

HEMATOLOGY

Dr. I. Quirt

Susan Armstrong and Tara Weir, editors

Eyal Cohen, associate editor

ANEMIA	2	LEUKEMIAS	26
Clinical Approach to Anemia		Acute Leukemia (AML, ALL)	
IRON METABOLISM	3	Bone Marrow Transplantation	
Iron Intake (Dietary)		Myelodysplastic Syndromes	
Physiologic Causes of Increased Fe Requirements		CHRONIC MYELOPROLIFERATIVE	28
Iron Absorption		DISORDERS	
Iron Transport		Common Features	
Iron Storage		Polycythemia Rubra Vera	
Iron Indices		Chronic Granulocytic (Myelogenous) Leukemia	
Interpreting Iron Indices		Idiopathic Myelofibrosis	
Laboratory Features		Essential Thrombocythemia	
IRON DEFICIENCY	5	MALIGNANT CLONAL	32
Physiologic Causes		PROLIFERATIONS OF B CELLS	
Pathological Causes		Chronic Lymphocytic Leukemia	
Clinical Presentation		Plasma Cell Myeloma (Multiple Myeloma)	
Diagnosis		Light Chain Disease	
Iron Treatment		Monoclonal Gammopathy of Unknown Significance	
Anemia Refractory to Oral Iron		Macroglobulinemia of Waldenstrom	
SIDEROBLASTIC ANEMIA	6	Macroglobulinemia-Hyperviscosity Syndrome	
THE ANEMIA OF CHRONIC DISEASE	7	LYMPHOMAS	35
HEMOGLOBIN AND	7	Hodgkin's Disease and Non-Hodgkin's Lymphoma	
HEMOGLOBINOPATHIES		Staging	
Thalassemia		Hodgkin's Disease	
I. Heterozygous: β -Thalassemia Minor		Non-Hodgkin's Lymphoma	
II. Homozygous: β -Thalassemia Major		TUMOUR LYSIS SYNDROME	38
III. Alpha Thalassemias		WBC DISORDERS	38
Sickle Cell Anemia		Neutrophilia	
Megaloblastic Anemia		Leukemoid Reactions	
B ₁₂ Deficiency		Neutropenia	
Pernicious Anemia		Agranulocytosis	
Folate Deficiency		BLOOD PRODUCTS AND TRANSFUSIONS ...	40
Hemolytic Anemias		Red Cells	
I. Hereditary Hemolytic Anemia		Blood Groups	
Structural Abnormalities in Cytoskeleton		Platelets	
Enzymatic Abnormalities in RBC		Coagulation Factors	
Hemoglobinopathies		Group and Reserve Serum	
II. Acquired Hemolytic Anemia		Acute Complications of Blood Transfusions	
Autoimmune Hemolytic Anemia		Delayed Complications in Transfusions	
RBC Fragmentation Syndromes		APPROACH TO SPLENOMEGALY	43
Thrombotic Thrombocytopenic Purpura and		APPROACH TO BLOOD FILM	43
Hemolytic Uremic Syndrome		EXAMINATION	
APLASTIC ANEMIA	17	MEDICATIONS COMMONLY USED IN	44
HEMOSTASIS	18	HEMATOLOGY	
Three Phases of Hemostasis			
Tests of Hemostasis			
Thrombocytopenia and Other Disorders of Primary			
Hemostasis			
Idiopathic (Autoimmune)			
Thrombocytopenic Purpura			
Chronic (Adult-type) ITP			
Disorders of Secondary Hemostasis			
Hereditary			
Acquired			
Thrombosis			
Heparin-Induced Thrombocytopenia			

CLINICAL APPROACH TO ANEMIA

Table 1. Approach to Anemia	
Low or Normal Reticulocytes	High Reticulocytes
hypochromic microcytic (mean red cell volume MCV < 80) <ul style="list-style-type: none"> • iron deficiency • thalassemia • sideroblastic anemia • lead poisoning • chronic disease 	<ul style="list-style-type: none"> • treated nutritional deficiency
normochromic normocytic (80 < MCV < 100) <ul style="list-style-type: none"> • chronic disease • liver disease • uremia • endocrine disorders (hypo/hyperthyroid, Addison's) • connective tissue diseases • primary marrow abnormalities <ul style="list-style-type: none"> • myelodysplasia • infiltration (leukemia, myeloma, mets, infection) • myelofibrosis • aplasia 	<ul style="list-style-type: none"> • hemolytic anemia • post hemorrhagic anemia
macrocytic/megaloblastic (MCV > 100) <ul style="list-style-type: none"> • B₁₂ • folate • drugs (MTX, cyclophosphamide, nitrous oxide, arsenic) macrocytic <ul style="list-style-type: none"> • hypothyroidism • hypoplastic marrow, aplasia • liver disease • alcohol • smoking 	

History

- bleeding
- drugs e.g. ASA, NSAIDs
- family history and ethnic background
- diet
- malabsorption
- recent pregnancy

Symptoms

- general: fatigue, malaise, weakness
- CVS: palpitations, syncope, dyspnea
- neurologic: headache, vertigo, tinnitus

Signs

- CVS: tachycardia, systolic flow murmur, wide pulse pressure, CHF
- pallor: mucous membranes, conjunctivae (Hb < 90), skin creases (Hb < 75)
- ocular bruits (Hb < 55)
- splenomegaly
- lymphadenopathy
- rectal (occult blood)
- rare
 - koilonychia (spoon-shaped nails) as in iron deficiency anemia
 - telangiectasia as in hemolytic anemia
 - jaundice as in hemolytic anemia

CBC

- WBC or platelet count abnormal
 - marrow disease
 - hypersplenism
 - DIC
- WBC and platelet count normal
 - focused history, physical exam, CBC, and peripheral blood film (PBF)

RDW (Red Cell Distribution Width)

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

IRON METABOLISM

IRON INTAKE (Dietary)

- "average" Canadian adult diet = 10-20 mg Fe/day
- absorption = 5-10% (0.5-2 mg/day)
- Fe absorption increases with
 - increased erythropoiesis e.g. pregnancy
 - anemia
 - Fe depletion
- 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

- occurs in duodenum mainly with iron combining with apoferritin to form ferritin and then absorbed through villi

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 a beta-globulin called transferrin
- ❑ transferrin
 - 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 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 the 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 biopsy 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
 - 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)
 - 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

- ❑ Fe deficiency (uncomplicated): serum Fe is low, TIBC is elevated, saturation is very low and serum ferritin is very low
- ❑ anemia of chronic disease: serum Fe is slightly reduced, but the TIBC is low normal or reduced; therefore, saturation is normal or only slightly reduced; serum ferritin is normal or slightly increased
- ❑ iron overload: serum iron is elevated, TIBC is normal, saturation is elevated and serum ferritin is elevated

Table 3. Iron Laboratory Features

	ferritin	serum iron	TIBC	RDW	Saturation
iron deficiency	↓↓	↓	↑	↑	↓↓
chronic disease	↑/N	↓/N	↓/N	N	N
sideroblastic anemia	↑	↑	N	N	—
thalassemia	↑/N	↑/N	↓/N	↑/N	—
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)
 - hypochromia (Hb 90-100 g/L)

- most common cause of anemia in Canada
- imbalance of intake vs. requirements or loss

PHYSIOLOGIC CAUSES

- increased need for iron in the body
- infancy
- adolescence, menstruation
- pregnancy, lactation

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
- dry skin
- dysphagia (esophageal web, Plummer-Vinson ring)
- nails
 - brittle
 - koilonychia
- glossitis
- angular stomatitis
- pica (appetite for bizarre substances e.g. ice, paint, dirt)

DIAGNOSIS

- serum
 - ferritin < 20 is diagnostic of iron deficiency anemia
 - iron deficiency anemia unlikely if ferritin > 100
 - platelet count may be elevated
- peripheral blood film (see Colour Atlas E1)
 - hypochromic microcytosis
 - pencil forms
 - target cells (thin)
- bone marrow
 - intermediate and late erythroblasts
 - micronormoblastic maturation
 - Fe stain (Prussian blue) shows decreased iron in macrophages
 - decreased normal sideroblasts

IRON 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
- reticulocytes begin to increase after one week
- Hb normalizes by 10 grams per week
- ensure that the hemoglobin returns completely to normal
- if serum ferritin normal discontinue iron therapy

ANEMIA REFRACTORY TO ORAL IRON

- medication
 - poor preparation (e.g. expired)
 - drug interactions
- patient
 - poor compliance
 - bleeding continues
 - malabsorption (rare)
- physician
 - misdiagnosis

- ❑ group of disorders with various defects in porphyrin biosynthetic pathway leading to a reduction in heme synthesis and thus 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 mitochondria forms ring around the red blood cell nucleus
 - large
 - abnormal finding

Etiology

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

Diagnosis

- ❑ serum
 - 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 disorder
- ❑ oral pyridoxine (vitamin B6)
 - hereditary and secondary acquired forms usually responsive
 - myelodysplastic sideroblastic anemia not responsive

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
 - erythropoietin level is low in renal failure
- iron cannot be removed from its storage pool in hepatocytes and reticuloendothelial cells

Diagnosis

- 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 treated
- erythropoietin may normalize the hemoglobin value
- dose of erythropoietin required is lower for patients with renal disease
- only treat patients who can benefit from a higher hemoglobin level

HEMOGLOBIN AND HEMOGLOBINOPATHIES

Hemoglobin Structure and Production

- fetal hemoglobin, HbF ($\alpha_2 \gamma_2$) switches to adult forms HbA ($\alpha_2 \beta_2$) and HbA₂ ($\alpha_2 \delta_2$) at 3-6 months of life
- HbA constitutes 97% of adult hemoglobin
- HbA₂ constitutes 3% of adult hemoglobin
- 4 α genes are located on chromosome 16
- 2 β genes are located on chromosome 11
- beware of the possibility of mixed defects
 - e.g. β -thalassemia minor and sickle cell (HbS) trait

THALASSEMIA

I. HETEROZYGOUS: β -Thalassemia Minor

- common condition in Canada, particularly in Greeks, Italians, Chinese, and Blacks

Clinical Presentation

- mild or no anemia
- spleen may be palpable
- may be masked by Fe deficiency

Diagnosis

- serum
 - Hb 90-140 g/L, MCV < 70

- peripheral blood
 - microcytosis +/- hypochromia
 - target cells and oval-shaped cells ("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 beta chain synthesis due to point mutation in the beta gene promoter or enhancer on chromosome 11
- excess alpha chains relative to beta chain leading to ineffective erythropoiesis and hemolysis of RBC
- compensatory increase in HbF

Clinical Presentation

- start presenting at 3-6 months because of replacement of HbF by HbA
- severe anemia developing in the first year of life
- jaundice
- stunted growth and development (hypogonadal dwarf)
- gross hepatosplenomegaly (extramedullary hematopoiesis)
- skeletal 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 (early)
 - hemochromatosis (late, secondary to transfusions), usually 20-30 years old

Diagnosis

- serum
 - 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

- transfusions
- Fe chelators to prevent iron overload
- bone marrow transplant (if suitable donor)

III. ALPHA THALASSEMIA

Pathophysiology

- autosomal recessive
- deficit of alpha chains
- 4 grades of severity depending on the number of defective alpha genes
 - 1 - silent
 - 2 - trait
 - 3 - Hb H Disease (presents in adults)
 - 4 - Hb Bart's (hydrops fetalis)

- ❑ Hb Bart's made of 4 gamma chains; not compatible with life
- ❑ Hb H made of 4 beta chains, is unstable, and leads to inclusion bodies

Diagnosis

- ❑ peripheral blood film
 - microcytes, hypochromia, occasional target cells
 - screen for Hb H inclusion bodies
- ❑ Hb electrophoresis not diagnostic
- ❑ DNA analysis using alpha gene probe

Management

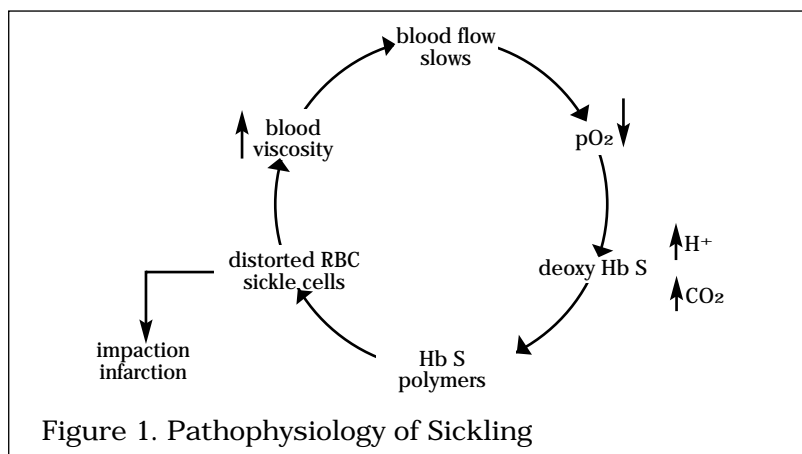
- ❑ same as beta thalassemia

SICKLE CELL ANEMIA

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

Mechanisms of Sickling

- ❑ at low pO₂, deoxy Hb S polymerizes, leading to rigid crystal-like rods that distort membrane = SICKLES (see Figure 1)
- ❑ the pO₂ level at which sickling occurs is related to the % of Hb S present
- ❑ if the patient is heterozygous (Hb AS), the sickling phenomenon occurs at a pO₂ of 40 mmHg
- ❑ if the patient is homozygous (Hb SS), sickling occurs at 80 mmHg
- ❑ sickling also aggravated by
 - increased H⁺
 - increased CO₂
 - increased 2,3-DPG
 - increased temperature and osmolality



Heterozygous: Hb S Trait

- ❑ clinical presentation
 - the patient will appear normal except at times of extreme hypoxia and infection
- ❑ diagnosis
 - serum: Hb normal
 - peripheral blood: normal except for 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 E5)
 - screening test: sickle cell prep
 - Hb electrophoresis (confirmatory test): Hb S fraction > 0.80

Management

- ❑ prevention 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 Hb F
 - causes derepression of the gene for Hb F or by initiating differentiation of stem cells in which this gene is active; presence of Hb F in the SS cells decreases polymerization and precipitation of Hb S
 - Note: hydroxyurea is cytotoxic and may cause bone marrow suppression

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

Table 4. Organs Affected by Vaso-Occlusive Crisis

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

MEGALOBLASTIC ANEMIA

- ❑ 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

- diet
 - rare (strict vegetarians)
- 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; often associated with hypoparathyroidism, hypogammaglobulinemia
 - 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
- associated with thyroid and adrenal deficiency
- often > 60 years old

Neurological Lesions in B₁₂ Deficiency

- cerebral (common; reversible with B₁₂ therapy)
 - confusion
 - 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 limb more than upper limb
- psychiatric symptoms
 - dementia
 - delirium
- never give folate alone to individual with megaloblastic anemia because it will mask B₁₂ deficiency and neurological degeneration will continue

Diagnosis

- serum
 - anemia often severe +/- neutropenia +/- thrombocytopenia
 - MCV > 120 femtoliters
 - 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 (see Colour Atlas E3)
 - oval macrocytes
 - hypersegmented neutrophils
- 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) of labelled B₁₂ (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
- watch for hypokalemia (due to return of potassium to intracellular sites) and thrombocytopenia

FOLATE DEFICIENCY

- 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 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 needs
 - 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 conception and early pregnancy has been linked to neural tube defects

Management

- 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

Classification

- hereditary causes
 - abnormal membrane (spherocytosis, elliptocytosis)
 - abnormal glycolytic pathway (hexokinase deficiency)
 - abnormal glutathione metabolism (G6PD deficiency)
 - abnormal hemoglobin synthesis (thalassemias, hemoglobinopathies)

- acquired causes
 - 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 (see Colour Atlas E2)
 - increased unconjugated bilirubin
 - increased urine bilinogen
 - increased LDH
- tests exclusive for intravascular hemolysis
 - reduced haptoglobin
 - 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 antigens 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; the RBC 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
- 22 per 100 000
- most common type of hereditary hemolytic anemia
- abnormality in spectrin

- blood film shows spherocytes (see Colour Atlas E16)
- increased osmotic fragility
- positive autohemolysis test
- sometimes confused with immune hemolytic anemia
- treatment: splenectomy (immunize against pneumococcus first)
avoid in childhood

Hereditary Elliptocytosis

- autosomal dominant
- 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
- neonatal jaundice
- chronic hemolytic anemia
- infection

Diagnosis and Management

- high index of suspicion
- transfusion in severe cases
- stop offending drugs or food
- G-6-PD 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

HEMOGLOBINOPATHIES (see Thalassemia/Sickle Cell Anemia Section)

II. ACQUIRED HEMOLYTIC ANEMIA

AUTOIMMUNE HEMOLYTIC ANEMIA

Autoimmune Hemolytic Anemia with Warm-Reacting Antibodies (IgG)

Pathophysiology

- RBC coated with IgG or complement (C3d) or both
- associated with extravascular hemolysis (mainly in spleen)

Classification

- idiopathic
- secondary to
 - lymphoproliferative disorders (CLL, Hodgkin's disease, non-Hodgkin's lymphoma)
 - autoimmune (SLE)
- drug induced (penicillin, quinine/quinidine, alpha methyl dopa)

Diagnosis

- positive direct antiglobulin test (direct Coombs') best detected at 37°C (hence "warm-reacting antibodies")
- spherocytes in blood film
- exclude delayed transfusion reaction

Management

- treat underlying cause
- corticosteroids
- splenectomy
- immunosuppressives

Autoimmune Hemolytic Anemia with Cold-Reacting Antibodies (IgM)

Pathophysiology

- either monoclonal or polyclonal IgM attached to RBC surface antigens in peripheral circulation where $4^{\circ}\text{C} < T < 37^{\circ}\text{C}$
- antibodies will detach from the surface antigen if $T >$ thermal amplitude
- thermal amplitude is the temperature at which IgM is attached to RBC surface
- associated with intravascular hemolysis

Classification

- idiopathic
- secondary to
 - lymphoproliferative disorders (CLL, Hodgkin's disease, non-Hodgkin's lymphoma)
 - infections (*Mycoplasma pneumoniae*, EBV)

Diagnosis

- positive cold agglutinin test best at 4°C
- positive direct Coombs' for complement at any temperature
- agglutination in blood film (see Colour Atlas E4)

Management

- treat underlying cause
- warm the patient above the thermal amplitude of the antibody
- plasmapheresis
- immunosuppressives

RBC FRAGMENTATION SYNDROMES

Classification

- cardiac and large vessel abnormalities
- small vessel disease (microangiopathic)
 - 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 5. Thrombotic Thrombocytopenia purpura (TTP) and Hemolytic uremic syndrome (HUS)

TTP	HUS
<ul style="list-style-type: none"> <input type="checkbox"/> predominantly adult <input type="checkbox"/> neurological symptoms (90%) <ul style="list-style-type: none"> • H/A, somnolence, confusion, focal neurological findings convulsion, stupor, coma <input type="checkbox"/> purpura (90%) due to severe thrombocytopenia <ul style="list-style-type: none"> • epistaxis, hematuria, hemoptysis and GI bleed <input type="checkbox"/> microangiopathic hemolytic anemia (see Colour Atlas E6) <input type="checkbox"/> fever (90-100%) <input type="checkbox"/> GI <ul style="list-style-type: none"> • N/V, abdominal pain <input type="checkbox"/> renal (40-80%) <ul style="list-style-type: none"> • abnormal UA, oliguria, ARF <input type="checkbox"/> etiology <ul style="list-style-type: none"> • idiopathic • familial • secondary TTP <ul style="list-style-type: none"> • infection <ul style="list-style-type: none"> • enterobacteriaceae • viral: flu, HIV • systemic diseases <ul style="list-style-type: none"> • SLE and other CVD • cancer and chemotherapeutics <input type="checkbox"/> diagnosis <ul style="list-style-type: none"> • by clinical picture • CBC: anemia, thrombocytopenia • PT, PTT: normal • ESR: normal • negative Coombs' 	<ul style="list-style-type: none"> <input type="checkbox"/> predominantly children <input type="checkbox"/> renal symptoms (90%) <ul style="list-style-type: none"> • abnormal UA, oliguria, ARF <input type="checkbox"/> purpura (90-100%) due to severe thrombocytopenia <ul style="list-style-type: none"> • epistaxis, hematuria, hemoptysis and GI bleed <input type="checkbox"/> etiology <ul style="list-style-type: none"> • <i>E. coli</i> serotype O157:H7 virotoxin <input type="checkbox"/> diagnosis <ul style="list-style-type: none"> • by clinical picture • the same as TTP • stool C+S

Management

- plasmapheresis with platelet transfusion is the treatment of choice
- steroid is treatment of choice only in mild diseases

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 (cell mediated)
- paroxysmal nocturnal hemoglobinuria
- marrow replacement
- congenital

Clinical Presentation

- occur 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 as SOB, pallor and fatigue
- presentation of neutropenia ranges from infection in the mouth to septicemia

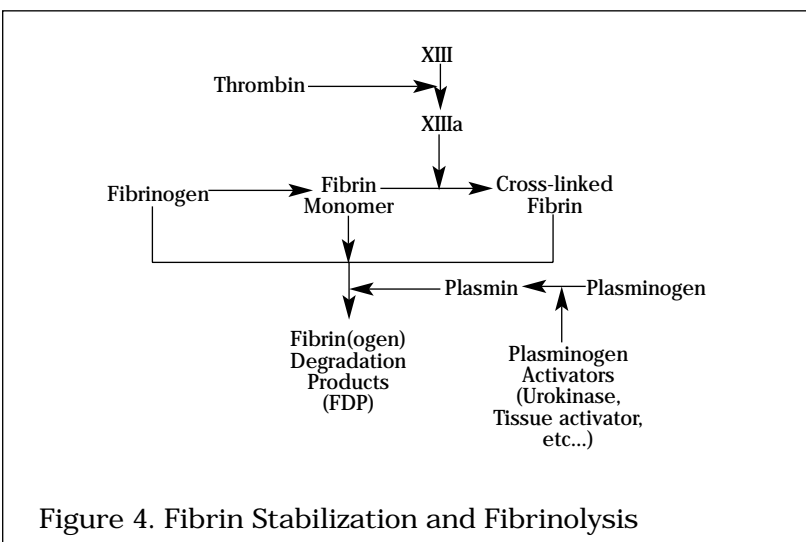
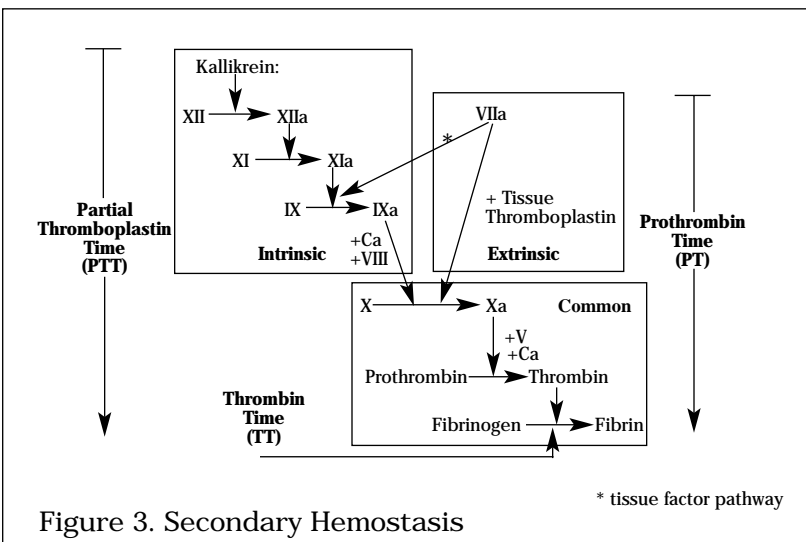
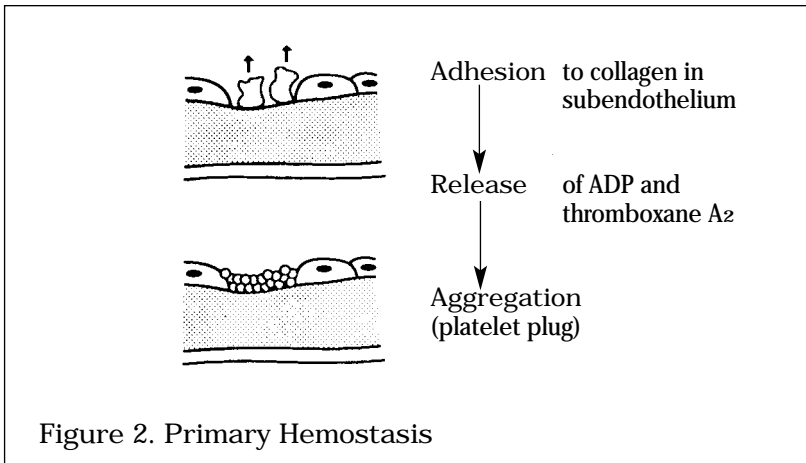
Diagnosis

- serum
 - neutrophil count $< 5.0 \times 10^9/L$
 - platelet count $< 20 \times 10^9/L$
 - corrected reticulocyte count $< 1\%$
- 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)
- cyclosporin
- 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

THREE PHASES OF HEMOSTASIS



TESTS OF HEMOSTASIS

Platelets

- number: count, estimate
- bleeding time
- aggregation

Coagulation

- PTT (partial thromboplastin time)
 - purpose: measure intrinsic pathway i.e. factors VIII, IX, XI and XII
 - normal: 25 seconds
- PT (prothrombin time)
 - purpose: measure the extrinsic pathway i.e. factor VII in particular
 - normal: 12 seconds
- INR (international normalized ratio)
 - ratio of patient's PT is compared to mean PT for a group of normal individuals
 - ratio is then adjusted for sensitivity of the lab's thromboplast determined by the international sensitivity index; thus $INR = (PT\ of\ patient / PT\ of\ the\ norm)$
 - use of INR permits doctors to obtain the appropriate level of anticoagulation independent of lab reagents and to follow published recommendations for intensity of anticoagulation
 - normal: 1
- TT (thrombin time)
 - purpose: measure deficiency of fibrinogen and inactivation of prothrombin
 - normal: 14-16 seconds

Fibrinolysis

- euglobulin lysis time

Other

- fibrinogen
- fibrinogen degradation products (FDPs)
 - indications
 - DIC
 - HELLP
 - microangiopathic hemolytic anemia
 - heparin induced thrombocytopenia
- specific factor assays
- tests of physiological inhibitors (antithrombins, protein S, protein C, hereditary resistance to APC)
- tests of pathologic inhibitors (lupus anticoagulant)

	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

Classification

I. 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

II. Platelets

- dysfunction
 - hereditary
 - von Willebrand's disease, others (rare)
 - acquired
 - drugs (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 (e.g. varicella, mumps, HIV, EBV, CMV, parvo)
 - increased destruction
 - drugs (quinidine, sulfas, thiazides, heparin)
 - ITP
 - allo-antibodies
 - HIV positivity
 - sepsis
 - increased consumption
 - DIC
 - microangiopathies (TTP)
 - sequestration
 - splenomegaly
 - dilutional
 - massive transfusion with stored blood

IDIOPATHIC (AUTOIMMUNE) THROMBOCYTOPENIC PURPURA (ITP)

Table 7. 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

Pathophysiology

- IgG autoantibody
- spleen
 - site of antibody production and platelet destruction
 - usually not palpable

Clinical Presentation

- insidious onset
- mucosal or skin bleeding
- easy bruising
- female with menorrhagia

Laboratory Results

- peripheral blood film: decreased platelets, large platelets
- bone marrow: plentiful megakaryocytes
- anti-platelet antibodies present in most

Management

- conservative if mild
- steroids: moderate dose, then taper (80% responsive)
- splenectomy if steroids fail
- other: immunosuppressives, platelets, plasma exchange, Danazol, IV gamma globulin

Prognosis

- fluctuating course
- major concern is cerebral hemorrhage at platelet counts < 5,000

DISORDERS OF SECONDARY HEMOSTASIS

Classification

I. Hereditary

- Factor VIII: Hemophilia A, von Willebrand's
- Factor IX: Hemophilia B (Christmas Disease)
- Factor XI
- other factor deficiencies 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
- mild (> 5% VIII), moderate (1-5%), severe (< 1%)

Clinical Presentation

- hemarthroses, hematomas, GI and GU bleeding
- bleeding in response to trauma (mild and moderate disease)
- spontaneous bleeding (severe disease)

Laboratory Results

- prolonged PTT, normal INR (PT)
- decreased factor VIII
- vWF usually normal or increased

Management

- minor but not trivial bleeding (e.g. hemarthroses)
 - heat treated Factor VIII concentrate (or cryoprecipitate)
- 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 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
- moderate to severe
 - as above but worse, occasionally soft-tissue hematomas, petechiae rare

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
- cryoprecipitate in selected cases
- conjugated estrogens

III. Factor IX Deficiency

- Christmas disease, hemophilia B
- X-linked recessive
- clinical picture identical with hemophilia A
- main treatment is Factor IX concentrate

IV. Factor XI Deficiency

- 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 (chronic, acute), DIC
- platelet dysfunction: EtOH
- 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
- biliary obstruction
- malabsorption e.g. celiac disease
- drugs
 - oral anticoagulants via inhibition of factors II, VII, IX, X and Protein C and Protein S
 - antibiotics eradicating gut flora which is 50 % of vitamin K supply
- hemorrhagic disease of newborn

Diagnosis

- PTT is normal but INR (PT) is elevated
- decreased factors II, VII, IX and X (because vitamin K dependent)

Management

- vitamin K 10-20 mg SC (not IM)

III. Disseminated Intravascular Coagulation (DIC)

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
- 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
 - 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 FDP's, short lysis time)
 - extent of fibrin deposition (urine output, urea, RBC fragmentation)

Management

- recognize early
- TREAT UNDERLYING DISORDER!
- life support measures
- replacement with plasma and platelets

THROMBOSIS

Virchow's Triad

- stasis
- hypercoaguable state
- endothelial injury

Mechanisms

- endothelial damage
- blood flow
 - stasis
 - turbulence
 - hyperviscosity
- blood components
 - platelets
 - contact factors
 - thrombin
 - Factor VIII
 - fibrin
- hypercoagulability
 - cancer
 - pregnancy
 - birth control pills
 - DIC
 - lipids
 - decrease of physiological inhibitors (antithrombin-III, protein C, protein S)
 - hereditary resistance to activated protein C (Factor V Leiden mutation)

Management (acute and prophylaxis)

- 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 8)

- thrombolytics
 - plasminogen activators (streptokinase, urokinase, TPA)
 - snake venom enzymes (ancrod)
- antiplatelet agents
 - ASA
 - sulfinopyrazone
 - dipyridamole

Table 8. Monitoring Coumadin Therapy (therapeutic ranges)

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

HEPARIN-INDUCED THROMBOCYTOPENIA

HIT-I

- non-immune
- decrease in platelet count usually seen early, 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 5 to 15 days into heparin therapy.
- 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 10⁹/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 (e.g. fever/chills, flushing, etc...), transient global amnesia

Laboratory Features

- many assays under development
- C-serotonin release assay is the one currently used in Toronto

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

ACUTE LEUKEMIA (AML, ALL)

- ❑ malignant disease
- ❑ clonal proliferation of immature hematopoietic cells
- ❑ malignant transformation of hematologic progenitor cells followed by cellular replication and expansion of the transformed clone

Pathophysiology

- ❑ uncontrolled growth of blasts in marrow leads to
 - suppression of normal hematopoietic cells which leads to marrow failure i.e. anemia, infections, bleeding complications
 - appearance of blasts in peripheral blood
 - accumulation of blasts in other sites e.g. lymph nodes, liver, spleen, skin, gums, CNS
 - metabolic consequences of a large tumour mass
- ❑ chronic myeloproliferative disorders can transform into AML
- ❑ myelodysplastic syndromes can transform into AML

Clinical Features of Acute Leukemia

- ❑ decrease in normal hematopoiesis
 - anemia
 - pallor, weakness, fatigue
 - thrombocytopenia
 - purpura
 - mucosal bleeding
 - associated with DIC (promyelocytic leukemia a type of AML)
 - neutropenia --> infections
 - septicemia
 - pneumonitis
 - skin and mucosa
- ❑ accumulation of blast cells in marrow
 - skeletal pain
 - bony tenderness, especially sternum
- ❑ accumulation of blast cells in other sites
 - lymphadenopathy, especially ALL
 - hepatosplenomegaly, especially ALL
 - gums, especially monocytic leukemia (a type of AML)
 - skin, especially monocytic leukemia
 - CNS, especially ALL e.g. N/V, H/A, blurring of vision, diplopia, papilledema +/- hemorrhage
 - gonads, especially ALL
 - Roth spots (oval retinal hemorrhages surrounding pale spot)
- ❑ 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 E7, E11)
 - decreased hemoglobin (usually normocytic, normochromic anemia) and platelets
 - variable leukocyte count
 - decrease in normal granulocytes
 - presence of blast cells
- ❑ bone marrow
 - usually hypercellular
 - increased blast cells (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, Ca^{2+} , and LFT's
- ❑ baseline urea and creatinine
- ❑ chest x-ray to r/o mediastinal compression and infection
- ❑ LP to r/o meningeal involvement as in ALL

Table 9. To Differentiate AML From ALL - Remember Big and Small	
AML	ALL
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

Management of Acute Leukemia

- to cure - defined as survival that parallels age-matched population
- first step is complete remission, defined as normal peripheral blood smear, normal bone marrow with no excess blasts, and normal clinical state
- leukemia will recur after complete remission if no further treatment given
- aims of treatment
 - eliminate abnormal clone - cytotoxic therapy
 - allow repopulation of marrow with normal hemopoietic cells (including bone marrow transplant)
 - supportive treatment
- eliminate abnormal clone

- ALL**
1. Induction
 2. Consolidation
 3. Intensification
 4. Maintenance
 5. Prophylaxis
CNS with XRT or MTX

- AML**
1. Induction
 2. Consolidation or BMT

- supportive care
 - prophylaxis against infection via regular C&S of urine, feces, sputum, oropharynx, catheter sites, perianal area
 - antibiotics if developed fever with C&S of all orifices and chest x-ray
 - platelet and red cell transfusions - CMV negative products
 - prevention and treatment of metabolic abnormalities

Prognosis

- achievement of first remission: 60-90%
- childhood ALL: 70% long term remission (> 5 years)
- adult ALL: 20% 5 year survival
- AML
 - median survival: 12-24 months
 - 5 year survival: 20%
- these statistics may be improved by BMT
- risk of leukostasis with WBC count > 100 000

BONE MARROW TRANSPLANTATION

- allows even more intensive therapy
- very high doses of chemo +/- whole body RT
- "marrow rescue"
 - allogeneic - HLA identical sibling
 - donor must be < 55 years
 - autologous - from self
- complications
 - cytopenias - especially neutropenia and thrombocytopenia
 - infections - especially opportunistic
 - drug toxicity

- graft rejection
- graft vs. host disease = graft versus leukemia (G vs. L)
- NB: A small amount of G vs. L may actually be beneficial as graft immune system destroys malignant host cells

MYELOYDYSPLASTIC 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)
- present with fatigue, infection, and/or bleeding related to bone marrow failure
- most common in elderly, usually > 70 and post-chemotherapy or radiation
- usually insidious in onset
- clinical presentation
 - fatigue, weakness, pallor, infections, bruising and rarely weight loss, fever, and hepatosplenomegaly
- diagnostic triad
 1. anemia \pm thrombocytopenia \pm neutropenia
 2. bone marrow hypoplasia
 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

Types

- 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)
- bone marrow transplant may be curative

CHRONIC MYELOPROLIFERATIVE DISORDERS

- clonal abnormalities of stem cell resulting in 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)

	PRV	CGL (CML)	IMF	ET
HCT	↑↑	↓/N	↓	N
WBC	↑	↑↑	↑/↓	N
PLT	↑	↑/↓	↑/↓	↑↑↑
LAP	↑↑	↓/N	↑/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

- 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

- poor tissue oxygenation
 - high altitude
 - chronic cardiovascular or pulmonary disease
 - hemoglobinopathies with increased O₂ affinity
- local renal hypoxia
 - renal artery stenosis
 - renal cysts

- ectopic production of erythropoietin
 - uterine leiomyoma
 - cerebellar hemangioma
 - hepatocellular CA
 - pheochromocytoma
 - renal cell CA
- spurious (decrease in plasma volume)

CHRONIC GRANULOCYTIC (MYELOGENOUS) LEUKEMIA

- disorder of middle-age characterized by an overproduction of myeloid cells

Clinical Features

- secondary to splenic involvement
 - upper left quadrant pain and fullness
 - 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
- 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
 - detection of this fusion gene is a diagnostic test for CML (present in over 90% of patients)
- leukocyte alkaline phosphatase (LAP)
 - a normal constituent of secondary neutrophil granules
 - low and often 0 (normal or increased in other chronic myeloproliferative diseases and reactive states)
- peripheral blood film (see Colour Atlas E9)
 - 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

Management

- hydroxyurea or occasionally busulfan
- allopurinol and antihistamines
- interferon
- only curative treatment is bone marrow transplantation

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

IDIOPATHIC MYELOFIBROSIS

- marrow replaced by fibrosis - abnormal megakaryocytes stimulate collagen deposition

Clinical Features

- as for CGL except no priapism or encephalopathy

Diagnostic Features

- often a significant degree of hemolysis due to hypersplenism and red cell fragmentation
- peripheral blood film (see Colour Atlas E14)
 - tear drop cells
 - red cell and megakaryocyte fragments
 - increased polychromasia
 - nucleated red blood cells and poikilocytes (red blood cells of irregular shape)
 - 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 transplantation

Complications

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

ESSENTIAL THROMBOCYTHEMIA

- overpopulation of platelets in absence of recognizable stimulus
- invariably above 400 000/mL

Clinical Features

- bleeding - although plentiful, platelets are not working
- thrombosis
- those secondary to splenic enlargement, high blood histamine, and rapid cell turnover - as with CGL 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 platelet

Diagnosis

- exclude other myeloproliferative diseases and secondary thrombocythemia

Management

- hydroxyurea
- ³²P
- plasmapheresis
- avoid splenectomy as spleen is removing unwanted platelets

Complications

- bleeding
- thrombosis
- leukemic transformation
- transformation to myelofibrosis

Note: 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

MALIGNANT CLONAL PROLIFERATIONS OF B CELLS

CHRONIC LYMPHOCYTIC LEUKEMIA

- indolent disorder of middle-age characterized by the clonal malignancy of poorly functioning B cells

Laboratory Values

- absolute lymphocytosis $> 5.0 \times 10^9/L$ (usually $> 10.0 \times 10^9/L$)
- smudge cells (see Colour Atlas E8)
- diffuse or focal infiltration of marrow by lymphocytes

Complications

- bone marrow failure
- bulky lymphadenopathy
- hypersplenism
- immune hemolytic anemia
- immune thrombocytopenia
- hypogammaglobinemia
- monoclonal gammopathy (IgM, IgD)
- hyperuricemia with treatment
- transformation to histiocytic lymphoma

Management

- the gentlest treatment that will control symptoms
 - observation
 - intermittent chlorambucil
 - corticosteroids
 - radiotherapy
 - intravenous chemotherapy
- currently no cure possible

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
- often presents with bone pain, anemia, and infection
- 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)
- IgG: 50%
- IgA: 25%

- IgM: 10% (macroglobulinemia)
- 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 e.g. pneumococcal diseases
- on exam: pallor, bone deformity, pathologic fractures, bone tenderness, hepato/splenomegaly, petechiae and purpura
- renal failure

Laboratory Features

- peripheral blood
 - rouleaux (see Colour Atlas E10)
 - rare plasma cells
 - normocytic anemia, thrombocytopenia, leukopenia
- bone marrow
 - focal or diffuse increase in plasma cells (see Colour Atlas E12)
 - primitive plasma cells
- 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)
- hypercalcemia (N/V, apathy, weakness, polydipsia, polyuria)
- creatinine increased
- increased ESR
- narrow anion gap (myeloma protein is a cation)

Diagnosis

- bone pain, anemia, increased ESR or increased rouleaux suggests myeloma
- classic diagnostic triad: diagnosis depends on demonstrating 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
- transformation to acute leukemia
- hyperviscosity syndrome (caused by M protein)
- amyloidosis (CHF, nephrotic syndrome, joint pain, carpal tunnel syndrome)

Management

- melphalan 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

Prognosis

- over 10 years of survival for most patients

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
- survival: kappa > lambda light chains

MONOCLONAL GAMMOPATHY OF UNKNOWN SIGNIFICANCE

(BENIGN MONOCLONAL GAMMOPATHY)

- 1% of the total population
- 3% of people > 70 years of age
- diagnosis
 - exclude myeloma
 - no rise in the M protein with time
- 10% of these 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:
 - congestive heart failure
 - headache
 - lethargy
 - dilutional anemia
- 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
- CNS symptoms
 - headache, vertigo, ataxia, stroke

Management of Macroglobulinemia

- chlorambucil or melphalan
- corticosteroids
- plasmapheresis for hyperviscosity

Table 11. Characteristics of B Cell Malignant Proliferation

	CLL	Macroglobulinemia	Myeloma
cell type	lymphocyte	plasmacytoid lymphocyte	plasma cell
protein	IgM if present	IgM	IgG, A, D or E
lymph nodes	very common	common	rare
hepato-splenomegaly	common	common	rare
bone lesions	rare	rare	common
hypercalcemia	rare	rare	common
renal failure	rare	rare	common
immunoglobulin autoimmune complications	common	infrequent	rare

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 involvement of spleen
- 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 > 38°C
- unexplained weight loss (> 10% of body weight in 6 months)
- night sweats

HODGKIN'S DISEASE

- 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
- bone marrow biopsy for Reed-Sternberg cell (see Colour Atlas E13)
 - 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
 - RFT to assess renal excretion of chemotherapeutics (e.g. creatinine)
 - LFT 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
- Stage III-IV: combination chemotherapy e.g. ABVD

Complications of Treatment

- diminished fertility
 - consider oophorectomy/sperm banking before radiation
- post-splenectomy sepsis
 - give pneumovax 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
- accelerated cardiovascular disease

Prognosis

- Stage I and II: 85%
- Stage IIIA: 70%
- Stage IIIB and IV: 50%

NON-HODGKIN'S LYMPHOMA

Clinical Features

- painless superficial lymphadenopathy usually > 1 lymph region
- constitutional symptoms: not as common as in Hodgkin's disease
 - fever
 - weight loss
 - night sweats
- 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
- bone marrow biopsy
- PBF 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 for thoracic involvement
- CT for abdominal involvement

Working Formulation for Subtypes of NHL

- low-grade
 - Stage I/II curable
 - Stage III/IV not curable but initially responds to therapy
 - despite long-term survival, rarely cured and usually die of lymphoma
- intermediate-grade
 - Stage I/II curable
 - 50-60% with Stage III/IV curable with combination chemotherapy
- high-grade
 - all stages: 30% curable with intensive combination chemo
- miscellaneous
 - composite
 - mycosis fungoides (cutaneous T-cell lymphoma)
 - true histiocytic
 - unclassifiable

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 often used, especially if the lymphoma is a type in which early dissemination is common
- Stage I or limited Stage II
 - uncommon except for Diffuse Large Cell
 - low-grade: radiotherapy
 - higher grades: radiotherapy, often with adjuvant chemotherapy
- generalized disease (extensive Stage II or Stage III-IV)
 - low-grade
 - asymptomatic: no treatment or gentle chemotherapy
 - symptomatic: single agent or mild combination
 - higher grades: aggressive combination chemotherapy

NHL Complications

- hypersplenism
- infection
- autoimmune hemolytic anemia and thrombocytopenia
- vascular obstruction (from enlarged nodes)
- Note: never give live vaccines like MMR and oral polio!

Indicators for Poor Prognosis

- > 60 years old
- poor response to therapy
- multiple nodal regions
- elevated LDH
- > 5cm nodes
- previous history of low grade disease or AIDS

Prognosis

- low grade: survival > 5 years
- high grade with local disease is curable with radiation
- high grade systemic disease: 40-50% in 2 years

- ❑ 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 - adequate IV hydration, allopurinol, correction of pre-existing metabolic abnormalities
 - symptomatic

WBC DISORDERS

NEUTROPHILIA

Definition

- ❑ ANC (absolute neutrophil count) $> 7.5 \times 10^9/\text{liter}$

Mechanisms

- ❑ 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 (because poor migration) common

LEUKEMOID REACTIONS

- ❑ blood findings resembling those seen in certain types of leukemia with immature WBC in the PBF
- ❑ myeloid leukemia mimicked by
 - pneumonia
 - other acute bacterial infections
 - intoxications
 - burns
 - malignant disease
 - severe hemorrhage or hemolysis
- ❑ lymphoid leukemia mimics (see Infectious Diseases Notes)
 - pertussis
 - TB
 - infectious mononucleosis (see Colour Atlas E15)
- ❑ monocytic leukemia mimicked by
 - TB

NEUTROPENIA

Definition

- ❑ ANC $< 2.5 \times 10^9/\text{liter}$

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

Etiology

- overwhelming infection
 - viral: HIV, hepatitis, EBV
 - bacteria: 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 e.g. penicillins
- marrow disease
 - low B₁₂/folate
 - bone marrow infiltration (hematologic malignancies > solid tumours)
 - aplastic anemia
- hereditary: cyclic neutropenia, Kostmann syndrome
- 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 r/o 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. SMX-TMP, ciprofloxacin, antifungal
- Filgrastim (G-CSF) - growth factor that stimulates neutrophil production

RED CELLS

Product	Indication
packed cells	symptomatic anemia bleeding with hypovolemia
frozen red cells	rare blood groups multiple alloantibodies

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

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

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

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

PLATELETS

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 $10 \times 10^9/L$
- single donor platelets should increase the platelet count by $40-60 \times 10^9/L$
- if an increment in the platelet count is not seen, alloantibodies, bleeding, sepsis or hypersplenism may be present

COAGULATION FACTORS

Product	Indication
Fresh frozen plasma	Depletion of multiple coagulation factors
Cryoprecipitate	Factor VIII deficiency Von Willebrand's disease Hypofibrinogenemia
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
 - the serum is kept frozen
- compatible blood can be issued immediately in an emergency or within 30 minutes electively

ACUTE COMPLICATIONS OF BLOOD TRANSFUSIONS

- minutes to hours

Febrile Nonhemolytic Transfusion Reactions

- due to antibodies stimulated by previous transfusions or pregnancies against antigens on donor lymphocytes, granulocytes, platelets
- signs and symptoms: chills, fever
- management and prevention
 - stop transfusion
 - acetaminophen
 - steroids
 - filtered blood
 - washed blood

Allergic (Urticarial) Reactions

- usually due to interaction between donor plasma proteins and recipient IgE antibodies
- management and prevention
 - antihistamines
 - slow infusion
 - steroids
 - washed blood

Anaphylaxis

- rare, usually in IgA deficient patients reacting against IgA in donor plasma
- management
 - IV epinephrine
 - IgA deficient blood components in future

Acute Hemolytic Transfusion Reactions

- usually 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
- 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

- 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 negative's)

DELAYED COMPLICATIONS IN TRANSFUSIONS

- days to weeks

Viral infection

- the risk of infections due to
 - 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
- it is due to alloantibodies that are too weak to be detected by indirect antiglobulin test or by crossmatch that leads to extravascular hemolysis
- 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 occurs in patients with repeated transfusion 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

Graft versus Host Disease

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

- immunologic-inflammatory
 - infections: subacute bacterial endocarditis, brucellosis, tuberculosis, infectious mononucleosis, cytomegalovirus, histoplasmosis, malaria, schistosomiasis
 - connective tissue diseases: rheumatoid arthritis, Felty's syndrome, SLE
 - sarcoidosis
- hematologic disorders
 - neoplastic: lymphomas, histiocytoses, myeloproliferative syndromes, chronic lymphocytic leukemia, acute leukemia
 - non-neoplastic: hemolytic anemias
- congestive splenomegaly due to portal hypertension: cirrhosis, portal or splenic vein thrombosis
- metabolic-infiltrative: Gaucher's, Niemann-Pick's, amyloidosis
- miscellaneous: cyst, abscess, cavernous hemangioma

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

APPROACH TO BLOOD FILM EXAMINATION

Size

- macrocytic
 - increased size
e.g. megaloblastic anemia, EtOH
- microcytic
 - reduced size
e.g. iron deficiency, thalassemia

Colour

- hypochromatic
 - increased in the size of the central pallor (normal = less than a half of the diameter of RBC)
 - decreased hemoglobin
e.g. anemia

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, thalassemia, Fe deficiency, megaloblastic anemia
- sickle cell = sickle-shaped RBC
e.g. sickle cell disorders, HbC
- target cell = bell-shaped, looks like target on dried film
e.g. liver disease, hemoglobin S and C, thalassemia, Fe deficiency
- teardrop cell (dardocyte) = 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
i.e. lead intoxication, thalassemia

MEDICATIONS COMMONLY USED IN HEMATOLOGY

Table 16. Drugs for Anemia

Drug	Common Formulary	Mechanism of Action	Clinical Uses	Common Side	Contraindications Effects
iron	iron gluconate iron sulphate iron fumarate	<input type="checkbox"/> for synthesis of hemoglobin	<input type="checkbox"/> iron deficiency anemia treatment and prevention <input type="checkbox"/> pregnancy	<input type="checkbox"/> in children: acute iron toxicity as <ul style="list-style-type: none"> • necrotizing enterocolitis • shock • metabolic acidosis • coma and death 	<input type="checkbox"/> iron overload
B ₁₂	cyanocobalamin hydroxycobalamin	<input type="checkbox"/> synthesis of folic acid and DNA	<input type="checkbox"/> B ₁₂ deficiency	<input type="checkbox"/> no significant toxicity	<input type="checkbox"/> N/A
folic acid	folic acid	<input type="checkbox"/> synthesis of	<input type="checkbox"/> folic acid	<input type="checkbox"/> no significant toxicity purines and thymidylate thus DNA	<input type="checkbox"/> N/A deficiency <input type="checkbox"/> pregnancy
erythropoietin	Epo	<input type="checkbox"/> stimulate RBC synthesis	<input type="checkbox"/> renal failure <input type="checkbox"/> marrow failure <input type="checkbox"/> myelodysplastic syndrome <input type="checkbox"/> autologous blood donation	<input type="checkbox"/> no significant toxicity	<input type="checkbox"/> N/A

Table 17. Chemotherapeutic Agents

Class	Example	Mechanism of Action	Common Toxicity	Examples of Clinical Use
alkylating agent	<ul style="list-style-type: none"> <input type="checkbox"/> nitrogen mustard <input type="checkbox"/> cyclophosphamide <input type="checkbox"/> nitrosurea <input type="checkbox"/> busulfan <input type="checkbox"/> cisplatin 	<ul style="list-style-type: none"> <input type="checkbox"/> cell cycle non-specific drugs <input type="checkbox"/> via alkylation of nucleophilic groups in base pairs <input type="checkbox"/> leading to cross-linking of bases or abnormal base-pairing or DNA breakage 	<ul style="list-style-type: none"> <input type="checkbox"/> marrow suppression <input type="checkbox"/> GI irritation <input type="checkbox"/> change in gonadal function <input type="checkbox"/> nitrogen mustard (cyclophosphamide): hemorrhagic cystitis <input type="checkbox"/> busulfan: adrenal insufficiency and pulmonary fibrosis 	<ul style="list-style-type: none"> <input type="checkbox"/> cyclophosphamide <ul style="list-style-type: none"> • breast CA • small cell lung CA • NHL <input type="checkbox"/> busulfan <input type="checkbox"/> CML <input type="checkbox"/> cisplatin <ul style="list-style-type: none"> • advanced ovarian CA • testicular CA
antimetabolites	<ul style="list-style-type: none"> <input type="checkbox"/> folic acid antagonist (methotrexate) <input type="checkbox"/> purine antagonist (mercaptopurine) <input type="checkbox"/> pyrimidine antagonist (5-FU) <input type="checkbox"/> hydroxyurea 	<ul style="list-style-type: none"> <input type="checkbox"/> all are cell cycle specific drugs <input type="checkbox"/> all inhibit DNA synthesis <ul style="list-style-type: none"> • methotrexate inhibits synthesis of tetrahydrofolate • mercaptopurine inhibits purine synthesis • 5-FU inhibits thymidylate synthesis • hydroxyurea inhibits nucleotide reductase 	<ul style="list-style-type: none"> <input type="checkbox"/> marrow suppression <input type="checkbox"/> oral mucositis <input type="checkbox"/> nausea and vomiting 	<ul style="list-style-type: none"> <input type="checkbox"/> methotrexate <ul style="list-style-type: none"> • breast CA • gestational trophoblastic CA • ovarian CA <input type="checkbox"/> mercaptopurine <ul style="list-style-type: none"> • AML <input type="checkbox"/> 5-FU <ul style="list-style-type: none"> • breast CA • GI CA • hepatocellular CA <input type="checkbox"/> hydroxyurea <ul style="list-style-type: none"> • CML
antibiotics	<ul style="list-style-type: none"> <input type="checkbox"/> anthracyclines (doxorubicin) <input type="checkbox"/> bleomycin <input type="checkbox"/> mitomycin-C 	<ul style="list-style-type: none"> <input type="checkbox"/> anthracycline is cell cycle non-specific which intercalates between base-pairs and thus blocks DNA and RNA synthesis <input type="checkbox"/> bleomycin is cell cycle specific (G2) which produces free radicals leading to DNA breaks and inhibits DNA synthesis <input type="checkbox"/> mitomycin-C is cell cycle non-specific which is metabolized in liver to alkylating agent 	<ul style="list-style-type: none"> <input type="checkbox"/> anthracyclines <ul style="list-style-type: none"> • marrow suppression • severe alopecia • cardiomyopathies <input type="checkbox"/> bleomycin <ul style="list-style-type: none"> • pulmonary fibrosis • pneumonitis • hypersensitivity • mucocutaneous reactions <input type="checkbox"/> mitomycin-C <ul style="list-style-type: none"> • myelo-suppression • nephrotoxic 	<ul style="list-style-type: none"> <input type="checkbox"/> anthracyclines <ul style="list-style-type: none"> • breast CA • AML • lymphomas <input type="checkbox"/> bleomycin <ul style="list-style-type: none"> • testicular CA • lymphomas <input type="checkbox"/> mitomycin-C <ul style="list-style-type: none"> • GI malignancies
alkaloids	<ul style="list-style-type: none"> <input type="checkbox"/> vinblastine <input type="checkbox"/> vincristine <input type="checkbox"/> podophyllotoxin (etoposide) <input type="checkbox"/> taxol 	<ul style="list-style-type: none"> <input type="checkbox"/> all are cell cycle specific <input type="checkbox"/> vincristine and vinblastine inhibit assembly of microtubules therefore mitotic spindles and M phase <input type="checkbox"/> podophyllotoxin activates topoisomerase II therefore DNA breaks down <input type="checkbox"/> taxol inhibits disassembly of microtubules therefore cells are stuck in M phase 	<ul style="list-style-type: none"> <input type="checkbox"/> all have marrow suppression <input type="checkbox"/> vincristine and vinblastine <ul style="list-style-type: none"> • neurotoxic with areflexia, peripheral neuritis and paralytic ileus <input type="checkbox"/> taxol <ul style="list-style-type: none"> • neurotoxic as above 	<ul style="list-style-type: none"> <input type="checkbox"/> vincristine and vinblastine <ul style="list-style-type: none"> • lymphomas • Wilm's tumor <input type="checkbox"/> podophyllotoxin <ul style="list-style-type: none"> • small cell lung CA • prostate CA • testicular CA <input type="checkbox"/> taxol <ul style="list-style-type: none"> • advanced breast CA • ovarian CA
hormones	<ul style="list-style-type: none"> <input type="checkbox"/> glucocorticoids <input type="checkbox"/> tamoxifen <input type="checkbox"/> flutamide <input type="checkbox"/> aminoglutethimide 	<ul style="list-style-type: none"> <input type="checkbox"/> tamoxifen <ul style="list-style-type: none"> • as a partial E2 antagonist <input type="checkbox"/> flutamide: androgen receptor antagonist <input type="checkbox"/> aminoglutethimide: aromatase inhibitor in E2 synthesis 	<ul style="list-style-type: none"> <input type="checkbox"/> glucocorticoid <ul style="list-style-type: none"> • refer to endocrinology under Cushing's syndrome <input type="checkbox"/> tamoxifen <ul style="list-style-type: none"> • menopausal symptoms • long term: retinopathy <input type="checkbox"/> aminoglutethimide <ul style="list-style-type: none"> • menopausal symptoms • skin rashes 	<ul style="list-style-type: none"> <input type="checkbox"/> glucocorticoids <ul style="list-style-type: none"> • CML • lymphomas <input type="checkbox"/> tamoxifen <ul style="list-style-type: none"> • breast CA <input type="checkbox"/> flutamide <ul style="list-style-type: none"> • prostate CA <input type="checkbox"/> aminoglutethimide <ul style="list-style-type: none"> • metastatic breast CA
others	<ul style="list-style-type: none"> <input type="checkbox"/> carboplatin <input type="checkbox"/> mitoxantrone 	<ul style="list-style-type: none"> <input type="checkbox"/> carboplatin <ul style="list-style-type: none"> • DNA binding <input type="checkbox"/> mitoxantrone <ul style="list-style-type: none"> • ?DNA breaks 	<ul style="list-style-type: none"> <input type="checkbox"/> carboplatin <ul style="list-style-type: none"> • myelo-suppression • nausea, vomiting • nephrotoxicity <input type="checkbox"/> mitoxantrone <ul style="list-style-type: none"> • cardiotoxicity • alopecia 	<ul style="list-style-type: none"> <input type="checkbox"/> carboplatin <ul style="list-style-type: none"> • ovarian CA <input type="checkbox"/> mitoxantrone <ul style="list-style-type: none"> • AML • NHL • breast CA • ovarian CA • lung CA

Table 18. Anticoagulants

Drug	Generic Drug	Mechanism of Action	Clinical Uses	Common Side Effects	Contraindications
heparin	liquaemin sodium	<ul style="list-style-type: none"> <input type="checkbox"/> a catalyst to antithrombin III <input type="checkbox"/> prolonged PT and PTT 	<ul style="list-style-type: none"> <input type="checkbox"/> MI <input type="checkbox"/> DVT <input type="checkbox"/> stroke, acute 	<ul style="list-style-type: none"> <input type="checkbox"/> bleeding leading to hemorrhagic stroke <input type="checkbox"/> heparin induced thrombocytopenia in 25% <input type="checkbox"/> prolonged use: osteoporosis 	<ul style="list-style-type: none"> <input type="checkbox"/> hypersensitivity to heparin <input type="checkbox"/> actively bleeding <input type="checkbox"/> hemophilia <input type="checkbox"/> thrombocytopenia <input type="checkbox"/> purpura <input type="checkbox"/> severe hypertension <input type="checkbox"/> bacterial endocarditis <input type="checkbox"/> ulceration in GI tract <input type="checkbox"/> during and after neurosurgery, lumbar puncture
low molecular weight heparin	danaparoid sodium dalteparin sodium	<ul style="list-style-type: none"> <input type="checkbox"/> activates antithrombin III 	<ul style="list-style-type: none"> <input type="checkbox"/> thrombosis prophylaxis <input type="checkbox"/> non-hemorrhagic stroke <input type="checkbox"/> hemodialysis 	<ul style="list-style-type: none"> <input type="checkbox"/> bleeding <input type="checkbox"/> thrombocytopenia is rare 	<ul style="list-style-type: none"> <input type="checkbox"/> same as above
warfarin	coumadin	<ul style="list-style-type: none"> <input type="checkbox"/> inhibits vit K dependent clotting factors II, VII, IX and X from undergoing gamma carboxylation in liver <input type="checkbox"/> prolonged PT or INR 	<ul style="list-style-type: none"> <input type="checkbox"/> DVT <input type="checkbox"/> PE <input type="checkbox"/> atrial fibrillation <input type="checkbox"/> 2-6 months after MI 	<ul style="list-style-type: none"> <input type="checkbox"/> bleeding and hemorrhagic stroke <input type="checkbox"/> teratogenic <input type="checkbox"/> cutaneous necrosis during 1st week of therapy 	<ul style="list-style-type: none"> <input type="checkbox"/> actively bleeding <input type="checkbox"/> hemophilia <input type="checkbox"/> purpura <input type="checkbox"/> ulceration of GI tract <input type="checkbox"/> pregnancy
Acetylsalicylic acid (ASA)	aspirin	<ul style="list-style-type: none"> <input type="checkbox"/> inhibits the synthesis of TXA₂ by platelets and therefore platelet aggregation 	<ul style="list-style-type: none"> <input type="checkbox"/> MI prevention <input type="checkbox"/> TIA 	<ul style="list-style-type: none"> <input type="checkbox"/> GI upset <input type="checkbox"/> gastric ulcers <input type="checkbox"/> bleeding <input type="checkbox"/> tinnitus, vertigo (high dose) <input type="checkbox"/> hyperventilation and polyps and ASA respiratory alkalosis (high dose) <input type="checkbox"/> metabolic acidosis, dehydration, hyperthermia, coma, death (v. high dose) <input type="checkbox"/> Reye's syndrome in children esp. with viral infection 	<ul style="list-style-type: none"> <input type="checkbox"/> bleeding <input type="checkbox"/> PUD <input type="checkbox"/> pregnancy <input type="checkbox"/> children <input type="checkbox"/> asthma and nasal hypersensitivity
Ticlid	ticlopidine	<ul style="list-style-type: none"> <input type="checkbox"/> inhibits AMP release by platelets 	<ul style="list-style-type: none"> <input type="checkbox"/> TIA <input type="checkbox"/> carotid stenosis 	<ul style="list-style-type: none"> <input type="checkbox"/> GI upset <input type="checkbox"/> bleeding <input type="checkbox"/> leukopenia 	<ul style="list-style-type: none"> <input type="checkbox"/> bleeding disorders