ANEMIA:

DEFINITION:
- Reduced # of circulating RBCs
- Reduced RBC mass
- Reduced Hgb concentration
- Reduced hematocrit (Hct)

ETIOLOGY:
- Nutritional deficiencies
  - Iron, vitamin B12, folic acid
- Disease-induced (acute/chronic)
  - ↓ RBC production
    - ex// BMD
  - ↑ RBC destruction
    - ex// hemolysis
  - ↑ RBC loss
    - ex// acute/chronic bleeding
- Drug-induced
  - Chloramphenicol, diclofenac, indomethacin, gold salts, phenytoin, carbamazepine, sulfa, chemo, etc

WHO CLASSIFICATION:

Normal (Hgb)	Women: 120-160 g/L Men: 140-180 g/L
Mild (grade 1)	100 g/L – LLN
Mod (grade 2)	Hb 80 – 99 g/L
Severe (grade 3)	Hb 65-79 g/L
Life-threatening (grade 4)	Hb < 65 g/L

TYPES & EXAMPLES:

Macrocytic	• B12-deficiency anemia • Folate-deficiency anemia
Microcytic	• Iron-deficiency anemia
Normocytic	• Cancer-related anemia • Anemia of CKD • Cardiorenal anemia • Acquired anemia in hospitalized pt

PATHOPHYSIOLOGY:

Erythropoietin	• Hormone stimulating proliferation & differentiation of erythroid precursors in bone marrow • Maintains RBC mass via feedback mechanism • Normal endogenous level = 10-20 units/L • 90% produced in kidney, 10% in liver • ↓ O_2-carrying capacity → renal peritubular cells → erythropoietin released into blood
Burst-forming units (BFUe)	• Earliest progenitors → eventually develops into a CFUe • Influenced by cytokines (IL-3, GM-CSF); moderately sensitive to erythropoietin
Colony-forming unit	• Differentiates into erythroblasts & reticulocytes • Highly sensitive to erythropoietin

CANCER-RELATED ANEMIA:

ETIOLOGY:

Cancer	Examples	• Non-Hodgkin's lymphoma • Multiple myeloma • Lung cancer • Ovarian cancer
	Contributing factors	• Stage of cancer • Bleeding • Nutritional deficiencies • Hemophagocytosis • Myelosuppression
Chemo-therapy	Examples	• Cisplatin • Carboplatin • Paclitaxel • Vinorelbine
	Contributing factors	• Duration of chemotherapy • Bone marrow suppression • Hemolysis • Nutritional deficiencies due to nausea & vomiting • Low erythropoietin production
Radiation therapy		

COMPLICATIONS:
- Debilitating fatigue
- Compromised QOL
- Depression
- Impaired cognitive fxn
- ↓ ability to complete ADLs
- CV complications
- Hypoxia
- Delay in cancer txt → cancer progression
- Death

GOALS OF THERAPY:
- Resolve signs and symptoms of anemia
- Treat underlying cause
- Improve quality of life
- Prevent recurrences
- Prevent complications
- Prevent/minimize treatment-related side effects

DIAGNOSIS & CLINICAL PRESENTATION:
- Normochromic: normal MCHC (Hgb concentration in RBC)
- Normocytic: normal MCV (RBC size), low MCV, if underlying iron-deficiency (low-ferritin)
- Cancer present for more than 1-2 months
- Mild-moderate in severity
- Low reticulocytes, if poor bone marrow function
- Low serum iron & TIBC, but normal/high ferritin
- Bone marrow aspirate: high hemosiderin
- Fatigue, paleness, dizziness, SOB, hypoxia, tachycardia, palpitations

TREATMENT OPTIONS:
- **Definitive therapy: cure cancer**
- **Supportive care, including RBC transfusions:**
  - Increase Hgb level quickly
  - Improve anemia symptoms rapidly
  - Improve health-related quality of life
  - Exceptions: patients with presence of multiple alloantibodies and those refusing transfusions based on religious beliefs
- **Erythropoiesis Stimulating Agents (ESA):**
  - Example: Erythropoietin (Epoetin), Darbepoetin
  - May take weeks to months to increase Hgb
  - May stimulate cancer progression and increase mortality

ESA:
- Indicated: palliative myelosuppressive chemotherapy-induced anemia in some patients (consider: risks vs. benefits; patient preference)
- Not indicated: curative myelosuppressive chemotherapy-induced anemia
- Caution: patients with cancer not receiving chemotherapy, due to increased risk of thrombosis and reduced survival
- Not to be initiated if Hb > 100 g/L
- Dose to lowest Hgb level, sufficient to avoid blood transfusions
  - Increased risk of death & serious CV events (thrombosis, HTN)
- Discontinue ESA if lack of response after 6-8 weeks of therapy

MONITORING PARAMTERS:
- S/S of anemia, including RBC, Hgb, Hct, MCV, etc
- Efficacy of RBC transfusions (if indicated): 1 unit RBC → ↑ Hgb by 10 g/L, ↑ Hct by 2-3% in an average 70 kg adult
- SEs of RBC transfusions: transfusion reactions (fever, chills, resp distress, hives, pruritis, hypersensitivty, hemolysis, etc) ; volume overload ; CHF ; iron overload; infection; contamination
- Cancer progression
- Chemotherapy and/or radiation therapy side effects

THROMBOCYTOPENIA:

DEFINITION:

- Platelet count below the LLN (< 150 x 10^9/L)
  - Normal adults: 150-450 x 10^9/L

Mild	100 – 150 x 10^9/L
Moderate	50-99 x 10^9/L
Severe	< 50 x 10^9/L

- Numbers must be interpreted in the context of the underlying disease
  - Lower values may be appropriate for certain conditions (ex// cancer-related thrombocytopenia)

PATHOPHYSIOLOGY:

- Decreased platelet production in bone marrow
- Destruction of peripheral platelets by antibodies
- Consumption of platelets by thrombi
- Dilution of platelets from fluid resuscitation or massive transfusion
- Sequestration (pooling) of platelets in the spleen due to portal hypertension and/or splenomegaly

ETIOLOGY:

Primary immune thrombocytopenia (ITP)	
Food & beverages	• Alcohol, quinine containing tonic water,
Infection/sepsis	• HIV, hepatitis C, Epstein-Barr virus, H. pylori, etc
Hypersplenism	• Due to chronic liver disease
Drug-induced immune thrombocytopenia (DITP)	• Heparin, LMWH, quinine, sulfonamides, acetaminophen, cimetidine, ibuprofen, naproxen, ampicillin, piperacillin, vancomycin, glycoprotein IIB/IIIA inhibitors (abciximab, tirofiban, eptifibatide, etc)
Heparin-induced thrombocytopenia (HIT)	• Uncommon side effect of unfractioned heparin (2.6%) or low-molecular-weight heparin (0.2%) • Independent of dose, schedule, or route of administration • Immune mediated HIT (Type 2) is far more serious (life-threatening) than non-immune mediate HIT (Type 1) • HIT may occur several days after initiation of heparin • Complications of HIT included skin necrosis, limb gangrene (sometimes requiring amputation), and organ infarction
Nutritional deficiencies	• Vit B12, folate, copper
Autoimmune disorders	• Lupus, rheumatoid arthritis
Inherited thrombocytopenia	• Fanconi syndrome
Other	• Pregnancy • Antiphospholid syndrome (APS) • Myelodysplasia
Cancer-related	• Cancer, chemotherapy, radiation therapy

CANCER-RELATED THROMBOCYTOPENIA:

ETIOLOGY:

- Cancer
- Chemotherapy
  - Predictable, dose-dependent myelosuppression
  - Affects all blood cell lines

Grade 1	75-150 x 10^9/L
Grade 2	50-74 x 10^9/L
Grade 3	25-49 x 10^9/L
Grade 4	< 25 x 10^9/L

- Radiation therapy

DIAGNOSIS, CLINICAL PRESENTATION & COMPLICATIONS:

- Platelet count below normal
- Potential causes identified (cancer, chemotherapy, radiation therapy, heparin, LMWH, other drugs, etc)
- Easy bruising
- Petechia, purpura
- Bleeding
- Delay in cancer txt → cancer progression
- Enlarged spleen
- Jaundice
- Thrombosis
- Death

GOALS OF THERAPY:

- Resolve S/S of thrombocytopenia
- Treat underlying cause
- Improve quality of life
- Prevent recurrences, prevent complications
- Prevent/minimize treatment-related side effects

TREATMENT OPTIONS:

- Treat underlying cause
- Assess and address potential drug therapy causes
  - IM injections, ASA/NSAID therapy, NHPs (ex// Ginkgo) should be avoided
  - Provide drug therapy alternatives, where appropriate
  - Anticoagulation therapy may need to continue, depending on indication and severity of thrombocytopenia
- Assess severity of thrombocytopenia
- Restrict physical activity if platelets < 50 x 10^9/L
- Infuse platelets, when indicated
- Consult with hematologist as appropriate

MONITORING PARAMTERS:

- S/S of thrombocytopenia, including platelet count
- Efficacy of platelet transfusions (if indicated)
- Side effects of platelet transfusions:
  - Transfusion reactions (fever, chills, respiratory distress, hives, pruritic, hypersensitivity, hemolysis, etc)
  - Volume overload, CHF
  - Infection, contamination
- Cancer progression
- Chemo and/or radiation therapy side effects

VENOUS THROMBOEMBOLISM (VTE):

DEFINITION:

Deep vein thrombosis (DVT)	• Formation of a blood clot in a deep vein
	  ○ Symptomatic: sx usually lead to radiologic confirmation of DVT
	  ○ Asymptomatic: incidental finding of DVT on imaging in pt w/o sx (ex// CT Scan)
	• Mostly occurs in lower leg or thigh, but can occur anywhere in the body
	  ○ Proximal DVT: clot located in popliteal, femoral or iliac veins
	  ○ Distal DVT: clot located below knee & confined to calf veins

Pulmonary embolism (PE)	• Blockage of a pulmonary artery by a blood clot (due to a pre-existing DVT or newly formed)

CLINICAL PRESENTATION

DVT	• Swelling (typically unilateral but can be bilateral) • Pain, redness, discoloration
PE	• SOB, tachypnea • Pleuritic chest pain, pleural rub • Hypoxia, hemoptysis • Tachycardia, right HF • Syncope

VTE CONTINUED:

PATHOPHYSIOLOGY: Virchow Triad

Vascular endothelial injury	• Surgery • Trauma
Alteration in blood flow (stasis)	• Heart failure • Increased blood thickness • Small blood clots • Prolonged immobilization
Alterations in constituents of blood	• Anticlotting factor deficiencies • Autoimmune disorders • Platelet disorders • Cancer

DIAGNOSIS:

DVT	• Compression ultrasonography (↑ sensitivity/specificity)

PE	• Spiral CT angiography
	• Magnetic resonance pulmonary angiograph
	  ○ If contrast media is contraindicated
	• Ventilation/perfusion (V/Q) scintigraphy (↓sensitivity/specificity)
	  ○ If severe renal failure

Atypical sites	• Ex// cerebral venous thrombosis, intra-abdominal thrombosis • MRI

CANCER-RELATED VTE:

ETIOLOGY & RISK FACTORS:

Patient-related factors	• ≥ 65 years • African American • Comorbidity (obesity, infection, renal disease, pulmonary disease, arterial thromboembolism) • Prior history of VTE • High pre-chemotherapy platelet count > 350 x 10^9/L • Heritable prothrombotic mutations • Immobilization
Cancer-related factors	• Primary site of cancer (ex// brain, gynecologic, hematologic, lung, pancreas, renal, stomach) • Initial 3-6 months after diagnosis • Current metastatic disease
Txt-related factors	• Recent major surgery • Active chemotherapy • Active hormonal therapy (ex// Tamoxifen) • Current or recent antiogenic therapy (Thalidomide, Lenalidomide, Bevacizumab) • Radiation therapy (possibly) • Current ESA • Presence of central venous catheters

COMPLICATIONS:
- Potential sign of underlying malignancy
- Interference with anticancer therapy → cancer progression
- Compromised QOL
- Hospitalization, mortality

GOALS OF THERAPY:
- Relieve signs and symptoms
- Treat underlying cause
- Prevent complications
- Improve QOL
- Prevent recurrences (secondary VTE prophylaxis)
- Prevent/minimize treatment-related side effects
- Prolong survival

TREATMENT OPTIONS:
- Low molecular weight heparin (LMWH): **1st choice**
- Warfarin therapy (overlap with initial LMWH or unfractioned heparin or fondaparinux until INR 2-3 for 2 days)
- Direct oral anticoagulants:
  - Dabigatran (direct thrombin inhibitor)
  - Rivaroxaban, apixaban, edoxaban (factor Xa inhibitors)
  - Lack of sufficient evidence for VTE txt in cancer
- Duration of therapy: 6 months or longer

MONITORING PARAMTERS:
- Signs and symptoms of VTE
- Efficacy of anticoagulation therapy
- Side effects of anticoagulation therapy: bleeding, thrombocytopenia, other side effects depending on specific drug therapy
- Lab markers:
  - aPTT for unfractioned heparin
  - anti-Xa levels for LMWH in renal failure & obesity
- Cancer progression
- Chemotherapy and/or radiation therapy side effects

PRIMARY VTE PROPHYLAXIS IN CANCER:
- Considered for high risk cancer patients:
  - Family hx of VTE
  - Presence of inherited thrombophilia
  - Comorbidities, older age, obesity, immobility, concomitant medications (including chemotherapy), etc
  - Metastatic cancer
  - Hospitalization
  - Surgery
- Not routinely recommended for ambulatory care patients with cancer at this time
- LMWH or unfractioned heparin are commonly used for primary VTE prophylaxis in cancer patients
- Mechanical prophylaxis has not demonstrated efficacy