MYELODYSPLASTIC SYNDROME

NO DISCLOSURES

MDS

- Heterogeneous group of clonal stem cell disorders with a variable clinical course
- Characterized by proliferation and ineffective maturation of hematopoietic precursors
- Results in pancytopenia
- Incidence increases with age

MDS ETIOLOGY

- TOXIC EXPOSURE: Smoking, Benzene
- SECONDARY-THERAPY RELATED: Chemo, RT
- INHERITED DISORDERS - Fanconi anemia
- DE NOVO

MDS ABNORMALITIES

QUANTITATIVE	QUALITATIVE
Anemia	Abnormal RBC
Neutropenia	Impaired neutrophil function
Thrombocytopenia	Impaired platelet function
Monoclonal Protein	
Autoimmune Features	Impaired immune regulatory function

MDS WHO CLASSIFICATION, 2008

- Refractory cytopenia with unilineage dysplasia
- Refractory cytopenias with multilineage dysplasia
- Refractory Anemia with Ringed Sideroblasts
- Refractory Anemia with Excess Blasts (RAEB-1 5-9%; RAEB-2 10-19% blasts)
- 5q- syndrome
- Unclassifiable
- Childhood MDS

MDS CYTOGENETICS

- Very Favorable: del(11q), -Y
- Favorable: 5q-, 20q-, normal
- Intermediate: Trisomy 8
- Unfavorable: Monosomy 7, 7q-, Multiple

MDS PROGNOSTIC FEATURES

- Percent Blasts
- Cytogenetics
- Number of Cell Lines Involved
- Age
- Primary vs. Secondary

MDS TREATMENT

- Erythropoietin (epoetin [Procrit], darbepoetin [Aranesp])
- Azacitidine (Vidaza)
- Decitabine (Dacogen)
- Lenalidomide (Revlamid) for 5q- syndrome only
- Bone Marrow/Stem Cell Transplant

MULTIPLE MYELOMA

no disclosures

PLASMA CELL DISORDERS

- Multiple Myeloma
- Monoclonal Gammopathy of Undetermined Significance (MGUS)
- Smoldering Multiple Myeloma (SMM)
- Solitary Plasmacytoma
- Waldenstrom's Macroglobulinemia
- Amyloidosis
- POEMS

MULTIPLE MYELOMA: CLINICAL PRESENTATION

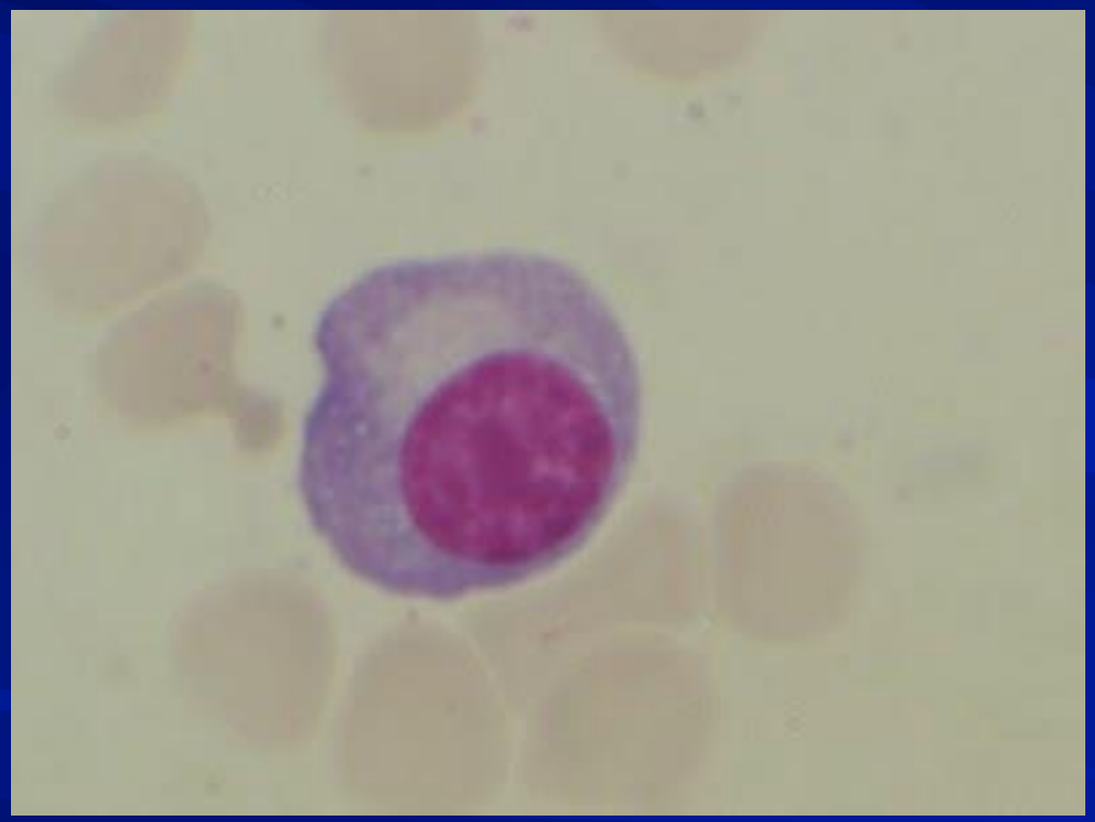
- Weakness and fatigue
- Bone pain
- Fractures
- Infection
- Renal failure
- Hypercalcemia

MULTIPLE MYELOMA: CLINICAL PRESENTATION

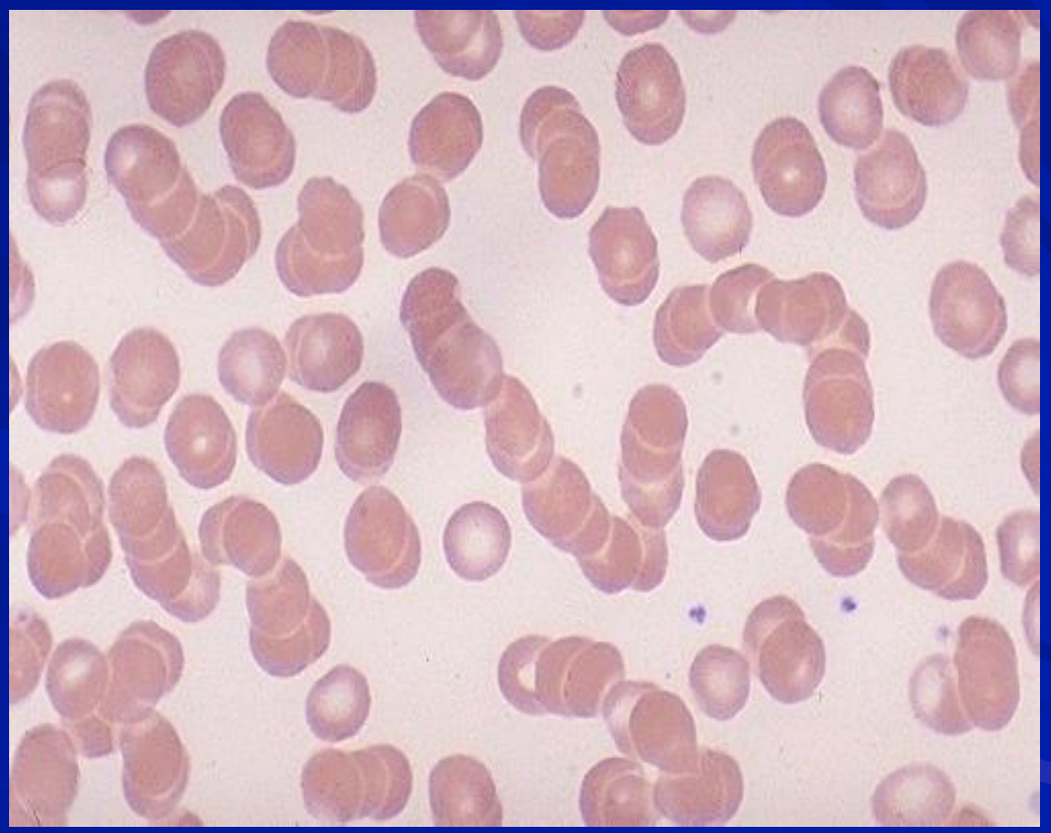
- Plasma cells in bone marrow-96%
- Monoclonal (M) Protein-93%
- Anemia-73%
- Lytic Bone Lesions-67%
- Renal insufficiency SCr ≥2-19%
- Hypercalcemia ≥11-13%

MULTIPLE MYELOMA

Plasma cell



Rouleux formation



M PROTEIN IN MYELOMA

- IgG (50%)
- IgA (20%)
- Light chain only (20%)
- Rarely IgD (2%)

MYELOMA WORK-UP

- Serum Protein Electrophoresis (SPEP) only identifies an M spike
- Immunofixation (IFX) identifies type and clonality (kappa/ lambda)
- 24 hour urine for PEP and IFX
- Skeletal survey
- Bone marrow biopsy
- CBC, serum creatinine, calcium, CMP
- B-2 microglobulin

MYELOMA DIAGNOSIS

- Evidence of monoclonal plasma cell disorder in serum or bone marrow
- Plus at least one or more of the CRAB features due to myeloma:

-Calcium (hypercalcemia)

-Renal insufficiency

-Anemia

-Bone lesions (lytic)

MYELOMA: TREATMENT

- Melphalan / Prednisone: avoid melphalan if transplant candidate
- Revlamid/Velcade/Dexamethasone
- Carfilzomib, pomalidomide, daratumumab, elotuzumab,
- Stem cell transplant
- Bisphosphonates

MGUS

- M spike < 3 grams and
- Plasma cells in bone marrow <10%
- No anemia or bone lesions
- Normal calcium and kidney function

SMM

- M spike >3 grams OR
- Bone marrow plasma cells >10%
- No anemia or bone lesions
- Normal calcium and kidney function

SOLITARY PLASMACYTOMA

- Single bony or extramedullary lesion
- M protein may be present
- Bone marrow: Negative
- Treatment: Radiation
- Median survival: 10 years
- 55% later develop myeloma

WALDESTROMS MACROGLOBULINEMIA

- AKA Lymphoplasmacytic lymphoma,
- A type of NHL which produces large amounts of abnormal proteins/macroglobulin

WALDENSTROM'S MACROGLOBULINEMIA

- IgM in serum
- Lymphoplasmacytoid appearance of cells in the marrow
- Adenopathy
- Hyperviscosity syndrome

WALDENSTROMS MACROGLOBULINEMIA

- Treatment

  Rituximab/Bendamustine

  Bortezamide increases risk of peripheral neuropathy

- Plasmapheresis if symptomatic hyperviscosity syndrome

AMYLOIDOSIS

- Group of diseases characterized by deposition of insoluble protein in organs and tissues resulting in organ dysfunction; classification based on the precursor proteins that form fibril deposits
- Diagnosis requires presence of amyloid fibers, typically in fat pad aspirate, stained with Congo Red reveals apple green birefringence under polarized light

AMYLOIDOSIS

Consider diagnosis if:

- Non-diabetic nephrotic syndrome
- Non-ischemic cardiomyopathy with an echo showing LVH
- Hepatomegaly or alk phos elevation without imaging abnormality
- Peripheral neuropathy with MGUS or CDP with autonomic features
- Atypical myeloma-monoclonal light chains in urine and modest marrow plasmacytosis

AMYLOIDOSIS

- Primary (AL) (light chain)
- Familial (mutated TTR)
- Secondary (SAA; protein A)
- Senile (unmutated TTR)
- Dialysis associated (beta 2-microglob)

AMYLOIDOSIS

- Primary: Fibrils are Ig light chains (AL)
  Deposited in heart, tongue, GI tract and skin. 21% have MM
- Secondary: Fibrils are protein A (AA)
  Deposited in liver, kidney and skin.
- Treatment: No FDA approved treatments
  bortezomid/dexamethasone, bendamustine
  Stem cell transplant

POEMS SYNDROME

- Overproduction of light chains, usually lambda, without significant plasma cells in marrow, many organ systems involved

POEMS SYNDROME

- Polyneuropathy-usually sensory
- Organomegaly-liver and spleen most common
- Endocrinopathies
- M protein
- Skin changes-hypertrichosis, thickening
- Sclerotic bone lesions

THROMBOCYTOPENIA

AND OTHER PLATELET DISORDERS

no disclosures

Etiologies of Thrombocytopenia

- Decreased Production
- Increased Consumption
- Destruction
- Dilution
- Sequestration

THROMBOCYTOPENIA IN HOSPITALIZED PATIENTS

- Sepsis
- Drugs: Heparin
  H2 Antagonists
  Antibiotics
- Dilutional
- DIC
- TTP

HEPARIN INDUCED THROMBOCYTOPENIA

- A fall in platelet count to <150,000 five or more days after starting heparin
- With or without thrombotic complications
- Other causes have been excluded
- +/- positive serological test for HIT

RISK OF HIT

- Unfractionated heparin 2.6%
- Low molecular weight heparin 0.2%
- Fondaparinux <0.2%

TREATMENT OF HIT

- STOP HEPARIN including LMW heparin
- Bivalirudin: Thrombin inhibitor
  Renal excretion
- Argatroban: Thrombin inhibitor
  Hepatic clearance
- Fondaparinux
- DO NOT USE WARFARIN ACUTELY!!- limb gangrene

DISSEMINATED INTRAVASCULAR COAGULATION

- Heterogenous group of clinicopathologic syndromes characterized by disregulated generation of thrombin leading to intravascular fibrin formation and secondary fibrinolysis (plasmin generation often resulting in hemorrhage, thrombosis and/or multi-organ system failure
- Often lab evidence for low-grade DIC(i.e., ICU patients with multi-organ system failure, septicemia, etc) with low platelets, elevated D-dimer, but normal INR/aPTT/fibrinogen: hemostatic intervention is not usually needed
- Clinically important when it causes bleeding and/or thrombosis

ISTH CRITERIA FOR DIC

- Does patient have disorder associated with overt DIC ? If yes, proceed; if no, do not use this algorithm
- Order: Platelet count, PT, Fibrinogen, D-dimer
- Score:
    - Platelet count: >100=0, 50-100=1, <50=2
    - Increased D-dimer: none=0, moderate=2, strong=3
    - Increased PT: <3 sec=0, 3-6 sec=1, >6 sec=2
    - Fibrinogen: >100=0, <100=1
- Interpret:
    - If >/=5: compatible with overt DIC
    - If <f: suggestive for non-overt DIC; repeat in 1 day

Taylor et al. Thromb Haemostasis 2001; 86:1327-30

PATHOGENESIS OF DIC: Depletion of Inhibitors

- Potential for bleeding:
  - depletion of alpha2-antiplasmin
- Potential for thrombosis:
  - depletion of antithrombin (ATIII)
  - depletion of protein C & S

DIC TREATMENT

- Treat underlying disorder
- Platelet, cryoprecipitate and FFP transfusions if bleeding and very low levels of platelets or fibrinogen
- Heparin (therapeutic dose)
  - if complications of thrombosis present
  - not recommended in patients at high risk of bleeding
- Heparin/LMWH (prophylactic dose)
  - non-bleeding, critically ill patient

DIC TREATMENT

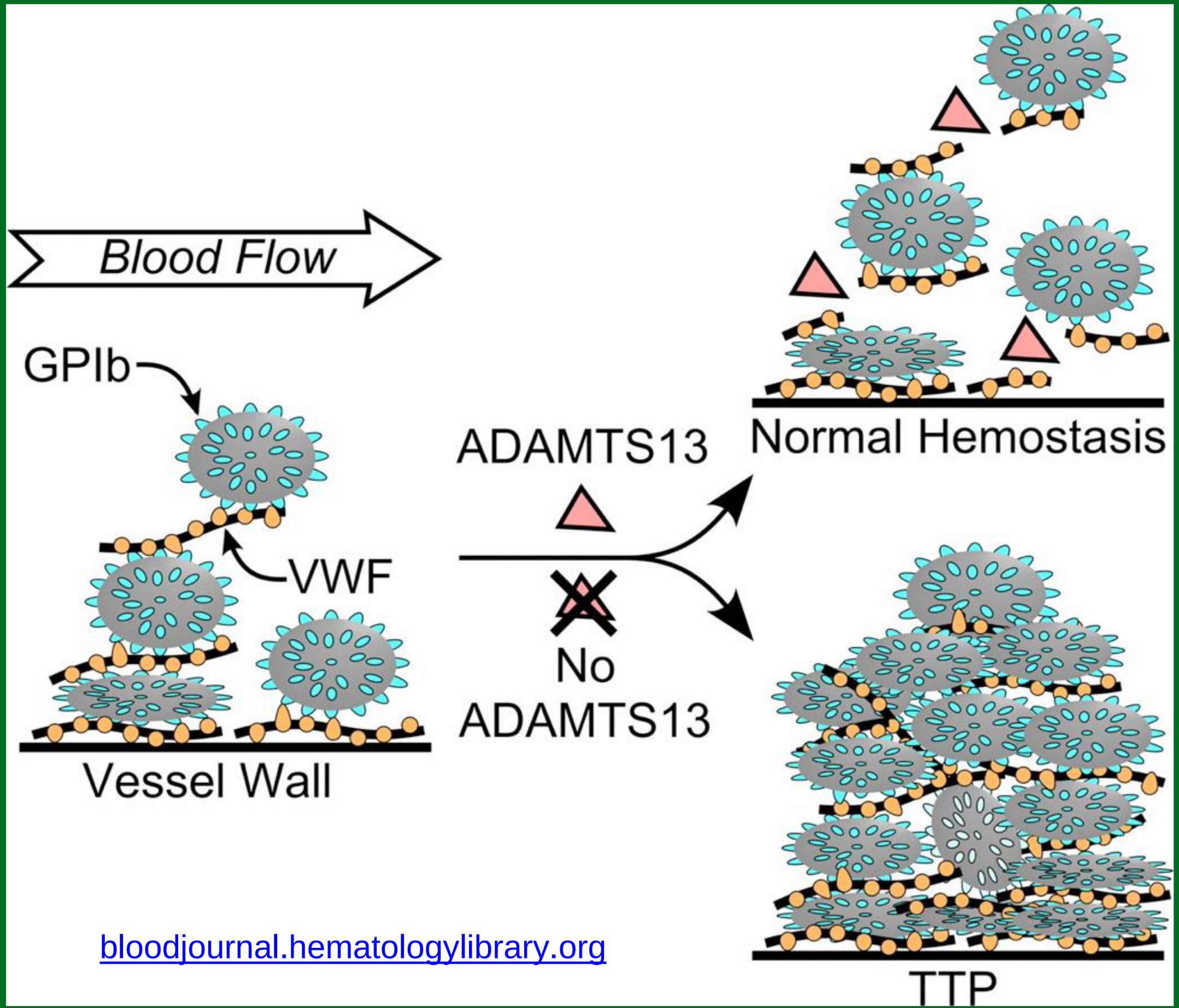
- Avoid antifibrinolytic therapy except in leukemia and trauma

- Antithrombin or Recombinant Thrombomodulin can be considered in some patients

- Consult your local hematologist

THROMBOTIC THROMBOCYTOPENIC PURPURA

- Due to autoantibodies against plasma protease ADAMTS13 that cleaves ultra large vWf multimers
- Congenital deficiency of ADAMTS13



bloodjournal.hematologylibrary.org

TTP ETIOLOGY

- Primary, congenital deficiency of ADAMTS13, no disease association
- Primary, but triggered by a disease or disorder: vaccination, viral infections (Coxsackie B, Echo, Epstein-Barr), pregnancy

TTP ETIOLOGY

- Secondary: Drug associated (quinidine, ticlopidine), HIV, collagen vascular disease
- Chemotherapy-mitomycin
- Bone marrow transplant

TTP DIAGNOSIS

- Thrombocytopenia 100%
- Schistocytic Hemolytic Anemia 100%
- Neurological Events 65%
- Renal impairment 50%
- Fever 25%

TTP TREATMENT

- Mild (no symptoms): Prednisone 200 mg daily
- Deterioration: Plasma exchange
  Plasma infusions

HEMOLYTIC-UREMIC SYNDROME

- Distinct syndrome

  -Distinct pathogenesis-no deficiency of vWD cleaving metalloproteinase

  -Distinct etiology-E. coli gastroenteritis

E. Coli 0157:H7 is an emerging infectious disease caused by transfer of a gene from Shigella dysenteriae to a strain of enteropathogenic E. coli

TREATMENT OF HUS

- Supportive in children
- Plasma infusion/pheresis for severe HUS and in adults
- Eculizumab (Solaris)

THROMBOCYTOPENIA IN OUTPATIENTS

- ITP
- Hypersplenism
- Secondary: SLE, Lymphoproliferative Disorders
- Aplasia, Myelodysplasia

PRIMARY IMMUNE THROMBOCYTOPENIC PURPURA

- Thrombocytopenia with normal CBC & blood smear
- No congenital disorders, MDS or carcinomatosis
- No drugs
- No viral infection
- No SLE or other autoimmune disease
- No lymphoproliferative disease

ITP PATHOPHYSIOLOGY

- Platelet associated antibodies
- Rapid platelet destruction
- Suppression of thrombopoiesis
- Antibodies to megakaryocyte antigens

ITP DIAGNOSIS

- History & Physical
- CBC and peripheral smear exam
- HIV & HCV testing
- Bone marrow biopsy & PAIgG testing not necessary for classic presentation

ITP TREATMENT

- Treat if count < 30K
- Platelet < 50 K and significant mucous membrane bleeding or risk factors for bleed (PUD)
- Hospitalization for patients < 20K and significant mucous membrane bleeding &/or noncompliant

ITP TREATMENT

- Prednisone 1 mg/kg Q day
- Improvement usually in 3 days with maximum in 2 weeks
- Allows increased platelet production
- Reduces rate of platelet destruction
- Dexamethasone-good response rate but high relapse risk in 3 months

ITP TREATMENT

- IVIg
- Anti-D (WinRho)
- Splenectomy
- Vinca alkaloids
- Cyclophosphamide
- Rituximab
- Thrombopoietin agonists: N-plate, Promacta

PLATELET TRANSFUSION PEARLS

- AVOID
- Current ARC recommendations:
  - Platelet count < 50K and bleeding
  - No bleeding, but platelet count < 5K, maybe
  - Dysfunctional platelets regardless of count and surgery required or patient bleeding

PLATELET TRANSFUSION PEARLS

- Rule of thumb:
  - –One unit single donor (pheresed) platelets
    - =Six units random donor platelets

Good result would be a rise in the platelet count by 30,000 one hour after transfusion

INHERITED PLATELET DISORDERS

- Glanzmann's thrombasthenia
- Bernard-Soulier
- Gray platelet syndrome
- Storage pool disease

INHERITED PLATELET DISORDERS

- Bleeding present at birth or can present later in life
- Manifestations include easy bruising, gingival bleeding, epistaxis, menorrhagia
- Bleeding time is prolonged in all these disorders

ACQUIRED PLATELET DISORDERS

- Result from medications, medical disorders, or hematologic disorders

MYELOPROLIFERATIVE DISORDERS

no disclosures

PRIMARY MYELOFIBROSIS

- Progressive generalized reactive fibrosis of bone marrow
- Associated development of hemopoiesis in spleen and liver (myeloid metaplasia)

Primary Myelofibrosis Pathogenesis

- Megakaryocytes release platelet derived growth factor and other cytokines to stimulate fibroblasts
- JAK-2 mutation positive in 50%
- Nonspecific cytogenetic abnormalities in 50%
- Transformation to acute leukemia 10-20%

Primary Myelofibrosis

- Symptoms
  - Weakness
  - Night sweats, weight loss
- Signs
  - Massive hepatosplenomegaly
  - Bone marrow failure
  - Portal hypertension
  - Pulmonary hypertension

Primary Myelofibrosis Lab Findings

- Anemia: tear-drop erythrocytes
- Initial elevation, then decline in WBC & platelet count
- JAK-2 positive in 50%
- Bone marrow fibrosis with increased megakaryocytes

Etiologies of Myelofibrosis

- Infections, ie-TB, osteomyelitis
- Hematological malignancies
- Metastatic cancer, esp breast & prostate
- High exposure to radiation
- Benzene toxicity
- Fluorine toxicity
- Paget's disease-focal fibrosis
- Osteopetrosis

Primary Myelofibrosis Treatment

- Hydroxyurea
- Transfusion as indicated
- Splenic irradiation or splenectomy
- JAK-2 inhibitors
- Erthropoietin supplementation
- Androgen therapy

Polycythemia vera

- Clinical Features
  - Symptoms: headaches, dyspnea, blurred vision, night sweats, pruritus (especially after hot shower)
  - Signs: plethoric facies, retinal venous engorgement, splenomegaly, hypertension, gout, thrombosis (aterial or venous), hemorrhage (GI, uterine, cerebral)

Polycythemia Vera

- Laboratory findings
  - Elevated hemoglobin and hematocrit
  - RBC volume increased
  - Leukocytosis-50%
  - Thrombocytosis-50%
  - Hypercellular bone marrow
  - Low erythropoietin
  - JAK-2 positive-95%

Polycythemia Vera

- Diagnosis
  - JAK-2 positive-no further work-up needed
  - JAK-2 negative
    - No cause of secondary erythrocytosis
    - Splenomegaly
    - Acquired genetic abnormality
    - Thrombocytosis +/- leukocytosis

Etiologies of Secondary Polycythemia

- Tumor related increase in erythropoietin
  - Renal cell cancer
  - Hepatocellular cancer
  - Uterine fibroids
- Hypoxemia
  - COPD
  - Sleep apnea
  - Massive obesity
  - High altitude
- Increased carboxyhemoglobin levels
  - Smoking
  - Chronic carbon monoxide exposure
- Hemoglobinopathy

Differential Diagnosis of Polycythemia

- Step 1
  - H&P, CBC w/diff, ferritin, renal & liver function tests, PFTs, ABG w/carboxyhemoglobin, erythropoietin
  - JAK-2: if negative proceed to step 2
- Step 2
  - Bone marrow biopsy w/cytogenetics
  - Abdominal US
- Step 3
  - O2 dissociation: heart & lung evaluation

Therapy of Polycythemia

- Phlebotomy to Hct < 45%
- Hydrea for platelet count > 400,000
- Aspirin 81 mg daily
- JAK-2 inhibitors

Thrombocytosis

Reactive:

- Hemorrhage
- Trauma
- Postoperative
- Chronic iron deficiency
- Malignancy
- Chronic infections
- Connective tissue diseases
- Postsplenectomy

Endogenous:

Essential thrombocythemia

Can also be seen in:

- Polycythemia vera
- Myelofibrosis
- CML

Essential thrombocythemia

- Clinical findings
  - Asymptomatic
  - Thrombosis (venous or arterial)
  - Hemorrhage (abnormal platelet function)
  - Splenomegaly
  - Erythromelalgia: burning sensation of hands & feet

Essential Thrombocythemia

- Laboratory Findings
  - Platelet count >400,000
  - Abnormal large platelets and megakaryocytic fragments on peripheral smear
  - JAK-2 positive-90%
  - Bone marrow with abnormal megakaryocytes
  - Platelet function studies abnormal
  - Treatment: same as for polycythemia

PORPHYRIA

Cheryl Kovalski, DO

No disclosures

Acute Porphyrias

Type	Enzyme defect	Inheritance	Biochemistry
Plumboporphyria	ALA dehydrates	autosomal recessive	Urine: inc ALA
Acute Intermittent Porphyria	PBG deaminase	autosomal dominant	Urine: inc PBG and ALA
Hereditary coproporphyria	copropor phyrinogen oxidase	autosomal dominant	Urine: inc ALA, PBG, coproporphyrin Stool: inc copropor
Variegate Porphyria	Protopor-phyrinogen oxidase	Autosomal dominant	Urine: inc ALA, PBG coproporphyrin Stool: inc proto & copro

ACUTE PORPHYRIA-PRESENTING SYMPTOMS

- Gastrointestinal: abdominal pain, vomiting, constipation, diarrhea
- Cardiovascular: tachycardia, systemic hypertension
- Neurologic: pain-extremities, back, chest, head; paresis, mental symptoms, convulsions, respiratory paralysis
- Precipitating factors: drugs, females of child-bearing years, fasting, dieting, stress, smoking
- www.porphyriafoundation.com, www.drugs-porphyria.org

CUTANEOUS PORPHYRIA

Porphyria cutanea tarda	Uroporphyrinogen decarboxylase	autosomal dominant	Urine: uroporphyrin
Heaptoerythro-poietic porphyria	Uroporphyrin-ogen decarboxylase	autosomal recessive	Urine: uroporphyrin
Erythropoietic Protoporphyria	Ferrochelatase	autosomal dominant	RBC: protoporphyrin
Congenital erythropoietic porphyria	Uroporphyrinogen III synthase	autosomal recessive	Urine, stool: coproporphyrin 1
X-linked protoporphyria	ALAS2	X-linked	

PORPHYRIA CUTANEA TARDA

- Most common porphyria
- Precipitating factors oxidize uroporphyrinogen which inhibits URO-D: increased iron stores, Hepatitis C, HIV, alcohol, estrogens, exposure to fungicide hexachlorobenezene
- Manifestations: bulous dermatosis, scarring, hyperpigmentation, hypertrichosis

PORPHYRIA CLINICAL APPROACH SUMMARY

- Symptomatic porphyria always has increased heme precursors; absence indicates symptoms not due to porphyria
- During asymptomatic periods, individuals with enzymaticc defect may have normal heme precursor levels
- Mutation analysis