblasts
  - iron deposited in the mitochondria forms a ring around the red blood cell nucleus
  - large
  - abnormal finding

Etiology

- hereditary
  - rare
  - X-linked (defective D-aminolevulinic acid synthetase – rate-limiting enzyme in heme synthesis)
  - median survival is 10 years
- acquired
  - primary
    - may be a preleukemic phenomenon (10%)
  - secondary
    - toxins
    - drugs (isoniazid), ethanol
    - neoplasms and consequent chemotherapy (alkylating agents)
    - collagen vascular disease

Diagnosis

- serum
  - iron overload: increased serum iron, normal TIBC, increased ferritin
- peripheral blood
  - dimorphic picture (normal and hypochromic population)
- bone marrow
  - required for diagnosis
  - bizarre megaloblastic changes
  - ring sideroblasts
  - increased iron stores

Management

- treatment of underlying cause
- oral pyridoxine (vitamin B6)
  - hereditary and secondary acquired forms usually responsive
  - myelodysplastic sideroblastic anemia not responsive

HEMOGLOBIN AND HEMOGLOBINOPATHIES

Hemoglobin Structure and Production

- 4 α genes are located on chromosome 16
- 2 β genes are located on chromosome 11
- heme group in center with iron
- fetal hemoglobin, HbF (δ2) switches to adult forms HbA (β2) and HbA2 (δ2) at 3-6 months of life
- HbA constitutes 97% of adult hemoglobin
- HbA2 constitutes 3% of adult hemoglobin
- beware of the possibility of mixed defects e.g. β-thalassemia minor and sickle cell trait

THALASSEMSIA

- defects in production of Hb β that leads to microcytosis

I. HETEROZYGOUS: β-Thalassemia Minor

- common among people of Mediterranean and Asian descent

Clinical Presentation

- depends on extent of disease
- mild or no anemia
- possible palpable spleen
- may be masked by Fe deficiency
HEMOGLOBIN AND HEMOGLOBINOPATHIES . . . CONT.

**Diagnosis**
- serum
  - Hb 90-140 g/L, MCV < 70
- peripheral blood
  - microcytosis + hypochromia
  - target cells and increased poikilocytosis (“fish RBC”) may be present
  - basophilic stippling usually present
- Hb electrophoresis
  - specific: Hb A2 increased to 0.025-0.05 (2.5-5%) (normal 1.5-3.5%)
  - non-specific: 50% have slight increase in HbF

**Management**
- not necessary to treat
- patient and family should receive genetic counselling

**II. HOMOZYGOUS: β-Thalassemia Major**

**Pathophysiology**
- autosomal recessive
- ineffective chain synthesis leading to ineffective erythropoiesis and hemolysis of RBC
- increase in HbF

**Clinical Presentation**
- initial presentation at 3-6 months due to replacement of HbF by HbA
- severe anemia develops in the first year of life
- jaundice
- stunted growth and development (hypogonadal dwarf)
- gross hepatosplenomegaly (extramedullary hematopoiesis)
- changes (expanded marrow cavity)
  - skull x-ray has “hair-on-end” appearance
  - pathological fractures common
- evidence of increased Hb catabolism (e.g. gallstones)
- death from
  - untreated anemia (transfuse)
  - infection (treat early)
  - hemochromatosis (late, secondary to transfusions), usually 20-30 years old

**Diagnosis**
- CBC
  - hemoglobin 40-60 g/L
- peripheral blood
  - hypochromic microcytosis
  - increased reticulocytes
  - basophilic stippling, target cells
  - postsplenectomy blood film shows Howell Jolly bodies, erythroblasts, and thrombocytosis
- Hb electrophoresis
  - Hb A: 0-0.10 (0-10%), (normal > 95%)
  - Hb F: 0.90-1.00 (90-100%)

**Management**
- transfusion
- Fe chelation to prevent iron overload (e.g. desferal)
- bone marrow transplant

**III. ALPHA THALASSEMIA**
- similar distribution to thalassemia but a higher frequency among Asians

**Pathophysiology**
- autosomal recessive
- deficit of α chains
- 4 grades of severity depending on the number of defective alpha genes
  - 1 - silent
  - 2 - trait
  - 3 - HbH Disease (presents in adults due to excess chain production)
  - 4 - Hb Bart’s (hydrops fetalis, not compatible with life)

**Diagnosis**
- peripheral blood film
  - microcytes, hypochromia, occasional target cells
  - screen for HbH inclusion bodies
- Hb electrophoresis not diagnostic
- DNA analysis using alpha gene probe
HEMOGLOBIN AND HEMOGLOBINOPATHIES . . . CONT.

Management
- same as β thalassemia

SICKLE CELL ANEMIA
- autosomal recessive
- amino acid substitution of valine for glutamate in position 6 of beta globin chain

Mechanisms of Sickling (see Figure 1)
- at low pO2, deoxy Hb S polymerizes, leading to rigid crystal-like rods that distort membranes = SICKLES
- the pO2 level at which sickling occurs is related to the percentage of Hb S present
  - in heterozygotes (Hb AS) sickling occurs at a pO2 of 40 mmHg
  - in homozygous (Hb SS), sickling occurs at a pO2 of 80 mmHg
- sickling is aggravated by
  - increased H+
  - increased CO2
  - increased 2,3-DPG
  - increased temperature and osmolality

![Figure 1. Pathophysiology of Sickling](image)

Heterozygous: Hb S Trait
- clinical presentation
  - patient will appear normal except at times of extreme hypoxia and infection
- diagnosis
  - serum: Hb normal
  - peripheral blood: normal except for possibly a few target cells
  - Hb electrophoresis (confirmatory test): Hb A fraction of 0.65 (65%); Hb S fraction of 0.35 (35%)

Homzygous: Hb S Disease
- clinical presentation
  - chronic hemolytic anemia
  - jaundice in the first year of life
  - vaso-occlusive crises (infarction) leading to pain, fever and leukocytosis
    e.g. acute chest syndrome (pulmonary infarct) associated with infection, such as parvovirus, leading to aplastic anemia, acidosis, dehydration, and hypoxia
  - susceptibility to infections by encapsulated organisms due to hyposplenism
  - retarded growth and development +/- skeletal changes
  - spleen enlarged in child and atrophic in adult
- diagnosis
  - peripheral blood: sickled cells (see Colour Atlas H6)
  - screening test: sickle cell prep
  - Hb electrophoresis (confirmatory test): Hb S fraction > 0.80

Management
- prevention of crises is the key
  - establish diagnosis
  - avoid conditions that favor sickling (hypoxia, acidosis, dehydration, fever)
  - vaccination in childhood e.g. pneumococcus, meningococcus
  - consider prophylaxis - penicillin V 250 mg PO bid
  - good hygiene and nutrition
- genetic counselling
- folic acid to avoid folate deficiency
HEMOGLOBIN AND HEMOGLOBINOPATHIES ... CONT.

- hydroxyurea to enhance production of HbF
  - causes depression of the gene for HbF or by initiating differentiation of stem cells in which this gene is active; presence of HbF in the SS cells decreases polymerization and precipitation of HbS
  - Note: hydroxyurea is cytotoxic and may cause bone marrow suppression

<table>
<thead>
<tr>
<th>Table 5. Organs Affected by Vaso-Occlusive Crisis</th>
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<tbody>
<tr>
<td><strong>Organ</strong></td>
</tr>
<tr>
<td>brain</td>
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<td>digits</td>
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<tr>
<td>femoral head</td>
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<td>bone</td>
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<td>ankle</td>
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**Treatment of Vaso-Occlusive Crisis**
- oxygen
- hydration (reduces viscosity)
- antimicrobials
- correct acidosis
- analgesics/narcotics (give enough)
- magnesium (inhibits potassium and water efflux from RBCs thereby preventing dehydration)
- exchange transfusion for CNS crisis
- experimental anti-sickling agents

**MEGALOBLASTIC ANEMIA**
- failure of DNA synthesis resulting in asynchronous maturation of RBC nucleus and cytoplasm
- non-megaloblastic anemia reflects membrane abnormality with abnormal cholesterol metabolism
- megaloblast = large, nucleated RBC precursor; macrocyte = large RBC

**Causes of Megaloblastosis**
- folate deficiency (seen after 4 months of decreased intake)
- B12 deficiency (seen after 10-15 years decreased intake)
- antimetabolite drugs
  - methotrexate
  - folate analogues (sulpha drugs)
  - purine/pyrimidine analogues (6-MP, 5-FU)
- nitrous oxide
- myelodysplasia/some cases of AML

**B12 DEFICIENCY**

**Etiology**
- if intake stops abruptly body stores last 3-4 years
- diet
  - strict vegetarian (rare)
- gastric
  - mucosal atrophy of pernicious anemia
  - post-gastrectomy
- intestinal absorption
  - malabsorption (e.g. Crohn's, celiac sprue, pancreatic disease)
  - stagnant bowel (e.g. blind loop, stricture)
  - fish tapeworm
  - resection of ileum as in Crohn's and celiac sprue
- rare genetic causes
HEMOGLOBIN AND HEMOGLOBINOPATHIES . . . CONT.

Pernicious Anemia
- auto-antibodies produced against gastric parietal cells leading to achlorhydria and no intrinsic factor secretion
  - intrinsic factor is required to stabilize B12 as it passes through the bowel
  - decreased intrinsic factor leads to decreased ileal absorption of B12
- female: male = 1.6:1
- may be associated with other autoimmune disorders e.g. thyroid and adrenal deficiency
- often > 60 years old

Neurological Lesions in B12 Deficiency
- cerebral (common; reversible with B12 therapy)
  - confusion
  - delirium
  - dementia
- cranial nerves
  - optic atrophy (rare)
- cord (irreversible damage)
  - subacute combined degeneration
  - posterior columns - paresthesias, disturbed vibration, decreased proprioception
  - pyramidal tracts - spastic weakness, hyperactive reflexes
- peripheral neuropathy (variable reversibility)
  - usually symmetrical
  - affecting lower limbs more than upper limbs

Diagnosis
- serum
  - anemia often severe +/- neutropenia +/- thrombocytopenia
  - MCV > 120
  - low reticulocyte count relative to the degree of anemia
- serum B12 and RBC folate
  - caution: low serum B12 leads to low RBC folate because of failure of folate polyglutamate synthesis in the absence of B12
- blood film
  - oval macrocytes (see Colour Atlas H2A)
  - hypersegmented neutrophils (see Colour Atlas H2B)
- bone marrow
  - differentiates between megaloblastic and myelodysplastic anemias
  - hypercellularity
  - failure of nuclear maturation
  - elevated unconjugated bilirubin and LDH due to marrow cell breakdown
- Schilling test to distinguish pernicious anemia from other causes
  - Schilling test: part 1
    - tracer dose (1g µg) of labelled B12 (cobalamin (Co*)), PO
    - flushing dose (1mg) of cold B12, IM to saturate tissue binders of B12 thus allowing radioactive B12 to be excreted in urine
    - 24 hour urine Co* measured
      - normal —> 5% excretion
  - Schilling test: part 2
    - tracer dose B12 (Co*) plus intrinsic factor, PO
    - flushing dose of cold B12, injected IM
    - 24 hour urine Co* measured
    - normal test result (> 5% excretion) = pernicious anemia
    - abnormal test result (< 5% excretion) = intestinal causes (malabsorption)

Management
- B12 100 µg IM monthly for life or oral B12
- watch for hypokalemia (due to return of potassium to intracellular sites) and thrombocythemia

FOLATE DEFICIENCY
- more common than B12 deficiency because folate stores are depleted in 3-6 months
- folate complexes with gastric R binder
- R binder is replaced by intrinsic factor in the duodenum
- this complex is absorbed in the jejunum

Etiology
- diet (folate is present in leafy green vegetables)
  - most common cause
  - e.g. infancy, poverty, alcoholism
- intestinal
  - malabsorption
HEMOGLOBIN AND HEMOGLOBINOPATHIES . . . CONT.

- drugs/chemicals
  - alcohol
  - anticonvulsants
  - antifolates (MTX)
  - birth control pills
- increased demand
  - pregnancy
  - prematurity
  - hemolysis
  - hemodialysis
  - psoriasis, exfoliative dermatitis

Clinical Presentation
- mildly jaundiced due to hemolysis of RBC secondary to ineffective hemoglobin synthesis
- glossitis and angular stomatitis
- rare
  - melanin pigmentation
  - purpura secondary to thrombocytopenia
- folic acid deficiency at time of conception and early pregnancy has been linked to neural tube defects

Management
- never give folic acid alone to individual with megaloblastic anemia because it will mask B12 deficiency and neurological degeneration will continue
- folic acid 15 mg PO/day x 3 months; then 5 mg PO/day maintenance if cause not reversible
- folic acid supplementation 1 mg PO/day will protect against elevated homocysteine levels (risk factor for CAD)

HEMOLYTIC ANEMIAS (HA) (see Colour Atlas H4)

Classification
- hereditary causes (intrinsic)
  - abnormal membrane (spherocytosis, elliptocytosis)
  - abnormal enzymes (pyruvate kinase deficiency, G6PD deficiency)
  - abnormal hemoglobin synthesis (thalassemias, hemoglobinopathies)
- acquired causes (extrinsic)
  - immune
    - hemolytic transfusion reaction
    - idiopathic immune HA
    - drugs
    - cold agglutinins
    - secondary autoimmune HA
  - non-immune
    - RBC fragmentation syndromes
    - paroxysmal nocturnal hemoglobinuria
    - liver disease
    - hypersplenism
    - march hemoglobinuria

Clinical Presentation
- jaundice
- cholelithiasis
- splenomegaly
- skeletal abnormalities
- leg ulcers
- regenerative crisis
- folic acid deficiency
- iron overload with extravascular hemolysis
- iron deficiency with intravascular hemolysis

Diagnosis
- indirect - not specific to hemolytic anemias
  - increased reticulocyte count
  - reduced haptoglobin
  - increased unconjugated bilirubin
  - increased urine bilirubin
  - increased LDH
- tests exclusive for intravascular hemolysis
  - serum free hemoglobin present
  - methemalbuminemia (heme + albumin)
  - hemoglobinuria (immediate)
  - hemosiderinuria (delayed)
HEMOGLOBIN AND HEMOGLOBINOPATHIES . . . CONT.

Antiglobulin Tests (Coombs’ Tests)
- direct Coombs’ test (direct antiglobulin test)
  - purpose: detect antibodies or complement on the surface of RBC
  - by adding anti-antibodies to the RBC; the RBC agglutinate in a positive test
  - indications
    - hemolytic disease of newborn
    - hemolytic anemia
    - AIHA
    - hemolytic transfusion reaction
- indirect Coombs’ test (indirect antiglobulin test)
  - purpose: detect antibodies in serum that can recognize antigens on RBC
  - by mixing serum with donor RBC and then anti-antibodies; RBCs agglutinate in a positive test
  - indications
    - cross-matching of recipient serum with donor’s RBC
    - atypical blood group
    - blood group antibodies in pregnant women
    - antibodies in AIHA

I. HEREDITARY HEMOLYTIC ANEMIAS

STRUCTURAL ABNORMALITIES IN CYTOSKELETON

Hereditary Spherocytosis
- autosomal dominant with variable penetrance
- incidence 22 per 100,000
- most common type of hereditary hemolytic anemia
- abnormality in spectrin (compound in RBC membrane)
- blood film shows spherocytes (see Colour Atlas H8)
- increased osmotic fragility
- sometimes confused with immune hemolytic anemia
- treatment: splenectomy (immunize against pneumococcus first); avoid in childhood

Hereditary Elliptocytosis
- autosomal dominant
- incidence 20-50 per 100,000
- abnormality in spectrin interaction with other membrane proteins
- 25-75% elliptocytes
- hemolysis is usually mild
- treatment: splenectomy for severe hemolysis (immunize against pneumococcus first)

ENZYMATIC ABNORMALITIES IN RBC

G6PD Deficiency

Clinical Presentation
- X-linked recessive
- oxidant drug-induced hemolysis
  - sulfonamides
  - primaquine
  - nitrofurantoin
  - acetanilid
- favism (fava beans)
- neonatal jaundice
- chronic hemolytic anemia
- infection

Diagnosis and Management
- high index of suspicion
- G6PD assay
  - should not be done when reticulocyte count is high in acute crisis.
  - PBF shows Heinz bodies (granules in red blood cells due to damaged hemoglobin molecules) and features of intravascular hemolysis
- transfusion in severe cases
- stop offending drugs or food
II. ACQUIRED HEMOLYTIC ANEMIAS

AUTOIMMUNE HEMOLYTIC ANEMIA

Table 6. Classification of autoimmune hemolytic anemia

<table>
<thead>
<tr>
<th></th>
<th>Warm</th>
<th>Cold</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibody Coating RBC</strong></td>
<td>• IgG</td>
<td>• IgM</td>
</tr>
<tr>
<td><strong>Temperature Detect by Coomb's</strong></td>
<td>• 37°C</td>
<td>• 4-37 ºC</td>
</tr>
<tr>
<td><strong>Direct Coombs Test</strong></td>
<td>• positive for antibodies</td>
<td>• positive for complement</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td>• idiopathic</td>
<td>• idiopathic</td>
</tr>
<tr>
<td></td>
<td>• secondary to lymphoproliferative disorder</td>
<td>• secondary to infection</td>
</tr>
<tr>
<td></td>
<td>• e.g. CLL, Hodgkin's</td>
<td>• e.g. mycoplasma, EBV</td>
</tr>
<tr>
<td></td>
<td>• secondary to autoimmune disease</td>
<td>• secondary to lymphoproliferative disorder</td>
</tr>
<tr>
<td></td>
<td>• e.g. SLE</td>
<td>• e.g. macroglobulinemia, CLL</td>
</tr>
<tr>
<td></td>
<td>• drug induced</td>
<td>• infection</td>
</tr>
<tr>
<td></td>
<td>• penicillin</td>
<td>• e.g. macroglobulinemia, CLL</td>
</tr>
<tr>
<td></td>
<td>• quinine</td>
<td>• e.g. Macroglobulinemia</td>
</tr>
<tr>
<td></td>
<td>• methyldopa</td>
<td>• vasculitis</td>
</tr>
<tr>
<td><strong>Blood Film (see Colour Atlas H5)</strong></td>
<td>• spherocytes</td>
<td>• agglutination</td>
</tr>
<tr>
<td><strong>Management</strong></td>
<td>• treat underlying cause</td>
<td>• treat underlying cause</td>
</tr>
<tr>
<td></td>
<td>• corticosteroids</td>
<td>• warm patient</td>
</tr>
<tr>
<td></td>
<td>• splenectomy</td>
<td>• plasmapheresis</td>
</tr>
<tr>
<td></td>
<td>• immunosuppression</td>
<td>• immunosupression</td>
</tr>
</tbody>
</table>

**RBC FRAGMENTATION SYNDROMES**

**Classification**
- cardiac and large vessel abnormalities (macroangiopathic)
- small vessel disease (microangiopathic) *(see Colour Atlas H7)*
  - thrombotic thrombocytopenic purpura (TTP)/ hemolytic uremic syndrome (HUS)
  - DIC
  - metastatic carcinoma
  - eclampsia
  - malignant hypertension
  - vasculitis
- infection (malaria, clostridia)
- drowning
- thermal injury

**Diagnosis**
- evidence of hemolysis, schistocytes, hemosiderinuria, hemoglobinuria

**Management**
- treat underlying disease, replace iron if indicated
THROMBOTIC THROMBOCYTOPENIC PURPURA AND HEMOLYTIC UREMIC SYNDROME

**Table 7. Thrombotic Thrombocytopenic Purpura (TTP) and Hemolytic Uremic Syndrome (HUS)**

<table>
<thead>
<tr>
<th>TTP</th>
<th>HUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• predominantly adult</td>
<td>• predominantly children</td>
</tr>
<tr>
<td><strong>neurological symptoms (90%)</strong></td>
<td><strong>purpura (90-100%) due to severe thrombocytopenia</strong></td>
</tr>
<tr>
<td>• H/A, somnolence, confusion, focal neurological findings, convulsion, stupor, coma</td>
<td>• microangiopathic hemolytic anemia</td>
</tr>
<tr>
<td>• purpura (90%) due to severe thrombocytopenia</td>
<td>• renal symptoms (90%)</td>
</tr>
<tr>
<td>• epistaxis, hematuria, hemoptysis and GI bleed</td>
<td>• abnormal UA, oliguria, ARF</td>
</tr>
<tr>
<td>• epistaxis, hematuria, hemoptysis and GI bleed</td>
<td>• etiology</td>
</tr>
<tr>
<td>• microangiopathic hemolytic anemia</td>
<td>• E. coli serotype O157:H7 virotoxin</td>
</tr>
<tr>
<td>• fever (90-100%)</td>
<td>• diagnosis</td>
</tr>
<tr>
<td>• GI</td>
<td>• by clinical picture</td>
</tr>
<tr>
<td>• N/V, abdominal pain</td>
<td>• same as TTP</td>
</tr>
<tr>
<td><strong>renal (40-80%)</strong></td>
<td>• stool C+S</td>
</tr>
<tr>
<td>• abnormal UA, oliguria, ARF</td>
<td>• idiopathic</td>
</tr>
<tr>
<td>• etiology</td>
<td>• paroxysmal nocturnal hemoglobinuria</td>
</tr>
<tr>
<td>• idiopathic</td>
<td>• marrow replacement</td>
</tr>
<tr>
<td>• familial</td>
<td>• congenital</td>
</tr>
<tr>
<td>• secondary TTP</td>
<td><strong>Clinical Presentation</strong></td>
</tr>
<tr>
<td>• infection</td>
<td>• occurs at any age</td>
</tr>
<tr>
<td>• enterobacteriaceae</td>
<td>• slightly more common in males</td>
</tr>
<tr>
<td>• viral: flu, HIV</td>
<td>• can present acutely or insidiously</td>
</tr>
<tr>
<td>• systemic diseases</td>
<td>• anemia or neutropenia or thrombocytopenia (any combination) +/- pancytopenia</td>
</tr>
<tr>
<td>• SLE and other CVD</td>
<td>• thrombocytopenia with bruising, bleeding gums, epistaxis</td>
</tr>
<tr>
<td>• cancer and chemotherapeutic drugs</td>
<td>• anemia with SOB, pallor and fatigue</td>
</tr>
<tr>
<td>• diagnosis</td>
<td><strong>Management</strong></td>
</tr>
<tr>
<td>• by clinical picture</td>
<td>• plasmapheresis is the treatment of choice</td>
</tr>
<tr>
<td>• CBC: anemia, thrombocytopenia</td>
<td>• steroid is treatment of choice only in mild disease</td>
</tr>
<tr>
<td>• PT, PTT: normal</td>
<td>• stool C+S</td>
</tr>
<tr>
<td>• ESR: normal</td>
<td>• negative Coombs’</td>
</tr>
</tbody>
</table>

*Key characteristics bolded

**APLASTIC ANEMIA**

- destruction of hematopoietic cells of the bone marrow

**Etiology**

- radiation
- drugs
  - anticipated (chemotherapy)
  - idiosyncratic (chloramphenicol, phenylbutazone)
- chemicals
  - benzene and other organic solvents
  - DDT and insecticides
- post viral e.g. hepatitis B, parvovirus
- idiopathic
  - often immune (T-cell mediated)
- paroxysmal nocturnal hemoglobinuria
- marrow replacement
- congenital

**Clinical Presentation**

- occurs at any age
- slightly more common in males
- can present acutely or insidiously
- anemia or neutropenia or thrombocytopenia (any combination) +/- pancytopenia
- thrombocytopenia with bruising, bleeding gums, epistaxis
- anemia with SOB, pallor and fatigue
APLASTIC ANEMIA . . . CONT.

- presentation of neutropenia ranges from infection in the mouth to septicemia
- absence of splenomegaly

**Diagnosis**
- serum
  - neutrophil count < 5.0 x 10⁹/L
  - platelet count < 20 x 10⁹/L
  - corrected reticulocyte count < 1%
- blood film
  - decreased normal RBC
- bone marrow
  - aplasia or hypoplasia of marrow cells with fat replacement

**Management**
- removal of offending agents
- supportive care (red cell and platelet transfusions, antibiotics)
- antithymocyte globulin (90-60% patients respond)
- cyclosporine
- allogeneic bone marrow transplantation
  - minimize blood products on presentation
  - only irradiated, leuko-depleted blood products should be used
  - CMV negative blood for CMV negative patients

HEMOSTASIS

THREE PHASES OF HEMOSTASIS

**Primary Hemostasis**
- goal is to rapidly stop bleeding
- vessel injury results in collagen and subendothelial structure exposure and release of vasoconstrictors
- blood flow is impeded and platelets come in contact with vessel wall
- platelets adhere to collagen and are activated resulting in change of shape and release of ADP and thromboxane A₂
- these factors further recruit and aggregate more platelets resulting in formation of hemostatic plug

![Diagram of Primary Hemostasis]

**Secondary Hemostasis**
- platelet plug formed through primary hemostasis is reinforced through process of secondary hemostasis and a stable plug is formed
- secondary pathways involved in the activation of coagulation factors include
  - intrinsic
    - activated when vessel wall remains intact
    - slow pathway
  - extrinsic
    - activated when there is injury to vessel wall
    - fast pathway
HEMOSTASIS . . . CONT.

Figure 3. Secondary Hemostasis

Figure 4. Fibrin Stabilization and Fibrinolysis

TESTS OF HEMOSTASIS

Table 8. Commonly Used Tests of Hemostasis

<table>
<thead>
<tr>
<th>Type of hemostasis</th>
<th>Test</th>
<th>Reference Range</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>platelet count</td>
<td></td>
<td>• to quantitate platelet number</td>
</tr>
<tr>
<td></td>
<td>bleeding time</td>
<td>2-12 mins</td>
<td>• platelet function</td>
</tr>
<tr>
<td></td>
<td>platelet aggregation</td>
<td></td>
<td>• platelet function</td>
</tr>
<tr>
<td>Secondary</td>
<td>PTT - depends on lab</td>
<td>22-35 s</td>
<td>• measures intrinsic pathway factors VIII, IX, XI, XII</td>
</tr>
<tr>
<td></td>
<td>PT - depends on lab</td>
<td>11-24 s</td>
<td>• measures extrinsic pathway factor VIII in particular</td>
</tr>
<tr>
<td></td>
<td>TT - depends on lab</td>
<td>14-16 s</td>
<td>• measures deficiency of fibrinogen inactivation of prothrombin</td>
</tr>
<tr>
<td></td>
<td>INR</td>
<td>1 is normal</td>
<td>• permits determination of coagulation status independent of laboratory performing measurement</td>
</tr>
<tr>
<td>Fibrinolysis</td>
<td>euglobulin lysis time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>• fibrinogen</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• fibrinogen degradation products (FDPs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• specific factor assays</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• tests of physiological inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(antithrombins, protein S, protein C,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>hereditary resistance to APC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• tests of pathologic inhibitors (e.g.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>lupus anticoagulant)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 9. Signs and Symptoms of Disorders of Hemostasis

<table>
<thead>
<tr>
<th></th>
<th>Primary (Platelet)</th>
<th>Secondary (Coagulation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface Cuts</td>
<td>excessive, prolonged</td>
<td>normal/slightly prolonged</td>
</tr>
<tr>
<td>Onset After Injury</td>
<td>immediate</td>
<td>delayed</td>
</tr>
<tr>
<td>Typical Type and Site of Bleeding</td>
<td>superficial i.e. mucosal (nasal, gingival,GI tract, uterine), petechiae</td>
<td>deep i.e. into joints, muscles, GI tract, GU tract, excessive, post-traumatic</td>
</tr>
</tbody>
</table>

**THROMBOCYTOPENIA AND OTHER DISORDERS OF PRIMARY HEMOSTASIS**

- inability to form an adequate platelet plug due to
  1. disorders of blood vessels
  2. disorders of platelets  
      - abnormal function  
      - abnormal numbers

**Classification**

**Vascular (Non-Thrombocytopenic Purpura)**

- hereditary  
  - hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu)  
  - connective tissue disorders
- acquired  
  - purpura simplex (easy bruising)  
  - senile purpura  
  - dysproteinemias  
  - Henoch-Schonlein Purpura  
  - scurvy  
  - Cushing's syndrome  
  - infections  
  - drugs

**Platelets**

- dysfunction  
  - hereditary  
    - von Willebrand's disease, others (rare)  
  - acquired  
    - drugs eg. ASA, EtOH, NSAIDs  
    - uremia  
    - myeloproliferative disorders  
    - dysproteinemias
- thrombocytopenia (usually acquired)  
  - decreased production  
  - drugs, toxins  
  - radiation  
  - marrow infiltrate or failure  
  - ineffective production  
  - megaloblastic anemias  
  - myelodysplasia  
  - vitamin B12, folic acid or iron deficiency  
  - viral infections eg. varicella, mumps, HIV, EBV, CMV, parvo  
  - increased destruction  
  - drugs eg. quinidine, sulfas, thiazides, heparin  
  - ITP  
  - allo-antibodies  
  - HIV positive  
  - sepsis
- increased consumption  
  - DIC  
  - microangiopathies (TTP)  
- sequestration  
  - splenomegaly  
- dilutional  
  - massive transfusion with stored blood
IDIOPATHIC (AUTOIMMUNE) THROMBOCYTOPENIC PURPURA (ITP)

Table 10. Idiopathic Thrombocytopenic Purpura

<table>
<thead>
<tr>
<th>Features</th>
<th>Acute ITP</th>
<th>Chronic ITP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Age</td>
<td>2-6 years</td>
<td>20-40 years</td>
</tr>
<tr>
<td>Sex Predilection</td>
<td>none</td>
<td>F &gt; M (3:1)</td>
</tr>
<tr>
<td>History of Recent Infection</td>
<td>common</td>
<td>rare</td>
</tr>
<tr>
<td>Onset of Bleed</td>
<td>abrupt</td>
<td>insidious</td>
</tr>
<tr>
<td>Platelet Count</td>
<td>&lt; 20 x 10⁹/L</td>
<td>30-80 x 10⁹/L</td>
</tr>
<tr>
<td>Duration</td>
<td>usually weeks</td>
<td>months to years</td>
</tr>
<tr>
<td>Spontaneous Remissions</td>
<td>80% or more</td>
<td>uncommon</td>
</tr>
</tbody>
</table>

CHRONIC (ADULT-TYPE) ITP
- most common cause of isolated thrombocytopenia
- diagnosis of exclusion

Pathophysiology
- IgG autoantibody
- spleen
  - site of antibody production and platelet destruction
  - usually not palpable (enlarged in ~ 10%)

Clinical Presentation
- insidious onset
- may be seen after mild viral illness or after immunization
- mucosal or skin bleeding
- petechiae and easy bruising
- hematuria
- melena
- epistaxis
- female with menorrhagia

Laboratory Results
- peripheral blood film: decreased platelets, large platelets
- bone marrow: plentiful megakaryocytes
  - critical test to rule out other causes of thrombocytopenia
- anti-platelet antibodies present in most
- increased bleeding time
- PT and PTT normal

Management
- conservative if mild
  - platelet count > 30,000, no mucosal bleeding
- steroids: moderate dose, then taper (80% responsive)
  - platelet count < 20-30,000 or evidence of mucosal bleeding
- splenectomy if steroids fail
- IV gamma globulin if steroids and splenectomy fail or if rapid response is required
- other: immunosuppressives, platelets, plasma exchange, Danazol

Prognosis
- fluctuating course
- overall relatively benign, mortality 1-2%
- major concern is cerebral hemorrhage at platelet counts < 5 x 10⁹/L

DISORDERS OF SECONDARY HEMOSTASIS

Classification

I. Hereditary
- Factor VIII: Hemophilia A, von Willebrand's disease
- Factor IX: Hemophilia B (Christmas Disease)
- Factor XI
- other factor deficiencies are rare
HEMOSTASIS . . . CONT.

II. Acquired
- liver disease
- DIC
- vitamin K deficiency
- circulating anti-coagulants (inhibitors)
- other e.g. primary fibrinolysis

HEREDITARY

I. Hemophilia A (factor VIII)
- X-linked, 1/5,000 males
- mild (> 5%), moderate (1-5%), severe (< 1%)

Clinical Presentation
- hemarthroses, hematomas, GI and GU bleeding
- bleeding in response to trauma (mild and moderate disease)
  • intracranial hemorrhage following head injury
- spontaneous bleeding (severe disease)

Laboratory Results
- prolonged PTT, normal INR (PT)
- decreased factor VIII (< 40% of normal)
- vWF usually normal or increased

Management
- minor but not trivial bleeding (e.g. hemarthroses)
  • heat treated Factor VIII concentrate
- major potentially life-threatening bleeding (e.g. multiple trauma)
  • heat treated Factor VIII concentrate
- prophylaxis (e.g. multiple dental extractions, surgery)
  • heat treated Factor VIII concentrate
- DDAVP in mild or moderate hemophilia A

II. Von Willebrand's Disease
- heterogeneous group of defects
- usually autosomal dominant
- qualitative or quantitative abnormality of vWF
  • vWF needed for platelet adhesion and acts as carrier for factor VIII
  • vWF exists as a series of multimers ranging in size
    • the largest ones are most active in mediation of platelet adhesion
    • both large and small complex with factor VIII
- both primary and secondary hemostasis affected
- usually mild to moderate in severity

Classification
- type I: decreased vWF in platelets and plasma (will see prolonged bleeding time, decreased factor VIII)
- type II A: decreased large and intermediate sized multimers in plasma and platelets (will see prolonged bleeding time, normal levels of factor VIII)
- type II B: largest multimers are missing from plasma but not from platelets

Clinical Presentation
- mild
  • asymptomatic
  • mucosal and cutaneous bleeding, easy bruising, epistaxis, menorrhagia, gingival bleeding
- moderate to severe
  • as above but worse, occasionally soft-tissue hematomas, petechiae (rare), GI bleeding, hemarthroses

Course
- may fluctuate, often improves during pregnancy and with age

Laboratory Results
- prolonged bleeding time and PTT
- decreased factor VIII (5-50%)
- normal platelet count (except in Type IIB)
- decreased ristocetin cofactor activity
- analysis of multimers

Management
- DDAVP is treatment of choice except in Type IIB
  • causes release of vWF and plasminogen activator from endothelial cells
    - in type II B, the appearance of the large multimers in the circulation can cause thrombocytopenia
- Hemate P in selected cases
- conjugated estrogens
HEMOSTASIS . . . CONT.

III. Factor IX Deficiency
- Christmas disease, Hemophilia B
- X-linked recessive, 1/30,000 males
- clinical and laboratory features identical to Hemophilia A
- main treatment is Factor IX concentrate

IV. Factor XI Deficiency (Rosenthal syndrome)
- autosomal recessive inheritance
- usually mild, often diagnosed in adulthood
- treatment: fresh frozen plasma

ACQUIRED

I. Liver Disease
- deficient synthesis of all factors except VIII
- aberrant synthesis: fibrinogen
- deficient clearance of hemostatic “debris” and fibrinolytic activators
- accelerated destruction due to dysfibrinogenemias: increased fibrinolysis, DIC
- thrombocytopenia: hypersplenism, folate deficiency, EtOH intoxication, DIC
- platelet dysfunction: EtOH abuse
- miscellaneous: inhibition of secondary hemostasis by FDPs
- peripheral blood smear: target cells
- diagnosis
  - factor V because it has the shortest half-life
  - elevated INR (PT), PTT and bleeding time
  - treatment: fresh frozen plasma, platelets

II. Vitamin K Deficiency

Etiology
- poor diet (especially in alcoholics)
- biliary obstruction
- chronic liver disease
- malabsorption e.g. celiac disease
- drugs
  - oral anticoagulants produce inhibition of factors II, VII, IX, X, Protein C & S
  - antibiotics eradicating gut flora which is 50% of vitamin K supply
- hemorrhagic disease of newborn

Diagnosis
- INR (PT) is elevated out of proportion to the elevation of the PTT
- decreased factors II, VII, IX and X (because vitamin K-dependent)

Management
- vitamin K 10-20 mg SC (not IM)
- Note: PT should improve within 24 hours, if not search for other causes

III. Disseminated Intravascular Coagulation (DIC)
- massive uncontrolled intravascular coagulation resulting in depletion of platelets, coagulation factors and fibrinogen
- not a primary disorder but a syndrome that complicates a number of other conditions

Clinical Conditions Associated with DIC
- activation of procoagulant activity
  - anti-phospholipid antibody
  - intravascular hemolysis (incompatible blood, malaria)
  - tissue factor
  - tissue injury (obstetric catastrophes, leukemia, tumours, liver disease, trauma, burns)
  - snakebite
  - fat embolism
  - heat stroke
- endothelial injury
  - infections
  - vasculitis
  - metastatic disease (adenocarcinoma)
  - aortic aneurysm
  - giant hemangioma
- reticuloendothelial injury
  - liver disease
  - splenectomy
HEMOSTASIS . . . CONT.

- vascular stasis
  - hypotension
  - hypovolemia
  - pulmonary embolus
- other
  - acute hypoxia/acidosis
  - extracorporeal circulation

**Signs of Microvascular Thrombosis (Early DIC)**
- neurological: multifocal, delirium, coma, seizures
- skin: focal ischemia, superficial gangrene
- renal: oliguria, azotemia, cortical necrosis
- pulmonary: ARDS
- GI: acute ulceration
- RBC: microangiopathic hemolysis

**Signs of Hemorrhagic Diathesis (Late DIC)**
- neurological: intracranial bleeding
- skin: petechiae, ecchymosis, oozing from puncture sites
- renal: hematuria
- mucosal: gingival oozing, epistaxis, massive bleeding

**Diagnosis**
- clinical picture
- laboratory
  - primary hemostasis: decreased platelets
  - secondary hemostasis: prolonged INR (PT), PTT, TT, decreased fibrinogen and other factors
  - fibrinolysis increased FDPs, short lysis time
  - extent of fibrin deposition: urine output, urea, RBC fragmentation

**Management**
- recognize early
- TREAT UNDERLYING DISORDER
- life support measures, O2, blood transfusion, fluid therapy
- replacement of hemostatic elements with platelet transfusion, FFP, cryoprecipitate

**THROMBOSIS**

**Virchow's Triad**
- stasis
- hypercoagulable state
- endothelial injury

**Etiology**
- endothelial damage
- blood flow
  - stasis
  - turbulence
  - hyperviscosity
- blood components
  - platelets
  - contact factors
  - thrombin
  - Factor VIII
  - fibrin
- hypercoagulable state due to
  - cancer
  - pregnancy
  - birth control pills
  - DIC
  - lipids
  - decreased physiological inhibitors (antithrombin-III, protein C, protein S)
  - hereditary resistance to activated protein C (Factor V Leiden mutation)
  - prothrombin variant 20210A
  - nephrotic syndrome
HEMOSTASIS … CONT.

Management (acute and prophylaxis)
- hyperhomocysteine anticoagulants
  - low molecular weight heparin
    - no test required
    - reduced incidence of HIT
  - unfractionated heparin
    - maintain PTT 1.5-2.5 x the normal control
  - coumadin (see Table 11)
  - hirudin

- thrombolytics
  - snake venom enzymes (ancrod)
  - plasminogen activators (streptokinase, urokinase, tPA)

- antiplatelet agents
  - ASA
  - sulfinopyrazone
  - dipyridamole

Table 11. Monitoring Coumadin (Warfarin) Therapy (therapeutic ranges)

<table>
<thead>
<tr>
<th>INR Range</th>
<th>Target</th>
</tr>
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<tbody>
<tr>
<td>1.5-2.5</td>
<td>2</td>
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<tr>
<td>2-3</td>
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<td>2-3</td>
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<td>2-4</td>
<td>3</td>
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<td>3-4.5</td>
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<td>3-4.5</td>
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</tbody>
</table>

HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

HIT-I
- non-immune
- decrease in platelet count usually seen early (48-72 hours post administration) but may take up to 1 week to appear
- transient thrombocytopenia, returns to normal once heparin discontinued
- no intravascular thrombosis
- likely due to platelet aggregation and sequestration

HIT-II
- immune-mediated
- typically occurs at day 5-15 of heparin therapy and decline is gradual
- HIT can begin sooner in patients who have received heparin in the past three months
- delayed-onset HIT occurs several days after discontinuing heparin
- typical platelet count in patients with HIT ranges from 25 to 100 x 10^9/L

Pathogenesis
- immunoglobulin-mediated adverse drug reaction
- pathogenic antibody, usually IgG recognizes a multimolecular complex of heparin and platelet factor 4, resulting in platelet activation via platelet Fc receptors and activation of the coagulation system

Clinical Complications
- cases of serious bleeding related to thrombocytopenia have been reported
- intravascular thrombosis
  - both venous (DVT, PE, venous gangrene) and arterial thrombi (MI, stroke, limb vessels) can form
  - heparin-induced skin necrosis
- unusual thrombotic complications include mesenteric artery or vein occlusion, adrenal hemorrhage and infarction
- acute platelet activation syndromes
  - acute inflammatory reactions (eg. fever/chills, flushing, etc.), transient global amnesia

Laboratory Tests
- C-serotonin release assay
- ELISA
  - measures binding of antibody in patients serum to PF4-heparin complex
**HEMOSTASIS . . . CONT.**

**Management**
- discontinuation of heparin
- platelet count should return to normal in a few days
- danaparoid (organon) is the preferred agent if anti-thrombic therapy is indicated
- low-molecular-weight heparin is less likely to cause HIT in de novo use but still carries an increased risk if previously sensitized with unfractionated heparin
- other alternatives include ancred and hirudin
- patient may be re-exposed to heparin only under careful supervision

**HEMATOLOGIC MALIGNANCIES**

**OVERVIEW**

**Myeloid**
- clonal stem cell neoplasms
  - acute myeloid leukemia (clonal proliferation of immature cells)
  - myeloproliferative disorders (proliferation of mature cells)
    - polycythemia rubra vera
    - chronic granulocytic (myelogenous) leukemia
    - idiopathic myelofibrosis
    - essential thrombocytemia
  - myelodysplastic syndromes (defective differentiation)

**Lymphoid**
- all cells arise from a single abnormal lymphoid precursor (B or T)
  - acute lymphoblastic leukemia (arise from stem cell)
  - lymphomas (arise from maturing lymphoid cell)
    - Hodgkin’s lymphoma
    - non-Hodgkin’s lymphoma
  - malignant clonal proliferation of B cells
    - chronic lymphocytic leukemia
    - plasma cell dyscrasias
    - light chain disease
    - monoclonal gammopathy of unknown significance
    - macroglobulinemia of Waldenstrom
    - macroglobulinemia-hyperviscosity syndrome

**MYELOID MALIGNANCIES**

**ACUTE MYELOID LEUKEMIA (AML)**
- failure of myeloid cell to differentiate beyond blast stage
- clonal proliferation of immature hematopoietic cells
- incidence increases with age
- associated with exposure to benzene, radiation and alkylating agents

**Pathophysiology**
- uncontrolled growth of blasts in marrow leads to
  - suppression of normal hematopoietic cells
  - appearance of blasts in peripheral blood
  - accumulation of blasts in other sites
  - metabolic consequences of a large tumour mass
- chronic myeloproliferative disorders and myelodysplastic syndromes can transform into AML

**Clinical Features of AML**
- decrease in normal hematopoiesis
  - anemia
  - pallor, weakness, fatigue, dyspnea on exertion
  - thrombocytopenia
    - purpura
    - mucosal bleeding
    - associated with DIC (promyelocytic leukemia- a type of AML)
  - neutropenia → infections
    - septicemia
    - pneumonitis
    - skin and mucosal infections
MYELOID MALIGNANCIES ... CONT.

- accumulation of blast cells in marrow
  - skeletal pain
  - bony tenderness, especially sternum
- accumulation of blast cells at other sites
  - lymphadenopathy
  - hepatosplenomegaly
  - gums
  - skin - leukemia cutis
  - CNS - N/V, H/A, papilledema +/- hemorrhage
  - gonads
  - eyes - Roth spots (oval retinal hemorrhages surrounding pale spot), blurred vision, diplopia
- metabolic effects - aggravated by treatment
  - increase in uric acid --> uric acid nephropathy
  - release of phosphates --> decrease in Ca^{2+} and Mg^{2+}
  - release of pro-coagulants --> DIC

**Diagnosis**

- peripheral blood film (see Colour Atlas H11)
  - decreased hemoglobin (usually normocytic, normochromic anemia) and platelets
  - variable leukocyte count
  - decrease in normal granulocytes
  - presence of blast cells (Auer Rods) – azurophilic granules within lysosomes
- bone marrow
  - usually hypercellular
  - increased blast cells - > 30% leukemic blasts for definitive diagnosis (normal < 5%)
  - decrease in normal erythropoiesis, myelopoiesis, megakaryocytes
- cytogenetics and molecular analysis
- INR (PT), PTT, FDP, fibrinogen in case of DIC
- increased uric acid, LDH and LFTs
- decreased Ca^{2+}
- baseline urea and creatinine
- chest x-ray to r/o mediastinal compression and infection

**Management of AML**

- cure - defined as survival that parallels age-matched population
- first step is complete remission- defined as normal peripheral blood smear, normal bone marrow with < 5% blasts, and normal clinical state
- leukemia will recur after complete remission if no further treatment given
- aims of treatment
  - eliminate abnormal clone - cytotoxic therapy
    - 1. Induction
    - 2. Consolidation or BMT
  - repopulation of marrow with normal hemopoietic cells
    - consider acceleration with hematopoietic growth factors
    - e.g. G-CSF, GM-CSF if increased incidence of severe infection
- supportive care
  - prophylaxis against infection via regular C&S of urine, feces, sputum, oropharynx, catheter sites, perianal area
  - antibiotics if fever with C&S of all orifices and chest x-ray
  - platelet and RBC transfusions - CMV negative products
  - prevention and treatment of metabolic abnormalities

**Prognosis**

- achievement of first remission
  - 70-80% if 60 years old, 50% if > 60 years old
  - median survival 12-24 months
  - 5 year survival 40%
- statistics may be improved by BMT – 50-60% cure rate
CHRONIC MYELOPROLIFERATIVE DISORDERS

- clonal myeloid stem cell abnormalities leading to qualitative and quantitative changes to erythroid, myeloid, and platelet cells
- may develop marrow fibrosis with time
- all disorders may progress to acute myelogenous leukemia
- mainly middle-aged and older patients

COMMON FEATURES
- increased
  - uric acid
  - LDH
  - serum B12
  - transcobalamin I
  - eosinophils
  - basophils
  - blood histamine (from basophils)
- pruritus
- bruising
- thrombosis
- peptic ulcer disease (histamine increases acid secretion)

<table>
<thead>
<tr>
<th>Table 12. Chronic Myeloproliferative Disorders</th>
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<tbody>
<tr>
<td>PRV</td>
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<tr>
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</tr>
<tr>
<td>HCT</td>
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<tr>
<td>WBC</td>
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<tr>
<td>PLT</td>
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<tr>
<td>LAP</td>
</tr>
<tr>
<td>marrow fibrosis</td>
</tr>
<tr>
<td>splenomegaly</td>
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<tr>
<td>hepatomegaly</td>
</tr>
</tbody>
</table>

PRV = polycythemia rubra vera  CGL = chronic granulocytic leukemia
IMF = idiopathic myelofibrosis ET = essential thrombocythemia
LAP = leukocyte alkaline phosphatase

POLYCYTHEMIA RUBRA VERA (PRV)
- autonomous overproduction of erythroid cells

Clinical Features
- secondary to high red cell mass and hyperviscosity
  - headache, dizziness, tinnitus
  - congestive heart failure
  - thrombosis
- secondary to platelet abnormalities
  - cerebrovascular accident
  - myocardial infarction
  - phlebitis
  - bleeding, bruising
- secondary to high blood histamine (from basophils)
  - pruritus, especially post-bath or shower
  - peptic ulcer
- secondary to high cell turnover
  - gout (due to hyperuricemia)

Management
- phlebotomy
  - if symptoms are due to erythrocytosis alone and platelet count normal or only slightly increased
- alkylating agents
  - if symptoms systemic or secondary to splenic enlargement
- antihistamines
- allopurinol
- 32P
Complications
- vascular complications (thrombosis, hemorrhage)
- myeloid metaplasia
- acute leukemia

Causes of Secondary Polycythemia
- spurious (decrease in plasma volume)
- poor tissue oxygenation
  - high altitude
  - cyanotic congenital heart disease or pulmonary disease
  - hemoglobinopathies with increased O2 affinity
  - carbon monoxide poisoning
- local renal hypoxia
  - renal artery stenosis
  - renal cysts
- ectopic production of erythropoietin
  - uterine leiomyoma
  - cerebellar hemangioma
  - hepatocellular cancer
  - pheochromocytoma
  - renal cell cancer

CHRONIC GRANULOCYTIC (MYELOGENOUS) LEUKEMIA (CML)
- overproduction of myeloid cells, erythroid cells and platelets in peripheral blood
- marked myeloid hyperplasia in bone marrow

Clinical Features
- disorder of middle age
- 40% asymptomatic
- secondary to splenic involvement
  - splenomegaly (most common physical finding)
  - shoulder tip pain due to splenic infarction
- secondary to high blood histamine
  - pruritus, peptic ulcer
- secondary to rapid cell turnover
  - fever, weight loss
- secondary to anemia
  - symptoms of anemia - most commonly fatigue
- secondary to gross elevation of the WBC (rare)
  - encephalopathy
  - priapism

Diagnostic Features
- Philadelphia (Ph1) chromosome
  - translocation between chromosomes 9 and 22
  - the c-abl proto-oncogene is translocated from chromosome 9 to “breakpoint cluster region” (bcr) of chromosome 22 to produce bcr-c-abl fusion gene, an active tyrosine kinase
  - detection of this fusion gene is a diagnostic test for CML (present in over 90% of patients)
- leukocyte alkaline phosphatase (LAP)
  - normal constituent of secondary neutrophil granules
  - low or absent (normal or increased in other chronic myeloproliferative diseases and reactive states)
- peripheral blood film (see Colour Atlas H10)
  - leukocytosis with early myeloid precursors
  - eosinophils and basophils may be increased
  - hypogranular basophils
- bone marrow
  - myeloid hyperplasia with a left shift, increased megakaryocytes and increased reticulin or fibrosis

Course/Outcomes
- chronic phase
  - normal bone marrow function
  - white blood cells differentiate and function normally
- accelerated phase
  - fever
  - marked increase in basophils
  - increased extramedullary hematopoiesis (unusual sites)
  - transformation —> disease similar to idiopathic myelofibrosis
  - pancytopenia secondary to marrow aplasia
CHRONIC MYELOPROLIFERATIVE DISORDERS . . . CONT.

- acute phase (blast transformation)
  - 2/3 develop a picture similar to AML
  - unresponsive to remission induction
  - 1/3 develop a picture similar to ALL
  - remission induction (return to chronic phase) achievable
  - sepsis
  - bleeding
  - thrombosis

Management
- symptomatic
  - allopurinol and antihistamines
- chronic phase
  - hydroxyurea or occasionally busulfan
  - interferon
  - STI 571
- only curative treatment is bone marrow transplantation

IDIOPATHIC MYELOFIBROSIS (IMF)
- marrow replaced by fibrosis - abnormal megakaryocytes stimulate collagen deposition

Clinical Features
- same as CML except no priapism or encephalopathy

Diagnostic Features
- significant hemolysis due to hypersplenism and red cell fragmentation
- peripheral blood film (see Colour Atlas H16)
  - tear drop cells
  - red cell and megakaryocyte fragments
  - increased polychromasia
  - nucleated RBCs and poikilocytes
  - giant abnormal platelets due to early release from marrow
  - leukoerythroblastic changes i.e. due to the space occupying lesions in the bone marrow, a variable number of erythroid and myeloid cells are released into the circulation
- bone marrow
  - replaced with fibrosis, difficult to aspirate
  - megakaryocytes normal or increased

Management
- transfusion
- erythropoietin
- androgens
- allopurinol and antihistamines
- folic acid if stores depleted
- desferoxamine for iron overload (iron and aluminum chelator)
- hydroxyurea in extremely small doses
- splenectomy in highly selected cases
- bone marrow transplant

Complications
- refractory anemia
- pancytopenia
- transformation to AML
- thrombosis and bleeding

ESSENTIAL THROMBOCYTHEMIA
- overproduction of platelets in absence of recognizable stimulus
- invariably above 400,000/mL

Clinical Features
- asymptomatic most common
- bleeding - although plentiful, platelets are not working
- thrombosis
- symptoms 2° to splenic enlargement, high blood histamine, and rapid cell turnover - as per CML and IMF

Laboratory Features
- defect in platelet function may be present
- elevation of phosphatase and potassium in plasma sample due to release of cytoplasmic content from aggregation of platelets
CHRONIC MYELOPROLIFERATIVE DISORDERS . . . CONT.

Diagnosis
- Exclude other myeloproliferative diseases and 2nd thrombocythemia

Management
- Hydroxyurea
- 32P
- Plateletpheresis
- Avoid splenectomy as spleen is removing unwanted platelets

Complications
- Bleeding
- Thrombosis
- Leukemic transformation
- Transformation to myelofibrosis

Clinical Pearl
- There is an asymptomatic “benign” form of essential thrombocythemia with a stable or slowly rising platelet count; treatment includes observation, ASA, sulfipyrazone or dipyridamole.

Causes of Secondary Thrombocythemia
- Infection
- Inflammation (IBD, arthritis)
- Malignancy
- Hemorrhage
- Fe deficiency
- Hemolytic anemia
- Post splenectomy
- Post chemotherapy

MYELODYSPLASTIC SYNDROMES

- Set of clonal disorders characterized by one or more cytopenias with anemia present
- Ineffective hematopoiesis despite presence of adequate numbers of progenitor cells (bone marrow is usually hyper-cellular)
- Considered preleukemic: 30-70% develop AML
- Most common in elderly, post-chemotherapy, benzene or radiation exposure
- Insidious onset
- Clinical presentation
  - Fatigue, weakness, pallor, infections, bruising and rarely weight loss, fever, and hepatosplenomegaly
- Diagnostic triad
  1. Anemia ± thrombocytopenia ± neutropenia
  2. Bone marrow hypercellular or normocellular
  3. Dysmyelopoiesis in bone marrow precursors
- Hematological changes
  - RBC: variable morphology with decreased reticulocyte count
  - WBC: decrease in granulocytes and abnormal function
  - Platelet: either too large or too small and thrombocytopenia

FAB Classification
- Refractory anemia (RA)
- Refractory anemia with ring sideroblasts (RARS)
- Refractory anemia with excess blasts (RAEB)
- Refractory anemia with excess blasts in transformation (RAEB-T)
- Chronic myelomonocytic leukemia (CMML)

Management
- Symptomatic: transfusion, antibiotics
- Hematopoietic growth factors (G-CSF, GM-CSF) may decrease risk of infection
- Erythropoietics
- AML induction chemotherapy: 50-60% remission, 90% relapse
- Bone marrow transplant may be curative
LYMPHOID MALIGNANCIES

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

Pathophysiology
- Develops from any lymphoid cell blocked at a particular stage of development.

Clinical Features
- See AML.
- 50% present with fever.

Diagnosis
- See AML.
- Leukemic lymphoblasts lack specific morphological or cytochemical features, therefore diagnosis depends on immunophenotyping.
- Immunology (B or T lineage).
- Cytogenetics.

Treatment
- See AML.
- Eliminate abnormal clone.
  1. Induction
  2. Consolidation
  3. Intensification
  4. Maintenance
  5. Prophylaxis: CNS with XRT or MTX.

Prognosis
- Depends upon response to initial induction or if remission is achieved following relapse.
- Achievement of first remission: 60-90%.
- Childhood ALL: 80% long term remission (> 5 years).
- Adult ALL: 30-40% 5 year survival.

Table 13. To Differentiate AML From ALL – Remember Big and Small

<table>
<thead>
<tr>
<th>AML (see Colour Atlas H11)</th>
<th>ALL (see Colour Atlas H13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>big people (adults)</td>
<td>small people (kids)</td>
</tr>
<tr>
<td>big blasts</td>
<td>small blasts</td>
</tr>
<tr>
<td>lots of cytoplasm</td>
<td>little cytoplasm</td>
</tr>
<tr>
<td>lots of nucleoli (3-5)</td>
<td>few nucleoli (1-3)</td>
</tr>
<tr>
<td>lots of granules and Auer rods</td>
<td>no granules</td>
</tr>
<tr>
<td>big toxicity of treatment</td>
<td>little toxicity of treatment</td>
</tr>
<tr>
<td>big mortality rate</td>
<td>small mortality rate</td>
</tr>
<tr>
<td>myeloperoxidase, sudan black stain</td>
<td>PAS (periodic acid schiff)</td>
</tr>
<tr>
<td>maturation defect beyond myeloblast or promyelocyte</td>
<td>maturation defect beyond lymphoblast</td>
</tr>
</tbody>
</table>

LYMPHOMAS

HODGKIN’S DISEASE AND NON-HODGKIN’S LYMPHOMA STAGING

- Stage I
  - Involvement of a single lymph node region or extralymphatic organ or site.
- Stage II
  - Involvement of two or more lymph node regions OR an extralymphatic site and one or more lymph node regions on SAME side of diaphragm.
- Stage III
  - Involvement of lymph node regions on BOTH sides of the diaphragm.
  - May or may not be accompanied by single extralymphatic site or splenic involvement.
- Stage IV
  - Diffuse involvement of one or more extralymphatic organs including bone marrow.
LYMPHOMAS ... CONT.

Subtypes
- A = Absence of B symptoms
- B = Presence of B symptoms

B Symptoms
- unexplained fever > 38°C
- unexplained weight loss (> 10% of body weight in 6 months)
- night sweats

HODGKIN’S DISEASE
- substantial number represents monoclonal B cell disorders
- bimodal distribution with peaks at the age of 20 years and > 50 years

Clinical Features
- lymphadenopathy (neck, axilla)
- B symptoms
- classical symptoms
  - pruritus
  - painful nodes following alcohol consumption

Diagnosis
- nodal biopsy (see Colour Atlas H15)
- bone marrow biopsy for Reed-Sternberg cell – polynucleated cells derived from B-cells
  - nodular sclerosis is the most common histological subtype

Work-up
- CBC
  - normocytic normochromic anemia
  - leukocytosis in 1/3 of patients
  - eosinophilia
  - platelet count is normal or increased in early disease but decreased in advanced disease
- biochemistry
  - RFTs to assess renal excretion of chemotherapeutics
  - LFTs to r/o liver involvement
  - uric acid
  - ESR to monitor disease progress
  - Ca²⁺, ALP, phosphate for bone metastasis
- chest x-ray to r/o mediastinal masses and lung metastases
- CT of chest, abdomen and pelvis

Management
- high cure rate
- Stage I-II: radiation therapy or chemotherapy plus local field radiation (less risk of second malignancy)
- Stage III-IV: combination chemotherapy eg. ABVD or MOPP
- relapse: high dose chemotherapy, bone marrow transplant

Complications of Treatment
- diminished fertility
  - consider oophoropexy/sperm banking before radiation
- post-splenectomy sepsis
  - immunize pre-splenectomy
- hypothyroidism
- secondary malignancies
  - < 2% risk of MDS, AML
  - usually within 4 years after exposure to alkylating agents and radiation
  - solid tumours in the radiation fields > 10 years after exposure
- accelerated cardiovascular disease

NON-HODGKIN’S LYMPHOMA

Clinical Features
- painless superficial lymphadenopathy usually > 1 lymph region
- usually presents as widespread disease
- constitutional symptoms (fever, weight loss, night sweats) not as common as in Hodgkin’s disease
- cytopenia: anemia +/- neutropenia +/- thrombocytopenia if bone marrow fails
- abdominal symptoms or signs
  - hepatosplenomegaly
  - retroperitoneal and mesenteric involvement (2nd most common site of involvement)
- oropharyngeal involvement in 5-10% with sore throat and obstructive apnea
LYMPHOMAS . . . CONT.

**Diagnosis**
- lymph node biopsy
  - fine needle aspiration occasionally sufficient, core biopsy preferred
- bone marrow biopsy
- peripheral blood film sometimes shows lymphoma cells

**Work-Up**
- CBC
  - normocytic normochromic anemia
  - autoimmune hemolytic anemia
  - advanced disease: thrombocytopenia, neutropenia, and leukoerythroblastic anemia
- biochemistry
  - increase in uric acid
  - abnormal LFTs in liver metastases
  - elevated LDH (rapidly progressing disease and poor prognostic factor)
- chest x-ray + CT for thoracic involvement
- CT for abdominal and pelvic involvement

**Revised European American lymphoma (REAL) Classification for Subtypes of NHL**
- several classification systems exist and may be used at different centres
  1. plasma cell disorders
  2. Hodgkin's lymphoma
  3. indolent lymphoma/leukemia
    - good prognosis: median survival 10 years
    - not curable if stage III/IV
    - 8 subtypes of NHL
  4. aggressive lymphoma/leukemia
    - shorter natural history
    - 30-60% cured with intensive combination chemotherapy
    - 5 year survival 50-60%
    - 2 main subtypes of NHL

**Management of NHL**
- localized disease (e.g. GI, brain, bone, head and neck)
  - surgery (if applicable)
  - radiotherapy to primary site and adjacent nodal areas
  - adjuvant chemotherapy
- indolent lymphoma
  - watchful waiting
  - radiation therapy
  - chemotherapy
- aggressive lymphoma
  - combination chemotherapy
  - aggressive consolidation with marrow or stem cell support

**NHL Complications**
- hypersplenism
- infection
- autoimmune hemolytic anemia and thrombocytopenia
- vascular obstruction (from enlarged nodes)
- Note: never give live vaccines e.g. MMR and oral polio

**Indicators of Poor Prognosis**
- > 60 years old
- poor response to therapy
- multiple nodal regions
- elevated LDH
- > 5cm nodes
- previous history of low grade disease or AIDS
MALIGNANT CLONAL PROLIFERATIONS OF B CELLS

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)
- indolent disease characterized by the clonal malignancy of poorly functioning B cells
- accumulation of neoplastic lymphocytes in blood, bone marrow, lymph nodes and spleen
- most common leukemia in western world
- mainly older patients
- up to 60% asymptomatic
- 9 year median survival, but varies greatly

Investigations
- absolute lymphocytosis > 5.0 x 10⁹/L (usually > 10.0 x 10⁹/L)
- lymphocytes small and mature
- smudge cells (see Colour Atlas H12)
- diffuse or focal infiltration of marrow by lymphocytes

Complications
- bone marrow failure
- bulky lymphadenopathy
- hypersplenism
- immune hemolytic anemia
- immune thrombocytopenia
- hypogammaglobulinemia
- monoclonal gammopathy (often IgM)
- hyperuricemia with treatment
- transformation to histiocytic lymphoma

Management
- the gentlest treatment that will control symptoms
  - observation if early, stable, asymptomatic
  - intermittent chlorambucil
  - corticosteroids
  - radiotherapy
  - chemotherapy
- no cure

PLASMA CELL MYELOMA (MULTIPLE MYELOMA)
- monoclonal malignancy of plasma cells engaged in the production of a specific protein (paraprotein)
  - characterized by replacement of bone marrow and bone destruction
- incidence: 3 per 100 000
- increasing frequency with age
- the protein produced is monoclonal i.e. one class of heavy chains and one type of light chains ("M" protein)
- light chains only: 15% (light chain disease)
- IgD (1%) and IgE are rare

Clinical Features
- onset between 40-70 years
- bone pain, tenderness, deformity
- weakness, fatigue (due to anemia)
- weight loss, night sweats with advanced disease
- abnormal bleeding (epistaxis, purpura)
- infection eg. pneumococcal diseases
- renal failure
- on exam: pallor, bone deformity, pathologic fractures, bone tenderness, hepatosplenomegaly, petechiae and purpura

Laboratory Features
- peripheral blood film (see Colour Atlas H14)
  - rouleaux
  - rare plasma cells
  - normocytic anemia, thrombocytopenia, leukopenia
- bone marrow
  - focal or diffuse increase in plasma cells (see Colour Atlas H9)
  - primitive plasma cells
- biochemistry
  - hypercalcemia (N/V, apathy, weakness, polydipsia, polyuria)
  - increased creatinine
  - increased ESR
  - narrow anion gap (myeloma protein is a cation)
- monoclonal protein on serum protein electrophoresis
- heavy chain and light chain types identified by serum immunoelectrophoresis
- decreased normal immunoglobulins
- urine electrophoresis (Bence-Jones protein, a light chain dimer)
MALIGNANT CLONAL PROLIFERATIONS OF B CELLS . . . CONT.

**Diagnosis**
- bone pain, anemia, increased ESR or increased rouleaux suggests myeloma
- classic diagnostic triad: must show increased numbers of atypical immature plasma cells
  1. greater than 10% abnormal plasma cells in bone marrow
  2. lytic bone lesions
  3. monoclonal protein spike in serum or urine

**Complications**
- bone abnormalities
  - osteoporosis, pathological fractures - common due to osteoclastic activating factor and PTHrp
  - lytic lesions are classical (skull, spine, proximal long bones, ribs)
  - osteoclast activating factor (hypercalcemia, normal ALP)
- renal failure secondary to
  - myeloma kidney (intratubular deposition of light chains)
  - hypercalcemic nephropathy
  - pyelonephritis
  - amyloidosis from chronic inflammation
  - obstructive uropathy
  - renal infiltration by plasma cells
  - hyperuricemia
  - hyperviscosity compromising renal blood flow
- recurrent bacterial infections
- anemia
- hyperviscosity syndrome (caused by M protein)
- amyloidosis (CHF, nephrotic syndrome, joint pain, carpal tunnel syndrome)
- transformation to acute leukemia

**Management**
- melphalan, cyclophosphamide or other alkylating agents
- corticosteroids
- radiotherapy to local painful lesions
- bisphosphonates
- follow serum or urine M protein as indicator of response
- early identification and treatment of complications
- treatment of renal failure
  - hydration
  - corticosteroids
  - plasmapheresis
- autologous stem cell transplant
- thalidomide

**Prognosis**
- median survival 24-30 months

**LIGHT CHAIN DISEASE**
- plasma cells produce only light chains
- 15% of patients with myeloma
- diagnosis
  - urine immunoelectrophoresis
  - serum studies often non-diagnostic as light chains can pass through glomerulus
- renal failure a MAJOR problem
- prognosis: survival kappa > lambda light chains

**MONOCLONAL GAMMOPATHY OF UNKNOWN SIGNIFICANCE (BENIGN MONOCLONAL GAMMOPATHY)**
- incidence: 0.15% in general population, 3% of people > 70 years of age
- diagnosis
  - exclude myeloma
  - < 10% plasma cells in bone marrow
  - no rise in the M protein with time
- 10% of patients develop multiple myeloma each year in the first 3 years

**MACROGLOBULINEMIA OF WALDENSTROM**
- uncontrollable proliferation of lymphoplasmacytoid cells (a hybrid of lymphocytes and plasma cells)
- monoclonal IgM para protein is produced
- symptoms: weakness, fatigue, bleeding (oronasal), recurrent infections, dyspnea, CHF, weight loss, neurological symptoms peripheral neuropathy, cerebral dysfunction
- signs: pallor, splenomegaly, hepatomegaly, lymphadenopathy, retinal lesions
MALIGNANT CLONAL PROLIFERATIONS OF B CELLS . . . CONT.

- bone marrow shows plasmacytoid lymphocytes
- bone lesions usually not present
- cold hemagglutinin disease possible
- normocytic anemia, rouleaux, high ESR if hyperviscosity not present
- watch for hyperviscosity syndrome

MACROGLOBULINEMIA-HYPERVISCOSITY SYNDROME

**Clinical Features**
- hypervolemia causing: CHF, headache, lethargy, dilutional anemia
- CNS symptoms: headache, vertigo, ataxia, stroke
- retina shows venous engorgement and hemorrhages
- bleeding diathesis
  - due to impaired platelet function, absorption of soluble coagulation factors e.g. nasal bleeding, oozing gums
- ESR usually very low

**Management**
- chlorambucil or melphalan
- corticosteroids
- plasmapheresis for hyperviscosity

<table>
<thead>
<tr>
<th>Table 14. Characteristics of B Cell Malignant Proliferation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cell Type</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Protein</strong></td>
</tr>
<tr>
<td><strong>Lymph Nodes</strong></td>
</tr>
<tr>
<td><strong>Hepatosplenomegaly</strong></td>
</tr>
<tr>
<td><strong>Bone Lesions</strong></td>
</tr>
<tr>
<td><strong>Hypercalcemia</strong></td>
</tr>
<tr>
<td><strong>Renal failure</strong></td>
</tr>
<tr>
<td><strong>Immunoglobulin Autoimmune Complications</strong></td>
</tr>
</tbody>
</table>

BONE MARROW TRANSPLANTATION
- allows even more intensive therapy for hematologic malignancies
- high doses of chemo +/- whole body radiation
- “marrow rescue”
  - autologous: from self
  - allogeneic: HLA identical sibling (donor must be < 55 years)
- complications
  - cytopenias - especially neutropenia and thrombocytopenia
  - infections - especially opportunistic
  - drug toxicity
TUMOUR LYSIS SYNDROME

- more common in diseases with large tumour burden and high proliferative rate (high grade lymphoma, leukemia)
- metabolic abnormalities
  - hyperuricemia
  - hyperkalemia
  - hyperphosphatemia
  - hypocalcemia
- complications
  - lethal cardiac arrhythmia
  - acute renal failure

Management
- prevention
  - aggressive IV hydration
  - alkalinization of the urine
  - allopurinol
  - correction of pre-existing metabolic abnormalities
- dialysis

WBC DISORDERS

NEUTROPHILIA

Definition
- absolute neutrophil count (ANC) > 7.5 x 10^9/liter

Mechanism
- increased mitosis/proliferation e.g. response to chronic infection
- decreased marrow storage pool e.g. acute response to infection
- decreased marginal pool e.g. acute response to infection
- decreased egress from circulating pool e.g. chronic steroids

Etiology
- acute infections especially bacterial
- inflammation
- metabolic derangement e.g. uremia, acidosis, gout
- acute hemorrhage or hemolysis
- malignant neoplasm and myeloproliferative disorders
- steroid therapy (due to poor migration)

LEUKEMOID REACTIONS
- blood findings resembling those seen in certain types of leukemia with immature WBC in the peripheral blood film
- myeloid leukemia mimicked by
  - pneumonia
  - other acute bacterial infections
  - intoxications
  - burns
  - malignant disease
  - severe hemorrhage or hemolysis
- lymphoid leukemia mimics (see Infectious Diseases Chapter)
  - pertussis
  - TB
  - infectious mononucleosis
- monocytic leukemia mimics
  - TB

NEUTROPENIA

Definition
- ANC < 2.5 x 10^9/liter

Mechanisms
- decreased stem cells e.g. aplastic anemia
- decreased mitosis e.g. marrow hypoplasia secondary to alkylating agents
- increased ineffective mitosis e.g. megaloblastic anemia
- increased peripheral destruction e.g. hypersplenism
- combinations e.g. lymphoma
- increased marginal pool or decreased storage pool egress e.g. viremia
WBC DISORDERS . . . CONT.

Etiology
- overwhelming infection
  - viral: HIV, hepatitis, EBV
  - bacterial: typhoid, miliary TB
- drugs and chemicals
  - examples: ionizing radiation, benzene, chemotherapeutic drugs, anti-inflammatory drugs
  - dose-dependent predictable e.g. anticonvulsants
  - dose-dependent idiosyncratic e.g. ASA, phenothiazine, indomethacin
  - dose-independent hypersensitivity
  - antibody-mediated eg. penicillins
- marrow disease
  - low B12/folate
  - bone marrow infiltration (hematologic malignancies > solid tumours)
  - aplastic anemia
- hereditary: cyclic neutropenia
- hypersplenism

Clinical Features
- fever, chills
- infection by opportunistic organisms
- painful ulceration on skin, anus, mouth and throat by opportunistic organisms
- septicemia in later stage

Diagnosis
- CBC
- bone marrow biopsy to rule out marrow failure

AGRANULOCYTOSIS
- virtually complete disappearance of granulocytes from the blood and granulocyte precursors from the marrow; drugs often implicated
- abrupt onset of
  - fever, chills and weakness
  - oropharyngeal ulcers
- drug induced (e.g. clozapine)
- highly lethal without vigorous treatment

Management
- discontinue offending drug
- antimicrobial therapy e.g. TMP-SMX, ciprofloxacin, antifungal
- Filgrastim (G-CSF) - growth factor that stimulates neutrophil production

APPROACH TO SPLENOMEGALY

Etiology
- infections
  - subacute bacterial endocarditis, TB, salmonella, EBV, CMV, histoplasmosis, malaria, toxoplasmosis, schistosomiasis, HIV/AIDS
- hematologic disorders
  - hemolytic anemia, hemoglobinopathies, Fe deficiency anemia
- congestive splenomegaly, portal hypertension: secondary
  - secondary to portal or splenic vein obstruction
  - secondary to intrahepatic disease
    - secondary to CHF
- infiltrative or metabolic diseases
  - lipid storage disease, mucopolysaccharidosis, glycogen storage disease, amyloidosis, tyrosinemia
- immunological
  - SLE, sarcoidosis
- neoplastic
  - leukemia, lymphoma, Hodgkin's disease
- epidermal cysts
- other
  - serum sickness, Felty's syndrome, osteopenosis

Mild Spleen Enlargement
- 0-4 cm below costal margin
- CHF, SBE, SLE, RA, thalassemia minor, acute malaria, typhoid fever

MCCQE 2002 Review Notes Hematology – H37
WBC DISORDERS . . . CONT.

Moderate Spleen Enlargement
- 4-8 cm below costal margin
- hepatitis, cirrhosis, lymphomas, infectious mononucleosis, hemolytic anemias, splenic infarct, splenic abscess, amyloidosis, acute leukemias, hemolytic anemias

Massive Spleen Enlargement
- > 8 cm below costal margin
- chronic leukemias, lymphoma, myelofibrosis, hairy cell leukemia, leishmaniasis, portal vein obstruction, polycythemia vera (end-stage), primary thrombocytopenia, lipid-storage disease, sarcoidosis, thalassemia major

BLOOD PRODUCTS AND TRANSFUSIONS

BLOOD GROUPS

Table 15. Blood Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Antigen</th>
<th>Antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>H</td>
<td>anti-A, anti-B</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
<td>anti-B</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
<td>anti-A</td>
</tr>
<tr>
<td>A B</td>
<td>A and B</td>
<td>nil</td>
</tr>
</tbody>
</table>

- group compatible uncrossmatched blood is safer than
- O-negative uncrossmatched blood - there is no universal donor

RED CELLS

Packed Cells
- stored at 4°C
- transfuse within 35 days of collection, otherwise hyperkalemia due to cell lysis
- transfuse within 7 days of collection if renal failure or hepatic failure is present to reduce solute load
- each unit will raise hematocrit by about 4% or hemoglobin by 10 gm/L (1 g/dL)

Selection of Red Cells for Transfusion
- donor blood should be crossmatch compatible (by mixing recipient serum with donor RBC)
- donor blood should be free of irregular blood group antibodies
- the donor blood should be the same ABO and Rh group as the recipient

PLATELETS

Table 17. Platelet Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random Donor (pooled)</td>
<td>thrombocytopenia with bleeding</td>
</tr>
<tr>
<td>Single Donor Platelets</td>
<td>potential BMT recipients</td>
</tr>
<tr>
<td>HLA Matched Platelets</td>
<td>refractoriness to pooled or single donor platelets</td>
</tr>
</tbody>
</table>

- each unit of random donor platelets should increase the platelet count by approximately 10 x 10^9/L
- single donor platelets should increase the platelet count by 40-60 x 10^9/L
- if an increment in the platelet count is not seen, alloantibodies, bleeding, sepsis or hypersplenism may be present
COAGULATION PRODUCTS

Table 18. Coagulation Factor Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh Frozen Plasma</td>
<td>Depletion of multiple coagulation factors</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>Factor VIII deficiency</td>
</tr>
<tr>
<td></td>
<td>Von Willebrand's disease</td>
</tr>
<tr>
<td></td>
<td>Hemophilia</td>
</tr>
<tr>
<td>Factor VIII Concentrate</td>
<td>Factor VIII deficiency</td>
</tr>
<tr>
<td>Factor IX Concentrate</td>
<td>Factor IX deficiency</td>
</tr>
</tbody>
</table>

Special Considerations
- Irradiated blood products
  - potential BMT recipients
  - immunocompromised patients
- CMV negative blood products
  - potential transplant recipients
  - neonates

GROUP AND RESERVE SERUM
- an alternative to holding crossmatched blood for individuals who may require transfusion
  - recipient’s ABO and Rh group is determined
  - recipient’s serum is tested for the presence of irregular blood group antibodies
  - serum is kept frozen
- compatible blood can be issued immediately in an emergency or within 30 minutes electively

ACUTE COMPLICATIONS OF BLOOD TRANSFUSIONS

Febrile Nonhemolytic Transfusion Reactions
- due to antibodies stimulated by previous transfusions or pregnancies against antigens on donor lymphocytes, granulocytes, platelets or to lymphokines that are released with storage of the cells
- signs and symptoms: chills, fever
- management and prevention
  - stop transfusion
  - acetaminophen
  - steroids
  - filtered blood
  - washed blood

Allergic Reactions
- usually due to interaction between donor plasma proteins and recipient IgE antibodies
- signs and symptoms: a spectrum from urticaria and generalized itching to wheezing to anaphylaxis
- management and prevention
  - antihistamines
  - slow infusion
  - steroids
  - washed blood
  - anaphylaxis may require IV epinephrine and IgA deficient blood components in future

Acute Hemolytic Transfusion Reactions
- most commonly due to incorrect patient identification
- intravascular hemolytic reaction due to complement activation
- signs and symptoms
  - muscle pain, back pain
  - fever, N/V, chest pain, wheezing
  - dyspnea, tachypnea (acute respiratory distress syndrome)
  - feeling of impending doom
  - hemoglobinemia
  - renal failure - DIC
  - hypotension and vascular collapse
  - patient under general anesthetic may present with bleeding
investigations
- repeat crossmatch and donor and recipient blood groups
- direct antiglobulin test (direct Coombs' test)
management
- stop transfusion
- hydrate aggressively
- transfuse with compatible blood products

Citrate Toxicity
- seen with massive transfusion and with liver disease
- toxicity secondary to hypocalcemia
- prevented by giving 10 mL of 10% calcium gluconate for every 2 units of blood

Hyperkalemia

Circulatory Overload
- signs: dyspnea, orthopnea, cyanosis, sudden anxiety, hemoptysis, crackles in lung bases
- with prior CHF and in elderly patients
- minimize the amount of saline given with the blood

Hemorrhagic State due to Dilutional Coagulopathy
- with massive transfusion
- packed cells contain no Factor VIII or V or platelets
- correct with fresh frozen plasma and platelets

Bacterial Infections
- never give blood > 4 hours after a bag has been entered!
- signs and symptoms: chills, rigors, fever, hypotension, shock, DIC (profound symptoms with Gram negatives)
- management: blood cultures, IV antibiotics, fluids

Delayed Complications in Transfusions
- days to weeks
- viral infection risks
  - HIV < 1:500,000
  - HBV < 1:250,000
  - HCV < 1:10,000

Delayed Hemolytic Transfusion Reaction
- may be delayed up to 5 to 10 days
- extravascular hemolysis due to alloantibodies that are too weak to be detected by indirect antiglobulin test or by crossmatch
- may be confused with autoimmune hemolytic anemia
- signs and symptoms: anemia, fever, history of recent transfusion, jaundice, positive direct Coombs' test
- further transfusion should be avoided

Iron Overload
- often with repeated transfusion for long periods of time, e.g. beta-thalassemia major
- use of iron chelators after transfusion can reduce the chance of iron overload
- complications include secondary hemochromatosis
  - dilated cardiomyopathy
  - cirrhosis
  - DM, hypothyroidism, delayed growth and puberty

Transfusion Associated GVHD
- transfused T-lymphocytes recognize and react against the "host" (recipient)
- between 4-30 days later
- most patients with this have severely impaired immune systems (e.g. Hodgkin's, NHL, acute leukemias)
- signs and symptoms: fever, diarrhea, liver function abnormalities, pancytopenia
- mortality about 90%
- prevention: gamma irradiation of blood components
# MEDICATIONS COMMONLY USED IN HEMATOLOGY

## Table 19. Drugs for Anemia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Common Formulary</th>
<th>Mechanism of Action</th>
<th>Clinical Uses</th>
<th>Common Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>iron</td>
<td>iron gluconate</td>
<td>for synthesis of hemoglobin</td>
<td>iron deficiency anemia treatment and prevention; pregnancy</td>
<td>in children: acute iron toxicity as necrotizing enterocolitis; shock; metabolic acidosis; coma and death</td>
<td>iron overload</td>
</tr>
<tr>
<td></td>
<td>iron sulphate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>iron fumarate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>cyanocobalamin</td>
<td>synthesis of folic acid and DNA</td>
<td>B12 deficiency</td>
<td>no significant toxicity</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>hydroxycobalamin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>folic acid</td>
<td>folic acid</td>
<td>synthesis of purines and thymidylate thus DNA</td>
<td>folic acid deficiency; pregnancy</td>
<td>no significant toxicity</td>
<td>N/A</td>
</tr>
<tr>
<td>erythropoietin</td>
<td>Epo</td>
<td>stimulate RBC synthesis</td>
<td>renal failure; marrow failure; myelodysplastic syndrome; autologous blood donation</td>
<td>no significant toxicity</td>
<td>N/A</td>
</tr>
</tbody>
</table>

## Table 20. Chemotherapeutic Agents

<table>
<thead>
<tr>
<th>Class</th>
<th>Example</th>
<th>Mechanism of Action</th>
<th>Common Toxicity</th>
<th>Examples of Clinical Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>alkylating</td>
<td>• nitrogen mustard</td>
<td>• cell cycle non-specific drugs; via alklylation of nucleophilic groups in base pairs; leading to cross-linking of bases or abnormal base-pairing or DNA breakage</td>
<td>• marrow suppression; GI irritation; change in gonadal function; nitrogen mustard (cyclophosphamide): hemorrhagic cystitis; busulfan: adrenal insufficiency and pulmonary fibrosis</td>
<td>• cyclophosphamide; breast CA; small cell lung CA; NHL; busulfan; CML; cisplatin; advanced ovarian CA; testicular CA</td>
</tr>
<tr>
<td></td>
<td>• cyclophosphamide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• nitrosourea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• busulanan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• cisplatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>antimetabolites</td>
<td>• folic acid antagonist (methotrexate)</td>
<td>• all are cell cycle specific drugs; all inhibit DNA synthesis; methotrexate inhibits synthesis of tetrahydrofolate; mercaptopurine inhibits purine synthesis; 5-FU inhibits thymidylate synthesis; hydroxyurea inhibits nucleotide reductase</td>
<td>• marrow suppression; oral mucositis; nausea and vomiting</td>
<td>• methotrexate; breast CA; gestational trophoblastic CA; ovarian CA; mercaptopurine; AML; 5-FU; CML; GI CA; blood stem cell; advanced ovarian CA; testicular CA; hydroxyurea; CML</td>
</tr>
<tr>
<td></td>
<td>• purine antagonist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(mercaptopurine)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• pyrimidine antagonist (5-FU)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• hydroxyurea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>antibiotics</td>
<td>• anthracyclines</td>
<td>• anthracycline is cell cycle non-specific; intercalates between base-pairs and thus blocks DNA and RNA synthesis; bleomycin is cell cycle specific (G2); produces free radicals leading to DNA breaks and inhibits DNA synthesis; mitomycin-C is cell cycle non-specific, metabolized in liver to alkylating agent</td>
<td>• anthracyclines; severe alopecia; cardiomyopathies; bleomycin; pulmonary fibrosis; pneumonitis; hypersensitivity; mucocutaneous reactions; mitomycin-C; myelo-suppression; nephotoxic</td>
<td>• anthracyclines; breast CA; AML; lymphomas; bleomycin; testicular CA; lymphomas; mitomycin-C; GI malignancies</td>
</tr>
<tr>
<td></td>
<td>(doxorubicin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• bleomycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• mitomycin-C</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 20. Chemotherapeutic Agents (continued)

<table>
<thead>
<tr>
<th>Class</th>
<th>Example</th>
<th>Mechanism of Action</th>
<th>Common Toxicity</th>
<th>Examples of Clinical Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>alkaloids</strong></td>
<td>• vinblastine</td>
<td>• all are cell cycle specific</td>
<td>• all have marrow suppression</td>
<td>• vincristine and vinblastine</td>
</tr>
<tr>
<td></td>
<td>• vincristine</td>
<td>• vincristine and vinblastine inhibit assembly of microtubules therefore mitotic spindles and M phase</td>
<td>• vincristine and vinblastine neurotoxic with areflexia, peripheral neuritis and paralytic ileus</td>
<td>• lymphomas</td>
</tr>
<tr>
<td></td>
<td>• podophyllotoxin (etoposide)</td>
<td>• podophyllotoxin activates topoisomerase II therefore DNA breaks down</td>
<td>• taxol</td>
<td>• podophyllotoxin small cell lung CA</td>
</tr>
<tr>
<td></td>
<td>• taxol</td>
<td>• taxol inhibits disassembly of microtubules therefore cells are stuck in M phase</td>
<td>• neurotoxic as above</td>
<td>• prostate CA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• vincristine and vinblastine</td>
<td>• vincristine and vinblastine neurotoxic with areflexia, peripheral neuritis and paralytic ileus</td>
<td>• testicular CA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• vincristine</td>
<td>• taxol</td>
<td>• taxol advanced breast CA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• vincristine and vinblastine</td>
<td>• vincristine and vinblastine neurotoxic with areflexia, peripheral neuritis and paralytic ileus</td>
<td>• ovarian CA</td>
</tr>
<tr>
<td><strong>hormones</strong></td>
<td>• glucocorticoids</td>
<td>• tamoxifen as a partial E2 antagonist</td>
<td>• glucocorticoid refer to Endocrinology under Cushing's syndrome</td>
<td>• glucocorticoids CML</td>
</tr>
<tr>
<td></td>
<td>• tamoxifen</td>
<td>• as a partial E2 antagonist</td>
<td>• tamoxifen</td>
<td>• lymphomas</td>
</tr>
<tr>
<td></td>
<td>• flutamide</td>
<td>• flutamide: androgen receptor antagonist</td>
<td>• tamoxifen</td>
<td>• tamoxifen</td>
</tr>
<tr>
<td></td>
<td>• aminoglutethimide</td>
<td>• aminoglutethimide: aromatase inhibitor in E2 synthesis</td>
<td>• aminoglutethimide</td>
<td>• breast CA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• aminoglutethimide: aromatase inhibitor in E2 synthesis</td>
<td>• menopausal symptoms</td>
<td>• prostate CA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• aminoglutethimide: aromatase inhibitor in E2 synthesis</td>
<td>• aminoglutethimide</td>
<td>• aminoglutethimide breast CA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• aminoglutethimide: aromatase inhibitor in E2 synthesis</td>
<td>• skin rashes</td>
<td>• metastatic breast CA</td>
</tr>
<tr>
<td><strong>others</strong></td>
<td>• carboplatin</td>
<td>• carboplatin DNA binding</td>
<td>• carboplatin myelosuppression</td>
<td>• carboplatin ovarian CA</td>
</tr>
<tr>
<td></td>
<td>• mitoxantrone</td>
<td>• mitoxantrone DNA binding</td>
<td>• mitoxantrone</td>
<td>• mitoxantrone AML</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• mitoxantrone DNA binding</td>
<td>• mitoxantrone</td>
<td>• NHL breast CA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• mitoxantrone DNA binding</td>
<td>• mitoxantrone</td>
<td>• breast CA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• mitoxantrone DNA binding</td>
<td>• mitoxantrone</td>
<td>• ovarian CA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• mitoxantrone DNA binding</td>
<td>• mitoxantrone</td>
<td>• lung CA</td>
</tr>
</tbody>
</table>

### REFERENCES


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