Anemias

- MCV < 82 (Microcytic)
  1. Iron deficiency
  2. Chronic disease
  3. Thalassemia
  4. Sideroblastic
- MCV >95 (Macrocytic) — Requires BM to differentiate
  - Megaloblastic
    - ↓ Vit. B12 (cobalamine)
    - ↓ Folate
  - Non megaloblastic
    - sometimes seen
    - ↑ LDH
    - ↑ intramedullary cellular destruction
    - 1. Hemolysis
    - 2. Blood loss
- MCV 82-95 (Normocytic) — Reticulocyte count
  - Increased (> 100000) RI ≥ 2.5
    - ① ✓ Coombs Test
    - ② Look @ peripheral smear
  - N/decreased (< 100000) < 2.5
    - 1. Renal failure
    - 2. Hypothyroidism
    - 3. Chronic disease → Defective mobilization of Fe from the RES
      - ↓ IL-6 induces Hepcidin synthesis
      - ↓'s 6I Fe absorption
      - ↓'s RES Fe release
    - 4. Aplastic anemia

Pica → craving for ice

Best Dx test: ↓ Ferritin (acute phase reactant)

RDW: Reflects anisocytosis
↑'d w/ Fe-Defic.
↑'d w/ ↑'d Retics (large RBCs)

MCHC: ↓ = hypochromia

- ring sideroblasts
- low MCV out of proportion to anemia
- ↑'d RBC count vs. Fe-Defic.

Reticulocyte Index (RI) = R% x Pt HCT/ 45 (If polychromasia divide number by 2)

Anemia of Chronic Disease And Iron Deficiency

Causes: Etoh, Lead, Malignancy, Pyridoxine Defic.

Tx: Epo, Pyridoxine

Fe-absorbed in proximal small bowel

Transferrin saturation <16%

Measure Serum Ferritin

- **<30 ng/ml** → **Iron deficiency Anemia**
  - -microcytosis
  - -hypochromia
  - -anisocytosis
  - ↑RDW
  - Tx: Vit. C (pt is on HD) → mobilizes Fe stores for erythropoiesis
  - Fe tx too
- **30-100 ng/ml** → **Measure ratio of soluble tranferrin receptor to log of serum ferritin**
  - **>2** → **Anemia of chronic disease plus iron deficiency**
  - **<1** → **Anemia of chronic disease**
- **>100 ng/ml** → rules out Fe-Defic.

Epo Failure
- Causes: ① Fe-Defic. ② Folate Defic. ③ Ongoing Blood loss ④ Fe Overload
- -vFe studies

20-30% of pt's w/ an inflammatory caused chronic dis. anemia have of identifiable underlying inflammato Dx.

Tx: Epo w/ target Hgb 11-12
- if ϕ response to Epo then add Fe

Various Hemoglobins

Adult (A)	(~96%)	$\alpha_2\beta_2$
Fetal (F)		$\alpha_2\gamma_2$ (Gamma)
A2	(~4%)	$\alpha_2\delta_2$
Barts		γ_4 (Gamma)
Hemoglobib H		β_4

Howell-Jolly Bodies
↳ post splenectomy

- Hgb A_2, Hgb C & HgbE all band together on Hgb electrophoresis

Thallasemia Syndromes (+ teardrop cells) — Hb electrophoresis

Beta thallasemia trait (one thallasemia gene) — mild microcytic anemia	↑ A2
Beta thallasemia major (two thallasemia gene) — Cooley's	↑ A2 and/or Hb F
Beta thallasemia intermedia (two genes but one is mild)	↑ A2 and/or Hb F
Alpha thallasemia carrier (deletion of 1 gene) — normal CBC (even MCV)	Normal
Alpha thallasemia trait (deletion of 2 genes) — mild microcytic anemia	Normal
Hb H disease (deletion of 3 genes) — Hgb 6-10	↑ Hb H — Heinz Bodies
Hydrops fetalis (deletion of 4 genes) → fatal	↑ Barts

↑'d GI Fe absorption

Tx: - Transfusions to Hgb 9-10
- Deferoxamine ± chelate Fe

common cause of death: Fe-CM Hemosiderosis

Don't ✓ for hereditary hemochromatosis unless (+) FH

→ α-thallasemia only can give normal electrophoresis

Macrocytic Anemias

(MCV > 100)

Megaloblastic (mild hemolysis) — Non Megaloblastic

Megaloblastic

1. Vit. B12 deficiency (meaty) — causes ↑ LDH + ↑ indirect bili — = cobalamine = poor memory + multisegmented PMNs
2. Folate deficiency (veggies)
3. Myelodysplastic syndrome
4. Side effect of anti-cancer drugs (Azathioprine, hydroxuurea, 5 FU)

absorbed in terminal ileum w/ IF

may see ↑'d methylmalonic acid + homocysteine levels in B12 Defic. but only ↑'d homocysteine level in folate defic. (methylmalonic acid is normal)

Non Megaloblastic

1. Alcoholism
2. Liver Disease
3. Hemolysis
4. Blood loss
5. Hypothyroidism
6. AZT

Complications of Pernicious Anemia

Defic. of IF
Ab's seen in 60%
Parietal cell Ab's in 90%
If Ab's ⊖ → schilling test
If Abnormal → repeat w/ IF
↓
If normalizes then Dx is pernicious
If still abnormal → terminal ileal dis.

1. **Neuro:** Peripheral neuropathy, ataxia, spastic paraplegia, loss of sense of vibration and position, dementia, psychosis
2. **GI:** Anorexia, weight loss, diarrhea, malabsorption, gastric carcinoma
3. Hypothyroidism and other autoimmune disorders

Causes of Folic Acid Deficiency

Can also ✓ Methylmalonic Acid
If ↑ then indicates B12 defic.
(if B12 level is borderline)

Inadequate intake — Alcoholics, malnutrition

Increased requirements — Chronic hemolysis, pregnancy

Malabsorption

Tropical & nontropical sprue, phenytoin, barbiturates, alcohol

Inhibitors of dihydrofolate reductase

Methotrexate, pyrimethamine, triamterene, pentamidine, trimethoprim, alcohol

Do not use together

Myelodysplastic Syndromes
- Pancytopenia
- Macrocytic anemia w/ normal B12/Folate
- Smear → hypogranulation w/ immature WBC's
- Pelger-Huet Anomaly
  - bilobed ← 2 segmented PMNs
- BM → Blasts (prognostic)
  - ↑'d Blasts → worse prognosis
  - if >20% Blasts → Leukemia
  - peripheral blasts

Tx: G-CSF, Epo, Transfusions

Causes:
- chemo
- Rad Tx
- most common cause of death → infex.

Lenalidomide
- only indicated for pure RBC Myelodysplasia

Tx: Cytarabine + anthracycline (AML) (worse prognosis than de novo AML) ↑'d acute leukemic transformation risk

Interpretation of Iron Studies

Disorder	Serum iron	TIBC	Transferrin sat.(nl-33%)	Ferritin	Marrow iron
1. Iron Deficiency	↓	↑	↓	↓	↓
2. Anemia of Chronic Disease	↓	↓	↓	N↑	N↑
3. Thalassemia trait	N	N	N	N↑	N↑
4. Sideroblastic Anemia	N↑	N↑	N↑	N↑	↑
5. Hemochromatosis	↑	↓	↑ (75%)	↑	↑

pathognomonic

Manifestations of Hemochromatosis

- most common genetic defect in Caucasians
- HFE gene mutation
- disease in homozygotes or compler heterozygotes

Skin: Pigmentation
CVS: Cardiomyopathy
Liver: Abnormal LFT'S, fibrosis, cirrhosis, carcinoma
Endocrine: Diabetes, hypopituitarism, hypogonadism
Joints: Arthritis
Infections: Vibrio vulnificus, Listeria, Yersinia, Salmonella, Klebsiella, E.coli, Rhizopus & Mucor

Biopsy w/ abnormal LFT's or ferritin 71000

Best screening test

Transferrin sat (>55%)

Screen 1st + 2nd degree relatives

- Ferritin
- Transferrin Sat
- Gene testing

Tx: Phlebotomy to Ferritin < 50 begin w/ Ferritin 300

Diagnosis of Hemolysis

	Intravascular	Extravascular
1. Reticulocytes	↑	↑
2. LDH	↑	↑
3. Bilirubin	↑	↑
4. Haptoglobin	↓	↓
5. Methemalbumin	↑	-
6. Urine hemosiderine	↑	-
7. Urine or plasma free Hb	+	-

Coombs Test (Antibody screen)

(+) test commonly seen w/ cephalosporins

Direct (Direct Antiglobulin Test (DAT))

Patient RBC's + anti-IGG or anti-C3 = Detects IGG or C3 on RBC's via agglutination

Indirect (Indirect Antiglobulin Test)

Normal RBC's + patient serum + anti-IGG = Detects serum antibodies via agglutination

Schistocytes + Thrombocytopenia
Dx - TTP

Interpretation of Direct Coombs

Schistocytes + Prosthetic valve
Dx - valve dysfunction

	Anti- IgG	Anti- C3	Diagnosis
1.	+	-	Warm antibody induced
2.	+	+	Warm antibody induced
3.	-	+	Cold antibody induced

RBC Agglutination w/ Hemolysis
Dx: cold Agglutinins

Spherocytes w/ Hemolysis
Dx: Autoimmune

Anti-IgG (+) → warm
Anti-C3 (+) → cold

Autoimmune Hemolytic Anemia

(spherocytes)

Spur cells
Dx: chronic alcoholism

	Warm-antibody induced	Cold-antibody induced
1. Site of Hemolysis	Extravascular	Extravascular
2. Antibody	IgG against Rh antigen	IgM against I antigen
3. Cold Agglutinins	-	(+)
4. Direct Coombs	+ IgG or + IgG & C3	- IgG, + C3
5. Causes	Idiopathic, Drug induced, Lymphoma, Leukemias, Solid tumors	Idiopathic Mycoplasma Inf. Infectious mono. Lymphoma, PCH
6. Treatment	Steroids, Splenectomy IV Gamma globulin Cyclophosphamide Azathiaprine Rituximab	Cyclophosphamide Chloraambucil Rituximab Steroids- limited value No role of splenectomy

Hereditary Spherocytosis
- peripheral smear
  - lots of spherocytes (almost ∅ RBC's that aren't spherocytes)
  - ↓ differentiates from autoimmune hemolysis
  - ↓ spherocytes (+) but ∅ all RBC's are spherocytes
- Coombs ⊖ (Direct)
- ↑'d MCHC → spherocytes carry more Hgb than normal RBC's
- ↑'d osmotic fragility in hypotonic solutions
  - ↓ water moves into cells
  - ↓ spherocytes burst

Drug Induced Hemolytic Anemia

Alpha methyldopa type (classical warm antibody) → warm Ab
Direct coombs (IGG +, C3 ±)
Indirect coombs positive without adding the drug

Penicillin type (Stable hapten) → cephalosporins too → warm Ab
Direct coombs (IGG +, C3 ±)
Indirect coombs positive only when drug added

Quinidine type (Unstable hapten) → cold Ab
Direct coombs (IGG -, C3 +)
Indirect coombs positive only when drug added

Hemolysis Associated With Fragmented RBC's (Schistocytes)

1. Thrombotic thrombocytopenic purpura (TTP) → abnormal vWF cleavage leads to ↑ vWF → plat. aggregation (microangiopathic)
2. Hemolytic uremic syndrome
3. DIC → Prolonged PT/PTT
4. Prosthetic cardiac valves
5. Vessel Disease: Vasculitis, malignant hypertension
6. Pregnancy: Preeclamsia, HELLP, fatty liver of pregnancy
7. Advanced malignancy (adenocarcinoma)
8. Drugs: Cyclosporin, quinine, ticlopidine

HUS
- bloody diarrhea
- ↑ LDH, schistocytes
- assoc. w/ E.coli O157:H7
- mainly in children
- Abx → ↑'d risk of HUS

shiga toxin in stools

Tx: - supportive
- H2O as needed
- ϕ plasma exchange
- ϕ Abx

S/S: - Hemolysis anemia
- Fever
- Thrombocytopenia
- Renal Dysfunction
- CNS Involvement

Classic pentad

Tx: plasma pheresis 1-1.5 plasma volume QDay
plasma infusion if pheresis ϕ available
Recurrence → steroid
- chr. by ↑ LDH too

Various Sickle Cell Syndromes

- chronic hemolysis

Sickle cell trait (SA) → mild presentation
Sickle cell anemia (SS)
Sickle C disease (SC) 50% HgbS + 50% HgbC
- eye involvement
Sickle cell/B thallasemia

most important prognostic factor:
HgF → protects against sickling

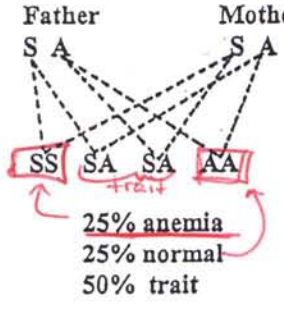
Sickle Cell trait	Sickle cell Anemia
Hb S < 50%, rest A	Hb S 75-95%, F 2-20 %, A2 2-4%
Crisis with severe hypoxia Splenic infarct Recurrent hematuria	Factors precipitating sickling 1. Hypoxia 2. Hypothermia 3. Acidosis 4. Dehydration 5. Hypertonicity

Tx: - Folate
- Vaccinations
- Hydroxyurea → ↑'s HgbF
- acute chest syndrome
- 1-2 crises/yr.

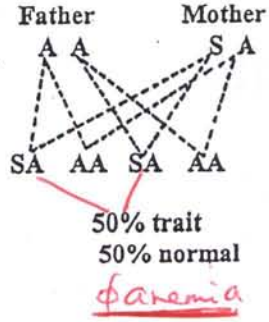
- routine transfusions in pregnancy w/ SCD are not needed unless acutely indicated

Sickle Cell Anemia

Both w/ Trait



(Trait)



ϕ anemia

Acute Chest Syndrome
- Fever
- chest pain
- dyspnea
- hypoxia
- CXR infiltrate
- requires SCD

Causes: (1) Fat Embolism (2) Thrombosis (3) Atelectasis (4) Pneumonia (5) combo of the 4
- leading cause of death in SCD

Tx: RBC Exchange Transfusions
Target Hgb > 10

- most common cause of death in sc children → PCN prophylaxis + pneumovax

Histories on Sickle Cell Anemia

1. Pain in chest, back, abdomen and legs → vasoocclusive crisis
   Tx: IVFs + analgesics
2. Sudden onset of LUQ abdominal pain → splenic infarct
3. Profound weakness + drop in HCT + reticulocyte count 10000 → aplastic crisis w/ Parvo B19
   ✓IgM Ab's to Parvovirus
4. Weakness + drop in HCT + reticulocyte count 150000 → Hemolytic crisis

Differentiate b/w w/ retic counts

5. Weakness + drop in HCT + enlarging spleen size → splenic sequestration crisis
   Tx: Splenectomy
6. Chest pain + fever + lung infiltrates + negative sputum gram stain and culture + no response to antibiotics + PO2 55 → acute chest syndrome due to pulm. infarct
   Tx: Plasmapheresis for PO_2 <60
7. SC disease with sudden pain in the hip + negative x-rays → avascular necrosis
   next step: MRI

8. SC patient w/ evolving CVA
   Tx: Plasmapheresis + get HgbS to < 30%
9. SC w/ osteomyelitis → Think Salmonella

Causes of Hemolysis in G6PD Deficiency

- may see normal G6PD levels

- chronic or episodic hemolysis
- self-limiting → older cells destroyed vs. young cells

smear shows RBC's w/ "blisters" → bite cells

PNH:
- Hemolysis w/ pancytopenia
- confirm Dx:
  - absence of CD-59 Ag on blood cells
  - ↑'d risk of thrombosis
  - ↑'d risk of leukemic transformation → AML ← Aplastic anemia

Bacterial & viral infections
Metabolic acidosis
Drugs

1. Primaquine	2. Pamaquine	3. Dapsone
4. Sulfonamides (bactrim)	5. Nitrofurantoin	6. Vitamin K
7. Acetanilid	8. nalidixic acid	9. Doxorubicin
10. Furazolidone	11. Methylene blue	12. Phenazopyridine

Congenital Spherocytosis
Tx: splenectomy
- spherocytes
- RUQ stones
- ↑LDH

+ Fe-Defic. due to blood loss

Tx: oral anticoags
oral Fe
oral Folate
Eculizumab
Stem cell transp

Causes of Aplastic Anemia

Dry BM Tap → Aplastic Anemia (Hypocellular BM) or Myelofibrosis or Hairy cell leukemia
- TRAP ⊕
- filamentous lymphs

Idiopathic
Radiation
Drugs: Chloramphenicol, Gold, Phenylbutazone, Carbonic anhydrase inhibitors, Alcohol, Chemotherapy
Infections: CMV, Parvovirus, Hepatitis, EB virus

Tx: Allogenic stem cell transplant (<50 y.o.)
Immunosuppressants (anti-thymocyte glob + cyclosporine)

Spur cell Anemia
- EtoH
- acanthocytes (thorn)
- poor prognosis

Hematological Manifestations of HIV Infection

1. Immune thrombocytopenia (w/ any CD4 count)
2. Anemia of chronic disease → Tx w/ Epo even w/ normal Epo levels endogenously
3. Aplastic crisis secondary to Parvovirus B19
4. AZT induced anemia (↑MCV) → macrocytic but non megaloblastic
5. TTP

Blood Product Compatibility

In Emergencies: O⊖ → universal donor; AB plasma or plat → ϕ hemaglutinin

Rh Incompatibility: - causes extravascular hemolysis - few symptoms

must be compatible for plasma + RBCs

Pt's Group	Whole Blood	PRBC'S	Frozen Plasma	Platelets
O	O	O	O, A, B, AB	O, A, B, AB
A	A	A, O	A, AB	A, AB
B	B	B, O	B, AB	B, AB
AB	AB	AB, O, A, B	AB	AB

universal donor's

Adverse Effects of Blood Transfusion

1. Acute hemolytic transfusion reaction → hypotension, tachycardia, hemoglobinuria (major incompatibility) — Tx: stop transfusion, pressors if needed, Epi, steroids
2. Delayed hemolytic transfusion reaction → few days later (minor)
3. Febrile nonhemolytic transfusion reaction → anti-HLA Ab's to WBC's; fevers/chills/N/V; Tx: anti-pyretics, use leukocyte filtered-blood in future transfusion
4. Allergic reaction → caused by plasma; Prevention: Tx washed RBC's
5. Anaphylaxis → selective IgA Defic. (avoid IgA⊖ blood)
6. Transfusion-related acute lung injury (TRALI) → diffuse interstitial alveolar infiltrates (acute pulm. edema); donor anti-HLA Ab's agglut. receiver WBC's; Tx: supportive - usually symptoms resolve over ~2 days
7. Septic reactions
8. Graft-versus-host disease (GvHD) → immunocompromised pt's; - use Gamma-radiated blood products (irradiated)
9. CMV infection → - use CMV⊖ blood products if immunocompromised and pregnant women; leukoreduced ← products

↑MCV, target cells → Hgb C dis. (Lysine → Glutamic acid substitution); Tx: ϕ

Bleeding Disorders

	Primary hemostasis (Platelet & blood vessels)	Secondary hemostasis (Coagulation defects)
Bleeding after trauma	Immediate	Delayed
Site of bleeding	Superficial	Deep visceral
Bleeding time ← measures platelet function	↑	N
PFA closing time	↑	N
PTT / PT	N	one or both increased depending on the defect

Disorders of Platelet Function

vs. normal in Hemophilia

↑ BT ← normal PT ↑ PTT
Menorrhagia
↓ vWF
↓ Factor VIII
Surgical bleeding
↓ Ristocetin Cofactor Assay
Tx: women → OCP's ↓ menorrhagia

Vascular Injury

1. Platelet Adhesion-----1. von Willebrand's Disease
   2. Bernard-Soulier Syndrome (Absence Gp1b receptors)
2. Release Reaction-----1. Cyclooxygenase Inhibitors (Ex.) NSAIDs
   2. Granule Storage Pool Defects
3. Aggregation----------1. Glanzmann's Thrombasthenia (Absence of GpIIb/IIIa receptors) → plat's do not aggregate

von Willebrand's Disease

		Treatment
Type 1 (60-80%) Autosomal dominant	Mild-moderate quantitative deficiency of vWF and factor VIII (5-30% of normal plasma)	Desmopressin
Type 2 Autosomal dominant	Qualitative abnormality of vWF	Factor VIII-vWF concenterates
Type 3 Autosomal recessive	Very low levels of vWF (<1%) & factor VIII (1-10%) ↓ may have spontaneous bleeding	Negative alloantibodies: Factor VIII-vWF conc. Positive alloantibodies: Recombinant factor VIII

Immune Thrombocytopenia

Causes:
① Peripheral Destruction
② Platelet-Assoc. Ig

Plat's 730k
Tx: monitor ± BM Bx either

1. Idiopathic
2. Collagen vascular diseases
3. Lymphoproliferative disorders
4. Infections: HIV, IM, CMV, Toxo, Hepatitis, H. pylori
5. Drugs:
   Quinidine, quinine, heparin, thiazides, sulfonamides, linezolid, rifampin, vancomycin, carbamazepine, phenytoin, valproic acid, platelet inhibitors (abciximab, eptifibatide, tirofiban)
6. Antiphospholipid syndrome
7. Immune Deficiency
   (IGA deficiency, common variable hypogammaglobulinemia)

Tx: Prednisone 1 mg/kg/day → usually will see response w/in 3 wks; if ↓ response → BM Bx

Tx:
Plat's <30k → Prednisone then taper
If unable to taper → Splenectomy
Acute hemorrhage IV Ig, Plat's, ± Prednisone
exp. w/ regimens longer than 2 weeks

Heparin-Induced Thrombocytopenia
(HIT and HITT)

→ HIT w/ Thrombosis

Type I (Nonimmune)
Occurs soon after starting therapy, mild, self limited

Type II (Immune)
Usually occurs 5-15 days after starting therapy (maybe even 3-4 wks later)
50% drop in platelet count is suggestive of the diagnosis
30% risk of thrombosis (75% venous, 25% arterial)

Diagnosis: a) PF4-heparin antibody
b) 14C Serotonin release assay

Treatment: Lepirudin or Argatroban or Danaproid

Tx Options:
① HIT w/ thrombosis: Argatroban or Lepirudin
② HIT w/out thrombosis: Argatroban (only)

AFib on Hep + Coumadin
INR 1.5
Plat's 240 → 80
A: stop both Hep + Coumadin + start Argatroban

(Direct Thrombin Inhibitors) → until plat's recovers then coumadin

↓ more Heparin in lifetime
↳ 90% cross-reactivity w/ LMWH's

Causes of Thrombocytopenia in Pregnancy

1. Gestational (generally 3rd trimester) - ↓ Tx unless less than 70k
2. ITP
3. Preeclamsia
4. HELLP → low plat's
5. TTP
6. HUS

Drug-Induced Agranulocytosis
- causes: Bactrim
Tx: G-CSF

Inherited Thrombocytopenia
- differentiate from ITP w/ ↑MPV + should not respond to steroids like ITP does
- Ex.) May-Hegglin → giant plat's on peripheral smear

Platelet count goals
- 100,000 → Acute Intracranial Hemorrhage
- 40,000 → Severe Hemorrhage (Ex.) Pulmonary)
- 20,000 → Minor Bleeds
- 10,000 → Prophylaxis

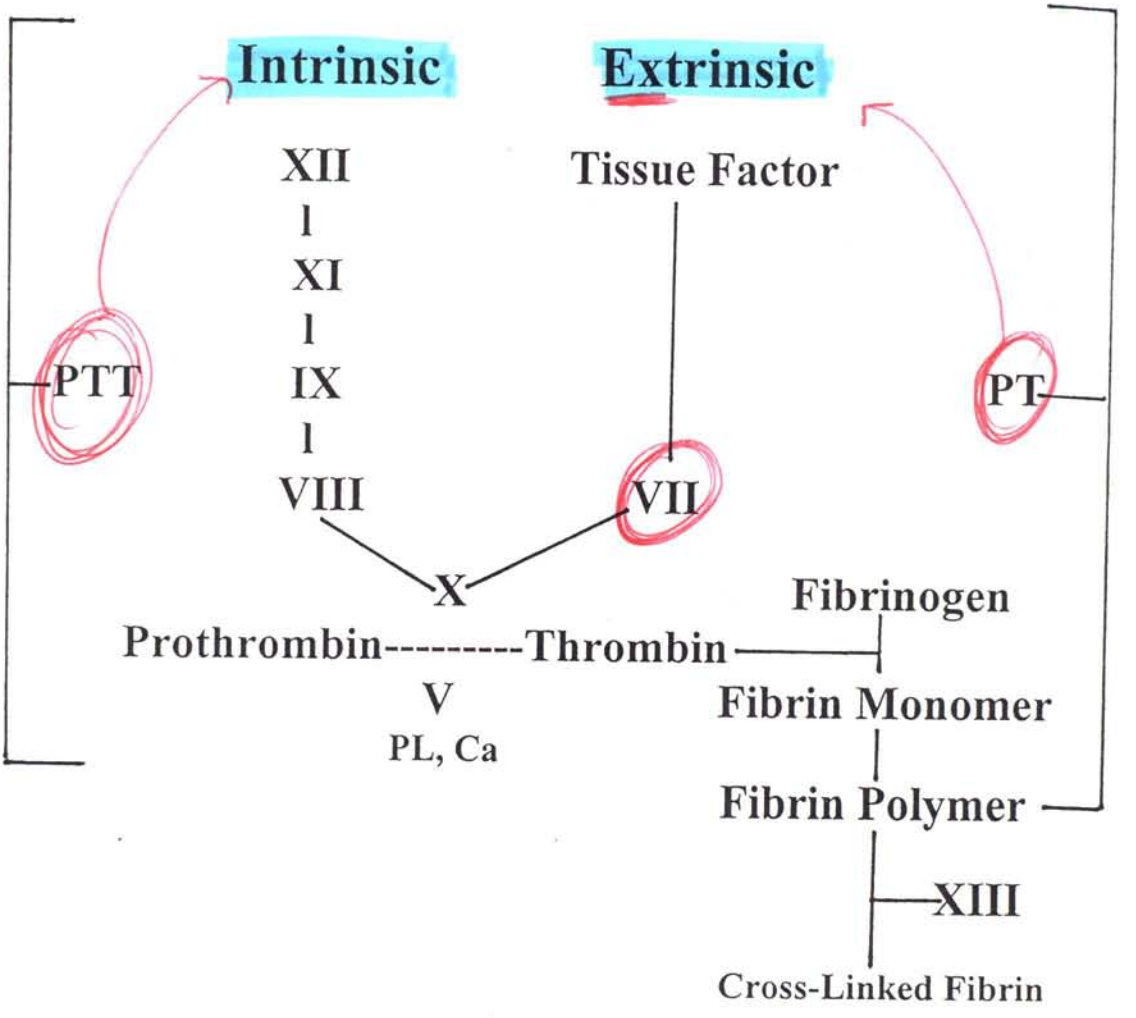
Acquired Causes of Platelet Dysfunction

Spurious Thrombocytopenia
- clumped plat's
- asymptomatic
- due to EDTA + draw again in Heparin tube (Green top)

Uremia
Cirrhosis
Dysproteinemias
Myeloproliferative & Myelodysplatic disorders
Von Willebrand's disease
Cardio-pulmonary bypass
Drugs: Aspirin, NSAIDS, Dipyridamole, Heparin, Penicillin,

Best Estimate For Post-op Bleeding D/O: History w/ focus on outcomes of prior surgeries

Blood Coagulation



Interpretation of Coagulation Tests

1. Prolonged PTT & Normal PT → Intrinsic Pathway
   - A. No Bleeding..... XII Deficiency
   - B. Mild or Rare Bleeding..... XI Deficiency
   - C. Frequent & Severe Bleeding..... VIII or IX Deficiency
   - D. Thrombosis..... Antiphospholipid syndrome
2. Prolonged PT & Normal PTT → Extrinsic Pathway
   - Factor VII Deficiency (Primary, early vitamin K deficiency, warfarin)
3. Both PTT & PT Prolonged
   - Defect in Common Pathway or Multiple Defects (DIC, liver disease, vitamin K deficiency)
4. Circulating Anticoagulant (Coagulation factor inhibitors)
   - PT & PTT are not corrected by normal plasma
5. Clot Solubility Test in 5 M Urea
   - Abnormal in factor XIII deficiency

Acquired Inhibitors
- malignancy (esp. lympho mas)
- autoimmune dz's
- post-partum

Factor VIII inhibitor more common than Factor IX inhibitor

Hemophilia
- X-linked
- very prolonged PTT (intrinsic)
- mixing study corrects PTT
- Tx: Factor VIII transfusion

Vascular pseudohemophilia

deep bleeding & mucosa

vs. vWDs
- mucosal bleeding
- mildly ↑'d PTT

- acquired → Ab's develop to Factor VIII
- autoimmune
- post-partum

PTT will not correct on mixing study

Tx: Plasmapheresis, PT complex

Causes of DIC

↑PT/PTT ↓Plat's
↑FSP's ↑schistocytes

Obstetrical syndromes

Abruptio placentae, retained dead fetus, eclamsia, amniotic fluid embolism, acute fatty liver of pregnancy

evacuate uterus (deliver) ASAP

Trauma

Infections

Malignancy

Vit. K Defic.
II, VII, IX, X
↑PT/PTT
Tx: vit. K

Hypercoagulable States

(Heriditary Thrombophilia)

1. Resistance to activated protein C (factor V leiden) - most common
2. Factor II 20210 mutation (prothrombin)
3. Antiphospholipid syndrome → ↓Plat's, ↑PTT, normal PT
   - does not correct on mixing study
4. Hyperhomocysteinemia
5. Antithrombin III deficiency
6. Protein C deficiency → may lead to warfarin necrosis if ϕ bridged w/ Heparin
7. Protein S deficiency
8. Dysfibrinogenemia

Asymptomatic ϕ Tx
Symptoms INR 2-3

- both also ↑ risk of arterial thrombosis

Testing for Hypercoagulable States

Indications:

1. Unprovoked venous thromboembolic event < 50 yrs
2. H/O of recurrent thrombotic episodes
3. H/O of first degree relative with thromboembolic event < 50yrs

Tests:

(Factor V Leiden)

1. Screen for resistance to activated protein C (APC) with a clotting assay; confirm positive assay genetically
2. Genetic test for prothrombin G20210A mutation
3. Functional assay for antithrombin III, protein C and protein S
4. Lupus anticoagulant/anticardiolipin antibodies
5. Fasting plasma homocystein

- levels are low in pregnancy for proteins → don't test them in pregnant pt's w/ a DVT

presence of DVT also ↓ levels of proteins C+S as well as antithrombin III levels → don't check them in DVT⊕ pt's.

Management of Hypercoagulable States

Anticoagulation

Asymptomatic	None
Thrombosis with transient triggering factor	3-6 months
Thrombosis without transient triggering factor	6 months

- More than one spontaneous thrombotic event
- One spontaneous life-threatening thrombotic event — Indfinite
- One spontaneous event in association with antiphospholipid antibody, antithrombin III deficiency, or more than 1 genetic or allelic abnormality (for example, homozygous factor V leiden or prothrombin G 20210A mutation; complex heterozygous for factor V leiden and prothrombin G 20210A mutation)

OCP's Options

① Estrogen-containing
- 4-fold ↑ risk for thrombus even w/ ∅ other risk factors
- 35-fold ↑ w/ Factor V Leiden and similar w/ other inherited hyper-coag states

② Progestin-only containing
- minimal ↑'d risk for thrombosis even w/ inherited hyper-coag states

Low-Molecular Weight Heparin

→ best option for DVT prevention in pt's w/ metastatic dis. (even better than coumadin)

As effective as unfractinated heparin
Predominantly anti-factor X activity
Prophylactic and treatment doses are different
Does not prolong PT & PTT
Major bleeding risk similar to unfractionated heparin
Remains active for 12-24 hrs
Effect cannot be reversed by protamine or fresh frozen plasma
Less likely to induce thrombocytopenia
Dose adjustment by measuring anti Xa levels (.5 to 1 unit) in:
- a) Renal insufficiency
- b) < 40 Kg or > 100 Kg
- c) Pregnancy
- d) Poor response to the drug

DVT Prophylaxis Post-Hip Fracture
- length of tx → 4-6 wks.
- Fondaparinux (OOC)

Management of Supratherapeutic INR Secondary to Warfarin

No bleeding

INR	Action
>Ther to 5.0	Omit warfarin
>5 to 9	Omit warfarin ± 1-2.5 mg oral vitamin K
>9 to 20	Omit warfarin + 5-10 mg oral vitamin K
>20	Hold warfarin + 10 mg IV vitamin K ± prothrombin complex concentrate ± fresh frozen plasma ± factor VIIa depending upon clinical emergency

Minor bleeding — 2 mg vitamin K S/C or 2.5 mg PO

Moderate bleeding — 5 mg vitamin K S/C or PO

Severe bleeding — Treat as INR >20 above

Patients at ↑ risk of bleeding

H/O of bleeding, stroke, renal insufficiency, anemia, hypertension

Myeloproliferative Disorders

Disorders

A. Polycythemia Vera
B. Primary Thrombocythemia
C. Myelofibrosis
D. CML

(100 % are positive for BCR-ABL mutation)

Common Features

1. Autonomous Proliferation of one or more hematopoietic cell lines
2. Splenomegaly
3. Marrow fibrosis
4. ↑Risk of bleeding & thrombosis
5. Fever, weight loss, night sweats
6. ↑Risk of Acute Leukemia

JAK2 V617F mutation

95%...Polycythemia Vera
50-60%...Myelofibrosis
50-60%...Primary Thrombocythemia

	Polycythemia Vera	Secondary Erythrocytosis
Hb/ HCT	↑	↑
WBC	↑	N
Platelets	↑	N
Erythropoietin	↓	↑
Splenomegaly	+	-
O2 saturation	N	< 92% if due to hypoxia
B12, B12 B. protein	↑	N
WBC ALKPO4	↑	N
Growth of Stem cells in vitro (BFU-E)	Spontaneous	With erythropoietin
JAK 2 mutation	+ 95%	-

Secondary Erythrocytosis

Neoplasm	: Renal, liver & cerebellum
Renal Lesions	: Polycystic disease, hydronephrosis
Hypoxia	: High altitude, lung disease, R>L shunts
Abnormal Hb	: Carboxy hemoglobin (smokers)
	High affinity variants (low p50 values)
	Methemoglobinemia
Hormonal	: Cushing's syndrome, steroids, androgens

Diagnostic Criteria for Polycythemia Vera

JAK2-positive polycythemia vera

(Diagnosis requires presence of both criteria)

1. High hematocrit (>52% in men or >48% in women)
2. Mutation in JAK2

Tx: Phlebotomy to Hct <45%
- Low-dose Aspirin
- Hydroxyurea

JAK2-negative polycythemia vera

(Diagnosis requires the presence of A1, A2, and A3, plus either another A criterion or two B criteria)

A1. Increased red cell mass (>25% above predicted value) or hematocrit >60% in men or > 56% in women
A2. Absence JAK2 mutation
A3. No cause for secondary erythrocytosis (normal O2 saturation and no elevation of serum erythropoietin)
A4. Splenomegaly
A5. Presence of acquired genetic abnormality (excluding BCR-ABL) in hematopoietic cells)
B1. Platelets >450000/uL)
B2. Neutrophil count > 10000/uL;>12500/uL in smokers
B3 Splenomegaly on radiography
B4. Endogenous erythroid colonies or low serum erythropoietin

Complications of Polycythemia Vera

- Ruddy complexion

1. Arterial & venous thrombosis
2. Myelofibrosis → Tx: Transfusion
3. Erythromelalgia (pain) Tx: ASA Phlebotomy or Hydroxyurea
4. Hyperuricemia
5. Massive splenomegaly
6. Pruritus
7. Thrombocytosis

Causes of Thrombocytosis

1. Iron deficiency
2. Splenectomy
3. Chronic infections
4. Recovery from acute infections
5. Neoplasms
6. After Rx of megaloblastic anemia
7. Blood loss or hemolysis
8. Chronic inflammatory diseases
9. Primary thrombocytosis

When To Tx Thrombocytosis:
- h/o thrombosis or hemorrhage
- Age >60 to <1.5 million

Tx: Aspirin plus Hydroxyurea or Anagrelide (not used in PCV)

CML Leukemoid Reaction

↑'d risk of leukemic transformation to AML

Tx: Gleevec

side effects: -maculopapular rash of trunk/ext's

Tx: -Stop drug -Let rash resolve -Re-initiate drug

Hydroxyurea → lowers WBC's acutely

	CML	Leukemoid Reaction
1. WBC ALKPO4 (LAP)	↓	N
2. Ph Chromosome	+	-
3. Eosinophilia	+	-
4. Basophilia	+	-
5. Vitamin B12	↑	N
6. B12 Binding Capacity	↑	N

Hyperviscosity Synd:
- HA's
- Dizziness
- Epistaxis
- Retinal vein dilation
- CHF
- Due to ↑ glob's

Tx w/ plasmapheresis

- CML → ↑ WBC's

leukopheresis

Multiple Myeloma

- Hypercalcemia
- Bone Pain
- Anemia

w/ severe osteoporosis + compression fx's

Tx: IV Pamidronate

- may see hypogammaglob in urine or blood but ∅ both

1. Marrow plasmacytosis (> 30%)
2. Plasmacytoma on tissue biopsy
3. Lytic bone lesions or other evidence of end organ damage (↑Ca, renal disease, anemia)
4. Serum and/or Urine M Component
   (IGG > 3.5 gm/dL, IGA > 2gm/dL, or urinary light chains > 1 gm/24hrs)

Manifestations of Multiple Myeloma

Dx: Amyloidosis (AL)

Ex.) Nephrotic range proteinuria w/ monoclonal protein spike on SPEP not quite diagnostic of myeloma

1. Bone Pain
2. Hypercalcemia
3. Infections
4. Renal Failure
5. Neuropathies
6. Hyperviscosity
7. Hematological disturbances
   ↳ (Anemia)

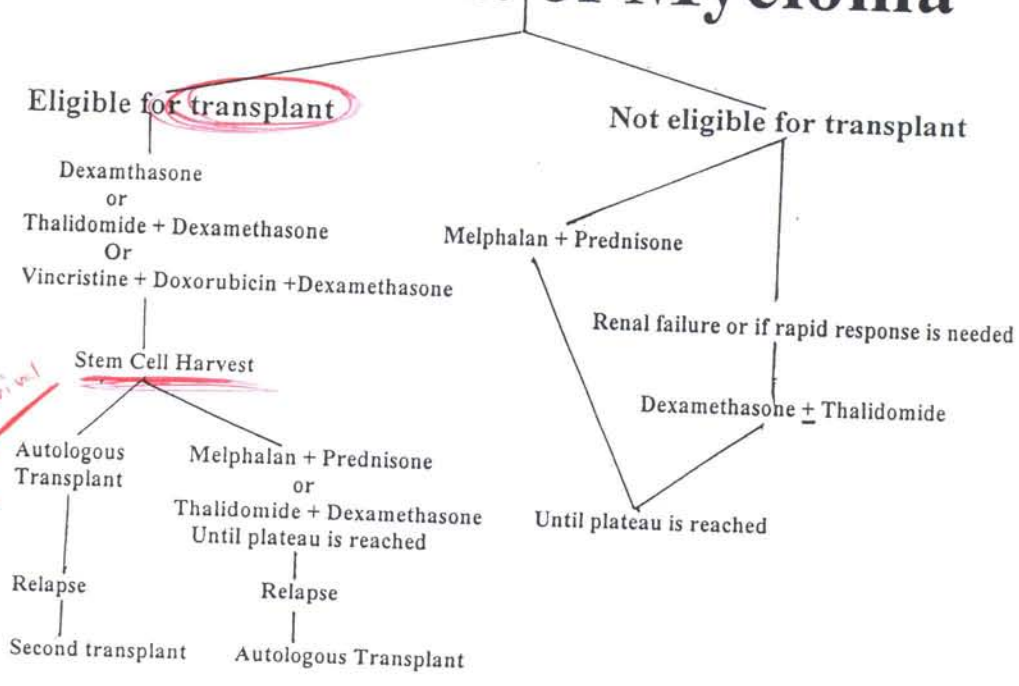
(nephrotic range) esp. proteinuria

	Multiple Myeloma	Monoclonal Gammopathy of Undetermined Significance (MGUS)
Marrow Plasmacytosis	> 30%	< 10%
M Component	IGA > 2 g/dL	<2 g/dL
	IGG > 3.5 g/dL	<3.5 g/dL
Bence Jones Protein (urine light chains)	> 1 gm/24h	< 1gm/24h
Lytic Bone Lesions	+	-
Hypercalcemia	+	-
Anemia	+	-
Renal Failure	+	-
Bone Marrow Labeling Index	> 1%	< 1%

Poor Prognostic Factors in Myeloma

1. Hb < 8.5 g/dL
2. IgG > 7g/dL or IGA > 5g/dL
3. Calcium > 12 mg
4. Urinary light chains > 12g/24h
5. > 3 lytic lesions
6. B2microglobulin > 6 mg/L

Treatment of Myeloma



Acute Leukemias

	AML	ALL
Size of Cells	large	Smaller than AML
Auer Rods	+	-
PAS Stain	-	+
Peroxidase Stain	+	-
Terminal Transferase	-	+
CNS Involvement	+	+ + +
Hepatosplenomegaly	+	+ + +
Lymphadenopathy	+	+ + +
Leukostasis	+ + +	+
Tumor Lysis Syndrome	+	+ + +

Monocytic Leukemia infiltrates gums + skin

Hairy Cell Leukemia:
- HSM
- Pancytopenia
- BM → fibrosis
- Tx: 2-CDA
- TRAP+

DIC assoc. w/ promyelocytic leukemia (t, 15:17)
Tx: Trans retinoic acid

occlusion of microcirculation (usually w/ Blasts > 100k)
Tx: Leukopheresis

Indications of Chemotherapy in CLL

Note: ↓ WBC cutoff

- monoclonal B-cells
- CD-5 Ag's
- ↓ risk of acute leukemic transformation

CLL vs. CML

CLL → BM preponderance of mature lymphs

CML → BM preponderance of all cells

1. Anemia (< 11 g/dL)
2. Thrombocytopenia (<100000/uL)
3. Marked systemic symptoms
4. Disfiguring lymphadenopathy
5. Symptomatic organomegaly
6. Autoimmune hemolytic anemia or thrombocytopenia unresposive to steroids
8. Short lymphocyte doubling time (< 12 months)

Ex.) CBC shows lymphocytosis of 60%

↓

Next best test:
Diagnostic ← Flowcytometry
↓Diagnostic ← (↓peripheral Smear)

Tx: Fludarabine
Gammaglobulin

Treatment of Acute Leukemia

General Therapy:

Fever & Granulocytopenia: G-CSF, GM-CSF
Allopurinol before chemotherapy to prevent urate nephropathy
Platelet transfusion for platelet count < 10000/uL
Granulocyte transfusion in patients with serious infection not responding to antibiotics

ALL

Remission Induction:

Vincristine, prednisone, daunorubicin

Meningeal Leukemia Therapy:

Intrathecal methotrexate + intracranial radiation

Consolidation therapy:

Given to eradicate undetectable minimal residual disease
(methotrexate or cytosine arabinoside)

Remission Maintenance Therapy:

Given for several years...daily or intermittent administration of 6MP or methotrexate

Allogenic or Autologous Bone Marrow Transplant

Considered for patients in first remission whose prognosis for long term remission is poor or for patients who had a relapse and achieved a second complete remission

AML

Induction Therapy:

Cytosine arabinoside and daunorubicin

Consolidation Therapy:

Cytosine arabinoside

Bone Marrow Transplant

For patients with poor prognostic factors