HEMATOLOGY

Dr. I. Quirt
Adriana Cipolletti, Jeremy Gilbert and Susy Hota, chapter editors
Leora Horn, associate editor

APPROACH TO THE BLOOD FILM

Size
- ❑ macrocytic
  - increased size
  - e.g. low B_{12}, 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)

Normal	Increased
anemia of chronic disease	iron deficiency
thalassemia	dual deficiency (e.g. iron and folate)
	myelodysplastic syndrome
	AIHA
	liver disease
	pernicious anemia
	folate deficiency

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 2. Differential Diagnosis of Anemia Based on MCV

Hypochromic microcytic (MCV<80)	Normochromic normocytic (80<MCV<100)		Macrocytic (MCV>100)

• Fe deficiency
• Thalassemia
• Lead Poisoning
• Sideroblastic
• Chronic disease (some cases)
	Low Reticultocytes:
	• Myelodysplasia
	• Infiltration (leukemia, myeloma, mets, infection)
	• Myelofibrosis
	• Aplasia
	• Chronic Disease (some cases)
	• Liver Disease
	• Uremia
	• Endocrine (hyper/hypothyroid, Addison's)
		High Reticulocytes:
		• Hemolytic anemia
		• Post-hemorrhagic anemia
		• Treated nutritional deficiency
			• Megaloblastic
			  • B12
			  • Folate
			  • Drugs
			• Myelodysplasia
			• Liver Disease
			• Alcohol
			• Reticulocytosis

Hematological History

- ❑ ID: background: Mediterranean, Asian, black (thalassemia), black (sickle 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 — 2x basal need
- ❑ puberty-growth spurt, menarche — 3x basal need
- ❑ pregnancy-maternal RBC, fetus — 4x basal need
- ❑ blood donation — 4x basal need
  - 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 3. Intraluminal Factors in Absorption of Non-Heme Iron

Promoters	Inhibitors
Gastric HCl	Achlorhydria Antacids
Reducing agents • ascorbic acid	Oxidants
In Fe^{2+} form	In Fe^{3+} form
Inorganic form	Organic form
Soluble chelators • amino acids • sugars • alcohol	Non-absorbable chelators • phosphate (milk) • phytates (cereals) • oxalate (spinach) • tannin (tea)

IRON TRANSPORT

❑ majority of non-heme Fe in plasma is bound to transferrin
❑ transferrin
- 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
- ferric Fe complexed to a protein called apoferritin
- hepatocytes are main site of ferritin storage
- minute quantities are present in plasma in equilibrium with intracellular ferritin

❑ hemosiderin
- aggregates or crystals of ferritin with the apoferritin partially removed
- macrophage-monocyte system is main source of hemosiderin storage

IRON INDICES

❑ bone marrow aspirate is the gold standard test for iron stores
❑ serum ferritin
- single most important blood test for iron stores
- falsely elevated in inflammatory disease, liver disease (from necrotic hepatocytes), neoplasm and hyperthyroidism

❑ serum iron
- varies significantly daily
- a measure of all non-heme Fe present in blood
- virtually all serum iron is bound to transferrin
- only a trace of serum Fe is free or complexed in ferritin

❑ total iron binding capacity (TIBC)
- high specificity for decreased iron, low sensitivity
- measure of total amount of transferrin present in blood
- normally, one third of the TIBC is saturated with Fe, remainder is unsaturated

❑ saturation
- serum Fe divided by TIBC, expressed as a proportion or a %

INTERPRETING IRON INDICES

Table 4. Interpreting Iron Indices

	Ferritin	Serum Iron	TIBC	RDW	Saturation
Iron Deficiency	↓↓	↓	↑	↑	↓↓
Chronic Disease	↑/N	↓/N	↓/N	N	N
Sideroblastic Anemia	↑	↑	N	No (dimophic picture)	—
Iron Overload	↑	↑	N	—	↑

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 **L**ines on gingivae and epiphyses of long bones on X-ray
E: Encephalopathy and **E**rythrocyte basophilic stippling
A: Abdominal colic and microcytic **A**nemia
D: Drops: wrist and foot drop. **D**imercaprol and E**D**TA 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 centre with iron
- ❑ fetal hemoglobin, HbF (δ 2) switches to adult forms HbA (β2) and HbA2 (δ 2) 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-thalessemia minor and sickle cell trait

THALASSEMIA
- ❑ 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

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

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 pO_2, deoxy Hb S polymerizes, leading to rigid crystal-like rods that distort membranes = SICKLES
❑ the pO_2 level at which sickling occurs is related to the precentage of Hb S present
- in heterozygotes (Hb AS) sickling occurs at a pO_2 of 40 mmHg
- in homozygous (Hb SS), sickling occurs at a pO_2 of 80 mmHg

❑ sickling is aggravated by
- increased H^+
- increased CO_2
- increased 2,3-DPG
- increased temperature and osmolality

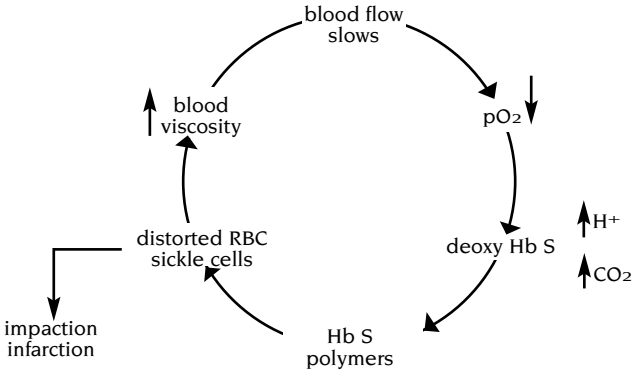

Figure 1. Pathophysiology of Sickling

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%)

Homozygous: 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

❑ 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 5. Organs Affected by Vaso-Occlusive Crisis

Organ	Problem
brain	seizures, hemiplegia
eye	hemorrhage, blindness
liver	infarcts, RUQ syndrome
lung	chest syndrome
gall bladder	stones
heart	hyperdynamic flow murmurs
spleen	enlarged (child); atrophic (adult)
kidney	hematuria; loss of renal concentrating ability
intestines	acute abdomen
placenta	stillbirths
penis	priapism
digits	dactylitis
femoral head	aseptic necrosis
bone	infarction, infection
ankle	leg ulcers

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

Pernicious Anemia
- ❑ auto-antibodies produced against gastric parietal cells leading to achlorhydria and no intrinsic factor secretion
  - intrinsic factor is required to stabilize B_{12} as it passes through the bowel
  - decreased intrinsic factor leads to decreased ileal absorption of B_{12}
- ❑ 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 B_{12} Deficiency
- ❑ cerebral (common; reversible with B_{12} 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 B_{12} and RBC folate
  - caution: low serum B_{12} leads to low RBC folate because of failure of folate polyglutamate synthesis in the absence of B_{12}
- ❑ 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 B_{12} (cobalamin (Co*)), PO
    - flushing dose (1mg) of cold B_{12}, IM to saturate tissue binders of B_{12} thus allowing radioactive B_{12} to be excreted in urine
    - 24 hour urine Co* measured
    - normal —> 5% excretion
  - Schilling test: part 2
    - tracer dose B_{12} (Co*) plus intrinsic factor, PO
    - flushing dose of cold B_{12}, injected IM
    - 24 hour urine Co* measured
    - normal test result (> 5% excretion) = pernicious anemia
    - abnormal test result (< 5% excretion) = intestinal causes (malabsorption)

Management
- ❑ B_{12} 100 µg IM monthly for life or oral B_{12}
- ❑ 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

- ❑ 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
- ❑ folate deficiency at time of conception and early pregnancy has been linked to neural tube defects

Management
- ❑ never give folate alone to individual with megaloblastic anemia because it will mask B_{12} 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 bilinogen
  - increased LDH
- ❑ tests exclusive for intravascular hemolysis
  - serum free hemoglobin present
  - methemalbuminemia (heme + albumin)
  - hemoglobinuria (immediate)
  - hemosiderinuria (delayed)

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

	Warm	Cold
Antibody Coating RBC	• IgG	• IgM
Temperature Detect by Coomb's	• 37°C	• 4-37 °C
Direct Coombs Test	• positive for antibodies	• positive for complement

Etiology	• idiopathic
	• secondary to lymphoproliferative disorder
	  • e.g. CLL, Hodgkin's
	• secondary to autoimmune disease
	  • e.g. SLE
	• drug induced
	  • penicillin
	  • quinine
	  • methyldopa
		• idiopathic
		• secondary to infection
		  • e.g. mycoplasma, EBV
		• secondary to lymphoproliferative disorder
		  • e.g. macroglobulinemia, CLL

Blood Film (see Colour Atlas H5)	• spherocytes	• agglutination
Management	• treat underlying cause • corticosteroids • splenectomy • immunosupression	• treat underlying cause • warm patient • plasmapheoresis • immunosuppresion

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)

TTP	HUS
• predominantly adult	• predominantly children
• **neurological symptoms (90%)**	
• H/A, somnolence, confusion, focal neurological findings, convulsion, stupor, coma	
• purpura (90%) due to severe **thrombocytopenia**	• **purpura (90-100%) due to severe thrombocytopenia**
• epistaxis, hematuria, hemoptysis and GI bleed	
• epistaxis, hematuria, hemoptysis and GI bleed	
• microangiopathic hemolytic anemia	• microangiopathic hemolytic anemia
• **fever (90-100%)**	
• GI	
• N/V, abdominal pain	
• **renal (40-80%)**	• **renal symptoms (90%)**
• abnormal UA, oliguria, ARF	• abnormal UA, oliguria, ARF
• etiology	• etiology
• idiopathic	• E. *coli* serotype O157:H7 virotoxin
• familial	
• secondary TTP	
• infection	
• enterobacteriaceae	
• viral: flu, HIV	
• systemic diseases	
• SLE and other CVD	
• cancer and chemotherapeutic drugs	
• diagnosis	• diagnosis
• by clinical picture	• by clinical picture
• CBC: anemia, thrombocytopenia	• same as TTP
• PT, PTT: normal	• stool C+S
• ESR: normal	
• negative Coombs'	

*Key characteristics bolded

Management
- ❑ plasmapheresis is the treatment of choice
- ❑ steroid is treatment of choice only in mild disease

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

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

Diagnosis
- ❑ serum
  - neutrophil count < 5.0 x 10^9/L
  - platelet count < 20 x 10^9/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 (50-60% 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

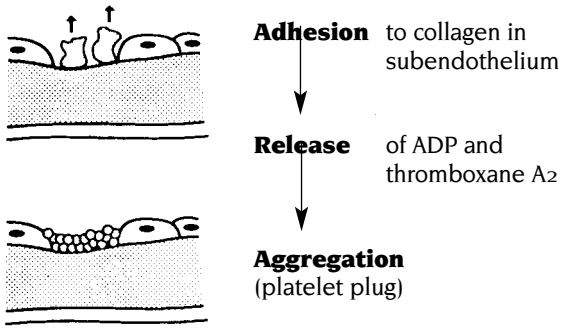

Figure 2. Primary Hemostasis

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

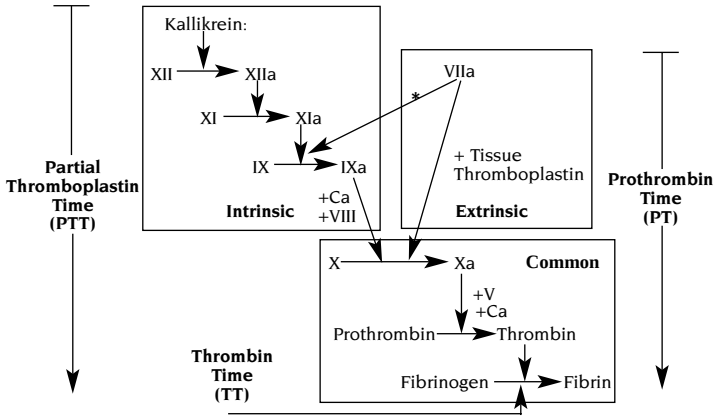

Figure 3. Secondary Hemostasis * tissue factor pathway

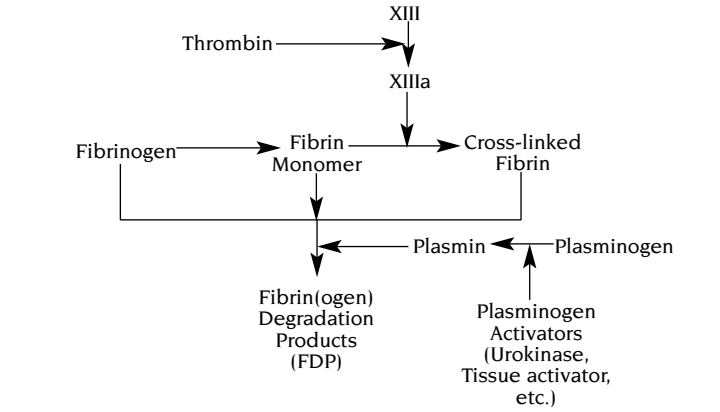

Figure 4. Fibrin Stabilization and Fibrinolysis

TESTS OF HEMOSTASIS

Table 8. Commonly Used Tests of Hemostasis

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

Table 9. Signs and Symptoms of Disorders of Hemostasis

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

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 B_{12}, 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

Features	Acute ITP	Chronic ITP
Peak Age	2-6 years	20-40 years
Sex Predilection	none	F > M (3:1)
History of Recent Infection	common	rare
Onset of Bleed	abrupt	insidious
Platelet Count	< 20 x 10^9/L	30-80 x 10^9/L
Duration	usually weeks	months to years
Spontaneous Remissions	80% or more	uncommon

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 10^9/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 deficiences are rare

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 (eg. hemarthroses)
    - heat treated Factor VIII concentrate
- ❑ major potentially life-threatening bleeding (eg. multiple trauma)
    - heat treated Factor VIII concentrate
- ❑ prophylaxis (eg. 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 IIA: decreased large and intermediate sized multimers in plasma and platelets (will see prolonged bleeding time, normal levels of factor VIII)
- ❑ type IIB: 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 IIB, the appearance of the large multimers in the circulation can cause thrombocytopenia
- ❑ Hemate P in selected cases
- ❑ conjugated estrogens

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

- ❑ 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)
- ❑ neurologic: intracranial bleeding
- ❑ skin: petechiae, eccyhmosis, 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
- ❑ hypercoaguable 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

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)

	INR	
	Range	**Target**
• pre-operative		
• surgery	1.5-2.5	2
• hip surgery	2-3	2.5
• prevention of venous thrombosis	2-3	2.5
• active venous thrombosis, pulmonary embolism and prevention of recurrent venous thrombosis	2-4	3
• prevention of arterial thrombo-embolism including mechanical heart valves	3-4.5	3.5
• INR should never exceed 5		

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

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 ancrod and hirudin
- ❑ patient may be re-exposed to heparin only under careful supervision

HEMATOLOGIC MALIGNANCIES

OVERVIEW

Myeloid
- ❑ clonal stem cell neoplasms
  - i. acute myeloid leukemia (clonal proliferation of immature cells)
  - ii. myeloproliferative disorders (proliferation of mature cells)
    - polycythemia rubra vera
    - chronic granulocytic (myelogenous) leukemia
    - idiopathic myelofibrosis
    - essential thrombocythemia
  - iii. myelodysplastic syndromes (defective differentiation)

Lymphoid
- ❑ all cells arise from a single abnormal lymphoid precursor (B or T)
  - i. acute lymphoblastic leukemia (arise from stem cell)
  - ii. lymphomas (arise from maturing lymphoid cell)
    - Hodgkin's lymphoma
    - non-Hodgkin's lymphoma
  - iii. 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

- ❑ 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 hematopoetic 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 B_{12}
  - transcobalamin I
  - eosinophils
  - basophils
  - blood histamine (from basophils)
- ❑ pruritus
- ❑ bruising
- ❑ thrombosis
- ❑ peptic ulcer disease (histamine increases acid secretion)

Table 12. Chronic Myeloproliferative Disorders

	PRV	CGL (CML)	IMF	ET
HCT	↑↑	↓/N	↓	N
WBC	↑	↑↑	↑/↓	N
PLT	↑	↑/↓	↑/↓	↑↑↑
LAP	↑↑	↓	↑/N	↑/N
marrow fibrosis	±	±	+++	±
splenomegaly	+	+++	+++	+
hepatomegaly	–	+	++	–

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
- ❑ ^{32}P

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 O_2 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, erythoid 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

❑ 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 2º 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 2° thrombocythemia

Management
❑ hydroxyurea
❑ ^{32}P
❑ 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, sulfinpyrazone 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

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

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

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

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

HODGKIN'S DISEASE
- ❑ substantial number represents monocloncal 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
  - Ca^{2+}, 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

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 10^9/L (usually > 10.0 x 10^9/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
- ❑ hypogammaglobinemia
- ❑ 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, hepato/splenomegaly, 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)

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

- ❑ 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 14. Characteristics of B Cell Malignant Proliferation

	CLL	Macroglobulinemia	Myeloma
Cell Type	lymphocyte lymphocyte	plasmacytoid	plasma cell
Protein	IgM if present	IgM	IgG, A, D or E
Lymph Nodes	very common	common	rare
Hepatosplenomegaly	common	common	rare
Bone Lesions	rare	rare	common
Hypercalcemia	rare	rare	common
Renal failure	rare	rare	common
Immunoglobulin Autoimmune Complications	common	infrequent	rare

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 eg. megaloblastic anemia
- ❑ increased peripheral destruction e.g. hypersplenism
- ❑ combinations e.g. lymphoma
- ❑ increased marginal pool or decreased storage pool egress e.g. viremia

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 B_{12}/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 (eg. 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, osteoperosis

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

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 thrombocythemia, lipid-storage disease, sarcoidosis, thalassemia major

BLOOD PRODUCTS AND TRANSFUSIONS

BLOOD GROUPS

Table 15. Blood Groups

Group	Antigen	Antibody
O	H	anti-A, anti-B
A	A	anti-B
B	B	anti-A
A B	A and B	nil

Table 16. Red Cells

Product	Indication
Packed Cells	symptomatic anemia bleeding with hypovolemia
Frozen Red Cells	rare blood groups multiple alloantibodies

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

RED CELLS

Packed Cells
- ❑ stored at 4ºC
- ❑ 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

Product	Indication
Random Donor (pooled)	thrombocytopenia with bleeding
Single Donor Platelets	potential BMT recipients
HLA Matched Platelets	refractoriness to pooled or single donor platelets

- ❑ 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 FACTORS

Table 18. Coagulation Factor Products

Product	Indication
Fresh Frozen Plasma	Depletion of multiple coagulation factors
Cryoprecipitate	Factor VIII deficiency Von Willebrand's disease Hypofibrinogenemia Hemate P
Factor VIII Concentrate	Factor VIII deficiency
Factor IX Concentrate	Factor IX deficiency

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
- Note: anaphylaxis is rare, usually in IgA deficient patients reacting against IgA in donor plasma

❑ 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 fo every 2 units of blood

Hyperkalemia

Circulatory Overload
- ❑ signs: dyspnea, orthopnea, cynasosis, 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

Drug	Common Formulary	Mechanism of Action	Clinical Uses	Common Side Effects	Contraindications

iron	iron gluconate
	iron sulphate
	iron fumarate
		• for synthesis of hemoglobin	• iron deficiency anemia treatment and prevention
			• pregnancy
				• in children: acute iron toxicity as
				  • necrotizing enterocolitis
				  • shock
				  • metabolic acidosis
				  • coma and death
					• iron overload

B12	cyanocobalamin hydroxycobalamin	• synthesis of folic acid and DNA	• B12 deficiency	• no significant toxicity	• N/A
folic acid	folic acid	• synthesis of purines and thymidylate thus DNA	• folic acid deficiency • pregnancy	• no significant toxicity	• N/A
erythropoietin	Epo	• stimulate RBC synthesis	• renal failure • marrow failure • myelodysplastic syndrome • autologous blood donation	• no significant toxicity	• N/A

Table 20. Chemotherapeutic Agents

Class	Example	Mechanism of Action	Common Toxicity	Examples of Clinical Use

alkylating agent	• nitrogen mustard
	• cyclophosphamide
	• nitrosurea
	• busulfan
	• cisplatin
		• cell cycle non-specific drugs
		• via alkylation of nucleophilic groups in base pairs
		• leading to cross-linking of bases or abnormal base-pairing or DNA breakage
			• marrow suppression
			• GI irritation
			• change in gonadal function
			• nitrogen mustard (cyclophosphamide): hemorrhagic cystitis
			• busulfan: adrenal insufficiency and pulmonary fibrosis
				• cyclophosphamide
				  • breast CA
				  • small cell lung CA
				  • NHL
				• busulfan
				  • CML
				• cisplatin
				  • advanced ovarian CA
				  • testicular CA

antimetabolites	• folic acid antagonist (methotrexate)
	• purine antagonist (mercaptopurine)
	• pyrimidine antagonist (5-FU)
	• hydroxyurea
		• 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
			• marrow suppression
			• oral mucositis
			• nausea and vomiting
				• methotrexate
				  • breast CA
				  • gestational trophoblastic CA
				  • ovarian CA
				• mercaptopurine
				  • AML
				• 5-FU
				  • breast CA
				  • GI CA
				  • hepatocellular CA
				• hydroxyurea
				  • CML

antibiotics	• anthracyclines (doxorubicin)
	• bleomycin
	• mitomycin-C
		• 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
			• anthracyclines
			  • marrow suppression
			  • severe alopecia
			  • cardiomyopathies
			• bleomycin
			  • pulmonary fibrosis
			  • pneumonitis
			  • hypersensitivity
			  • mucocutaneous reactions
			• mitomycin-C
			  • myelo-suppression
			  • nephrotoxic
				• anthracyclines
				  • breast CA
				  • AML
				  • lymphomas
				• bleomycin
				• testicular CA
				  • lymphomas
				• mitomycin-C
				  • GI malignancies

Table 20. Chemotherapeutic Agents (continued)

Class	Example	Mechanism of Action	Common Toxicity	Examples of Clinical Use
alkaloids	• vinblastine • vincristine • podophyllotoxin (etoposide) • taxol	• all are cell cycle specific • vincristine and vinblastine inhibit assembly of microtubules therefore mitotic spindles and M phase • podophyllotoxin activates opoisomerase II therefore DNA breaks down • taxol inhibits disassembly of microtubules therefore cells are stuck in M phase	• all have marrow suppression • vincristine and vinblastine • neurotoxic with areflexia, peripheral neuritis and paralytic ileus • taxol • neurotoxic as above	• vincristine and vinblastine • lymphomas • Wilm's tumour • podophyllotoxin • small cell lung CA • prostate CA • testicular CA • taxol • advanced breast CA • ovarian CA
hormones	• glucocorticoids • tamoxifen • flutamide • aminoglutethimide	• tamoxifen • as a partial E2 antagonist • flutamide: androgen receptor antagonist • aminoglutethimide: aromatase inhibitor in E2 synthesis	• glucocorticoid • refer to Endocrinology under Cushing's syndrome • tamoxifen • menopausal symptoms • long term: retinopathy • aminoglutethimide • menopausal symptoms • skin rashes	• glucocorticoids • CML • lymphomas • tamoxifen • breast CA • flutamide • prostate CA • aminoglutethimide • metastatic breast CA
others	• carboplatin • mitoxantrone	• carboplatin • DNA binding • mitoxantrone • ?DNA breaks	• carboplatin • myelo-suppression • nausea, vomiting • nephrotoxicity • mitoxantrone • cardiotoxicity • alopecia	• carboplatin • ovarian CA • mitoxantrone • AML • NHL • breast CA • ovarian CA • lung CA

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