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

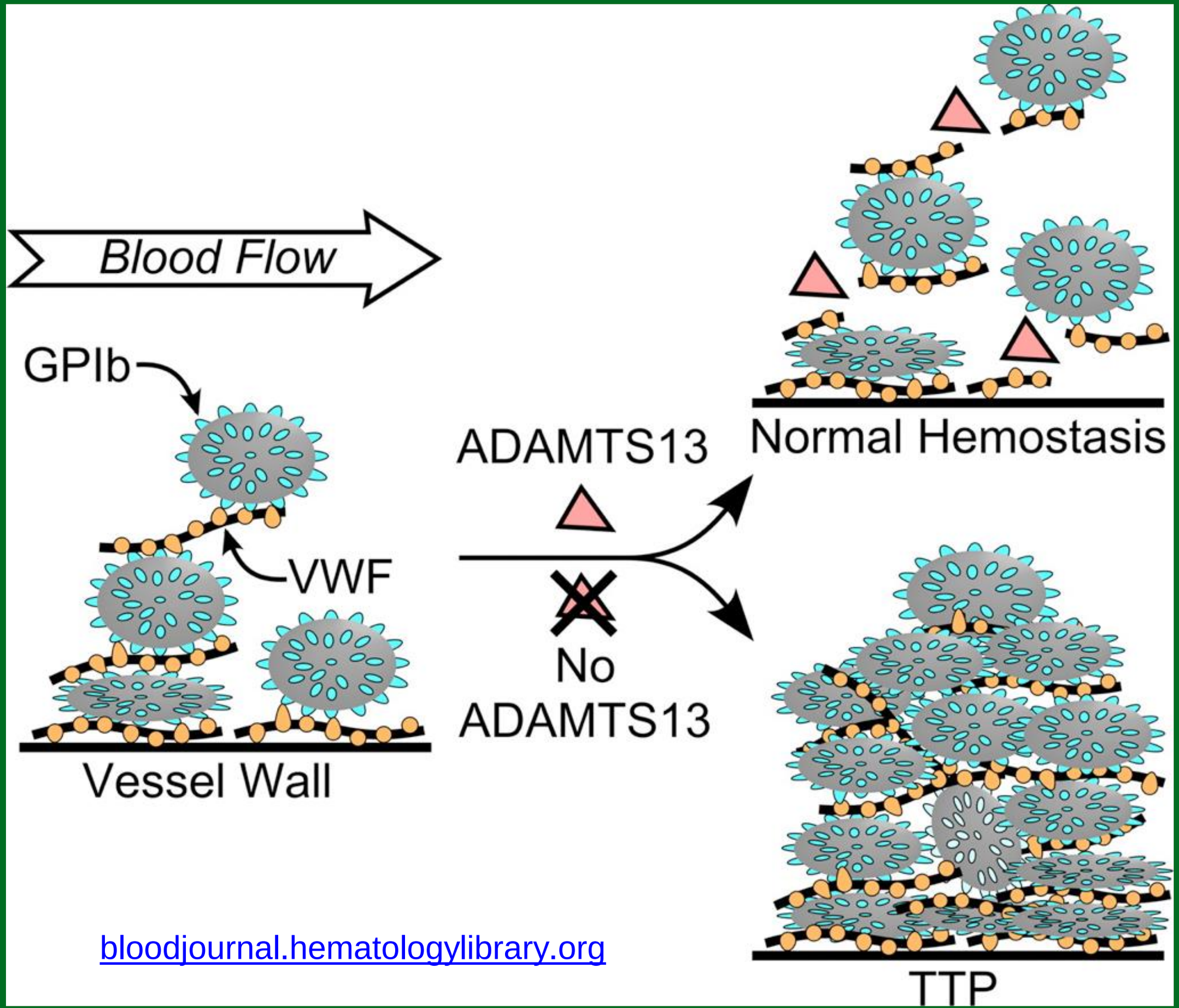
- Treat underlying disorder
- Platelet, cryoprecipitate and FFP transfusions if bleeding and very low levels of platelets or fibrinogen
- Heparin (therapeutic dose)
  - if complications of thrombosis present
  - not recommended in patients at high risk of bleeding
- Heparin/LMWH (prophylactic dose)
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

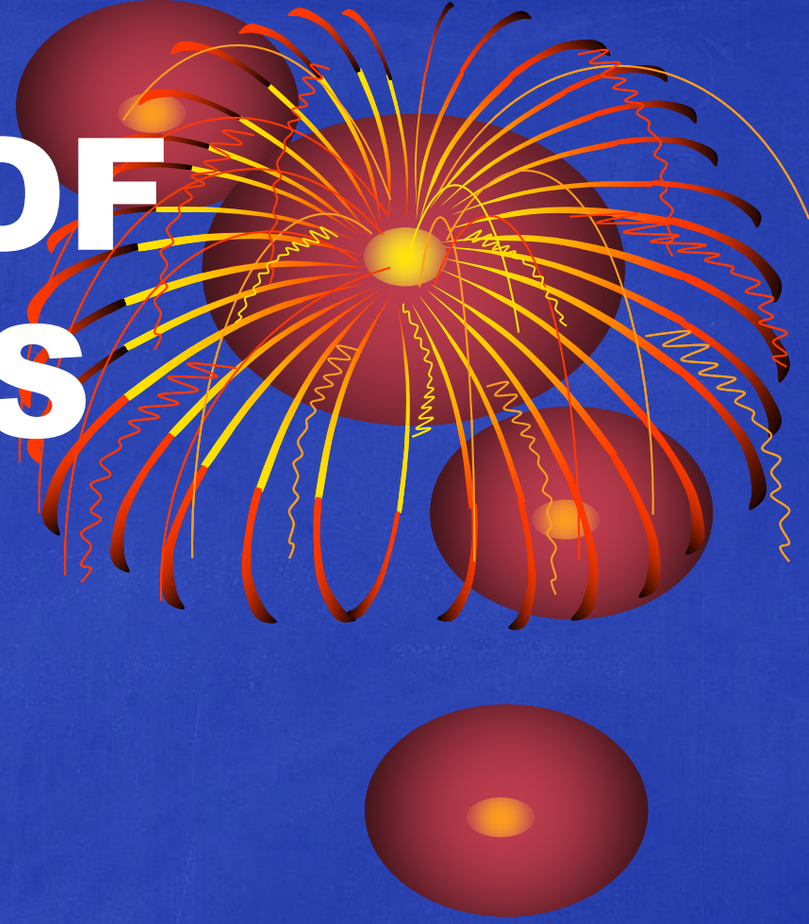
- Result from medications, medical disorders, or hematologic disorders

HEMOSTASIS

PHYSIOLOGICAL BLOOD CLOTTING IN RESPONSE TO INJURY OR LEAK

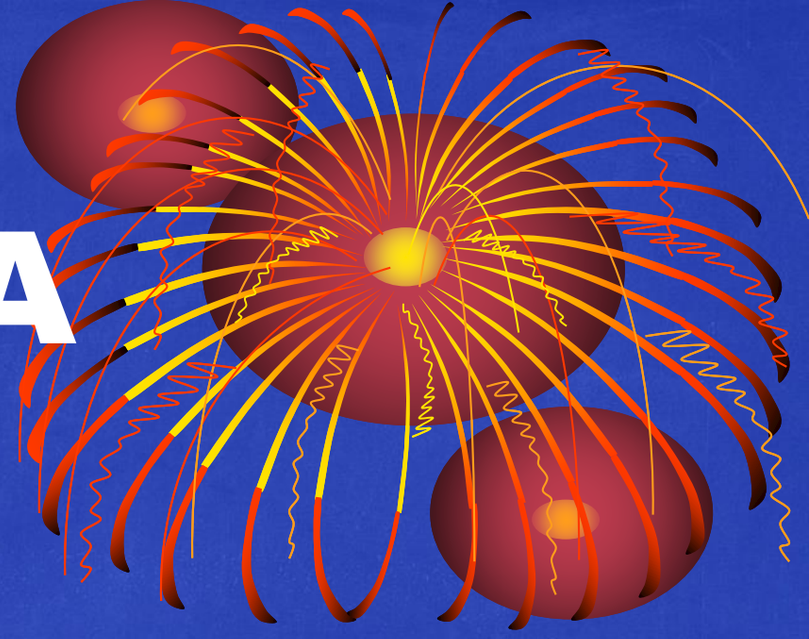
no disclosures

DISORDERS OF HEMOSTASIS



- HEMOPHILIA
- VON WILLEBRAND DISEASE

HEMOPHILIA



- A DEFECT IN THE THROMBIN PROPAGATION PHASE OF COAGULATION

HEMOPHILIA A OR B DIAGNOSIS

- BLEEDING TIME — Normal
- PT — Normal
- APTT — Prolonged
- FVIII:c or FIX:c
  - <1%=severe
  - 1-5%=moderate
  - 6-30%=mild
- vWF:Ag — Normal
- vWF:Rco — Normal

HEMOPHILIA

Bleeding as a function of clinical severity

Concentration of factor %

50-100: None

25-50: Bleeding after severe trauma

6-25: Severe bleeding after surgery
slight bleeding after minor trauma

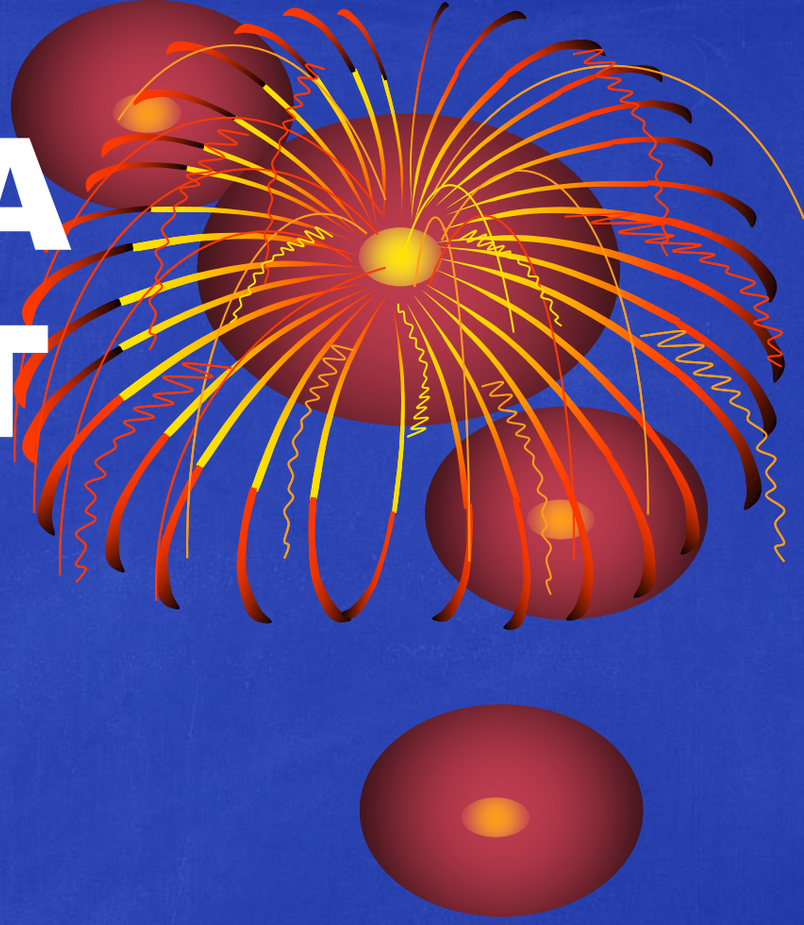
1-5: Severe bleeding after slight trauma

<1: Spontaneous bleeding mainly in joints or muscles

HEMOPHILIA: CLINICAL FEATURES

- Muco-cutaneous bleed
- Hemarthrosis
- Muscle bleeds
- Intra-cranial bleed
- Post-dental bleed
- Post-surgical bleed

HEMOPHILIA TREATMENT



- Factor replacement
- DDAVP
- Amicar

- All patients should be cared for life long in a bleeding disorder clinic

ACQUIRED HEMOPHILIA CHARACTERISTICS

- **AGE: MOST >50**
- **BLEEDING PATTERN: More severe soft tissue bleed; hemarthrosis less common**
- **INHIBITOR**
- **UNDERLYING DISORDER: usually none, but can be seen post partum, auto-immune disease, malignancy, drug reaction**

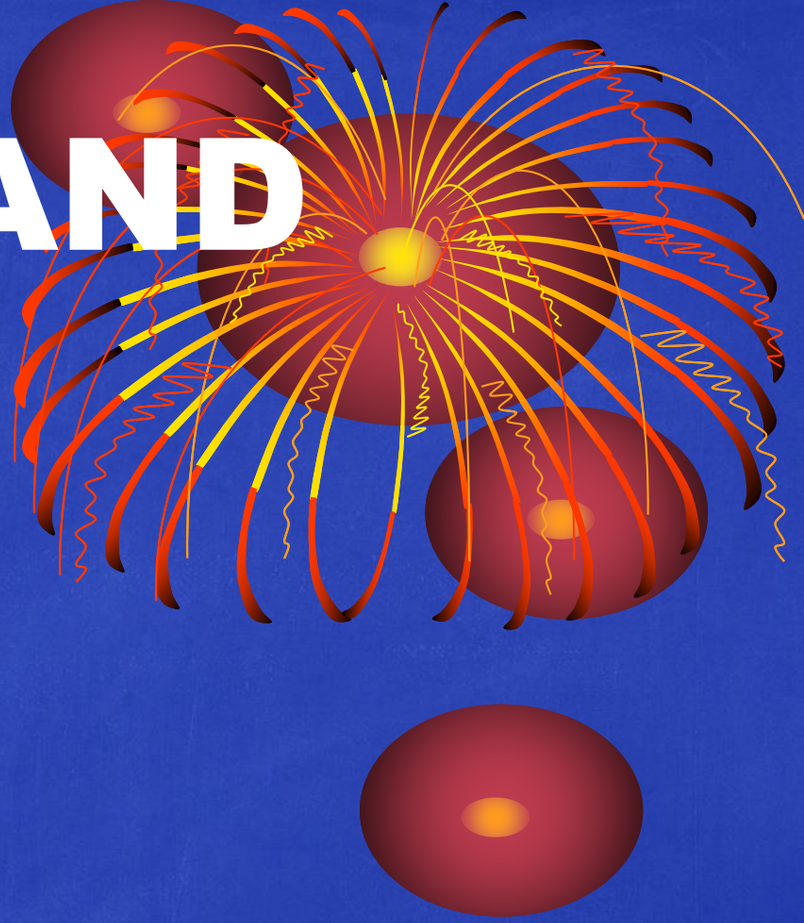
ACQUIRED HEMOPHILIA

- Major bleeding requiring transfusion: >75%
- Death due to bleeding: >15%
- Immediate Rx with appropriate activated factor products
- Long term: Attempt suppression of inhibitor

VON WILLEBRAND DISEASE

- Most common inherited bleeding disorder presenting with: mucocutaneous bleeds, nosebleeds, bleeding with dental work, heavy menses
- Family history of bleeding
- Decreased levels of VWF
- Autosomal Dominant
- Bleeding usually mild to moderate

VON WILLEBRAND DISEASE



- **DIAGNOSIS:**
  - **-FVIII activity**
  - **-VWF antigen**
  - **-Ristocetin Cofactor**
  - **-PFA**
  - **-RIPA**
  - **-VWF Multimers**

VWH CLASSIFICATION

- **Type 1: partial quantitative deficiency of VWF**
- **Type 2: qualitative defect in VWF**
- **Type 3: Total deficiency of VWF**

VWD CLASSIFICATION

TYPE	RIPA	MULTIMER PATTERN	VWF:RCo/Ag
1 Partial Quantitative	decreased or normal	uniform decrease but all present	1:1
Qualitative **2A** **2B**	 decreased increased	 decrease large multimers decrease large multimers	 decreased decreased
2M **2N**	decreased normal	uniform decrease, all present normal multimers	decreased 1:1
3 Severe deficiency	markedly decreased	Undetectable; usually cannot visualize	N/A

VWD: TREATMENT

- DDAVP
- Factor VIII concentrates that contain vWF
- Antifibrinolytics (Amicar, gelfoam w/thrombin)
- Severe types should be cared for lifelong at a bleeding disorder center

THROMBOSIS

PATHOLOGICAL BLOOD CLOTTING

no disclosures

HYPERCOAGUABLE STATES

- ACQUIRED:
  - Advancing age
  - Prior thrombosis
  - Immobilization
  - Major surgery
  - Malignancy
  - Estrogens
  - Pregnancy
  - Trauma
  - Paralysis
  - Malignancy
  - Antiphospholipid antibody syndrome
  - Myeloproliferative disorders
  - PNH
  - IBD
  - Nephrotic syndrome
  - HIT
  - Prolonged air travel
  - Central venous catheters
  - Obesity

HYPERCOAGUABLE STATES

- INHERITED

  Antithrombin III deficiency 20 fold RR

  Protein C deficiency 10 fold RR

  Protein S deficiency 10 fold RR

  Factor V leiden 3-8 fold RR

  Prothrombin gene mutation 3 fold RR

HYPERCOAGUABLE STATES: who to test

Strongly Thrombophylic Clinical History

- Age of onset <50
- Recurrent thrombosis
- Positive family h/o thrombosis, MI or CVA at young age
- Cerebral venous thrombosis
- Portal or mesenteric vein thrombosis (r/o MPD, PNH)

Consider: VTE associated with OCPs/HRT or pregnancy

Pregnancy loss in 2nd or 3rd trimester

HYPERCOAGUABLE STATES: who not to test

- Pts >/= 50 with first spontaneous VTE
- VTE in pts with active cancer
- Elderly pts, especially post-op VTE
- Retinal vein thrombosis
- Arterial thrombosis
- Women starting OTCs with no personal or family history of VTE

HYPERCOAGUABLE WORKUP

- Prothrombin gene mutation
- Factor V Leiden (Activated Protein C resistance)
- Antithrombin III
- Protein C activity
- Protein S assay, total & free
- Tests for antiphospholipid antibody syndrome:
- Lupus anticoagulant
- Anticardiolipin & B2-glycoprotein I antibodies

TREATMENT OF DVT/PE

- HEPARIN

  Unfractionated or LMW for 5 days
- WARFARIN

  Start day 1

  INR 2-3

  Treat 3-6 months

DIRECT ORAL ANTICOAGULANTS

- Dabigatran (Pradaxa)
- Rivaroxaban (Xarelto)
- Apixaban (Eliquis)
- KNOW YOUR DRUG

DOACs: When not to use

- Pregnancy associated VTE
- Cancer associated VTE
- Obese patients (>275 lbs)
- Very frail patients (<100 lbs)
- Renal dysfunction (cr cl <30; use with caution in cr cl 30-40)
- Patients on meds with major interactions
- Cautious with difficult patients (recurrent DVT/PE on anticoagulation
- Ensure patients comply and can acquire med

DURATION OF ANTICOAGULANT THERAPY

- First isolated, unprovoked distal DVT or proximal DVT/PE secondary to a transient risk factor: 3 months
- Second unprovoked DVT/PE: long-term
- VTE in setting of active cancer: LMWH at least 3 most vs long-term

DURATION OF ANTICOAGULANT THERAPY

SPECIAL SITUATIONS: Consider indefinite anticoagulation after first event in the following cases:

- Cancer-until resolved (consider LMWH)
- Antiphospholipid antibody syndrome
- Antithrombin III deficiency
- Protein C or S deficiencies
- Multiple genetic defects

DURATION OF ANTICOAGULATION

Criteria for long term oral anticoagulation :

- No resolution of triggering risk factor
- Sites and severity of thrombosis
- Identification of a prothrombotic defect
- Family thrombotic history
- Bleeding risk
- Patient preference (life style, occupation) with understanding of risks vs. benefits

THANK YOU!

- Questions? 248.210.7669

PORPHYRIA

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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: bullies dermatosis, scarring, hyper pigmentation, hypertrichosis

PORPHYRIA CLINICAL APPROACH

SUMMARY

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