Highs and Lows in Platelet Counts and Clots

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I have no relevant financial disclosures

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Learning Objectives

- Identify common causes of thrombocytosis and thrombocytopenia
- Identify phenotypes of bleeding diathesis and initial work-up
- Evaluate Patients with thrombotic events that need further evaluation

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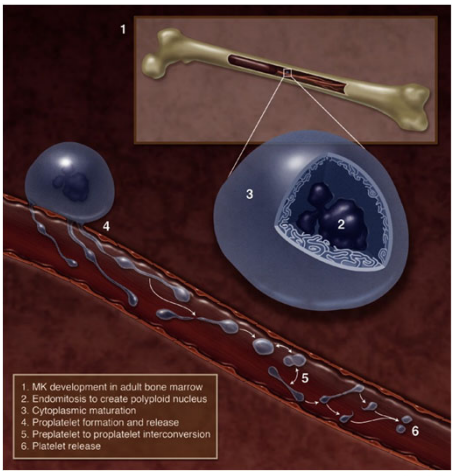
Our friend, the humble platelet

- Anuclear cell fragements 2-3 um in size
- Produced by megakaryocytes in the marrow in response to thrombopoetin (TPO) interacting with MPL (thrombopoetin receptor)
- Liver is primary site of TPO production.
- Formation takes 5 days
- Lifespan is ~9 days



Machleus, J Cell Bio, 2013

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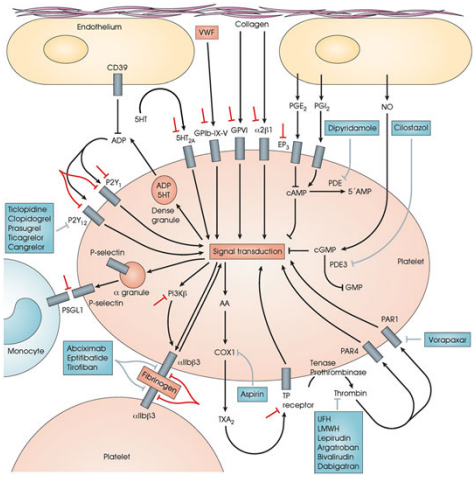

Externally, large network of glyoproteins and receptors

Peripheral zone with negative phospholipids and actin

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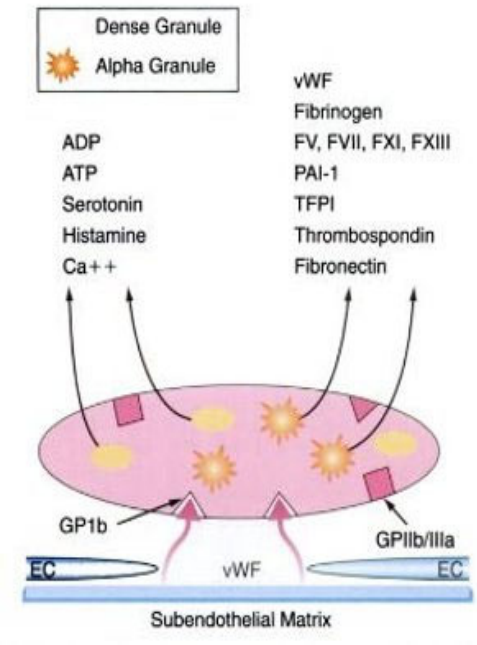

Epomedicine.com

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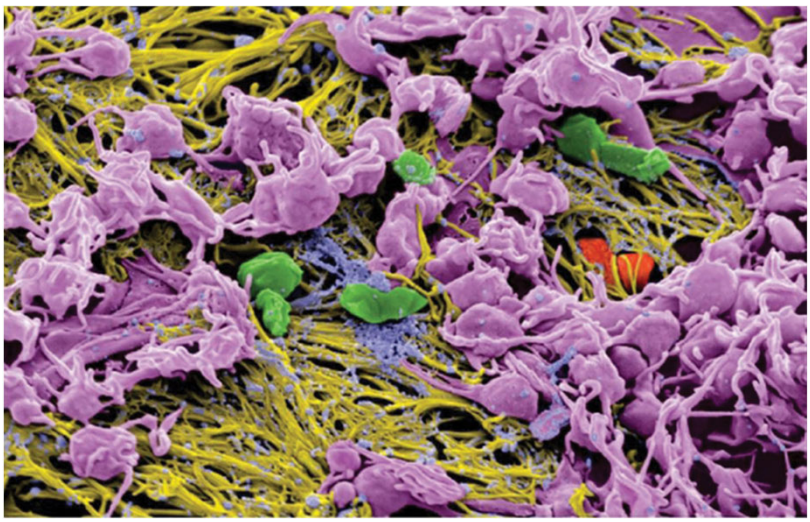

Platelets sit on fibrin strands

Gremmel, Semin
Thromb Hemost, 2016

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Patient 1

Patient is a 53 yo female with history of inflammatory bowel disease currently managed with sulfasalazine and diet recommended by The Internet who presents on routine f/u. She expresses fatigue, restless legs.

CBC is significant for WBC 9.6/uL with unremarkable differential, Hgb 12.2g/dl with MCV 84fL, and platelet count 620,000/mL.

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Thrombocytosis

- Generally considered > 450,000/mL
  - Extreme is > 1,000,000/mL
    Increases risk of thrombosis (and bleeding)
- Reactive
  - Inflammatory
  - Iron Deficiency
  - Splenectomy
- Clonal
  - Myleoproliferative Diseases

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Reactive Thrombocytosis

- By far, most common cause of thrombocytosis (88%)
  - Driven by increased interleukins, other cytokines in cases of stress
- Acute blood loss
- Inflammation
  - Autoimmune disease
  - Infection
- Exercise

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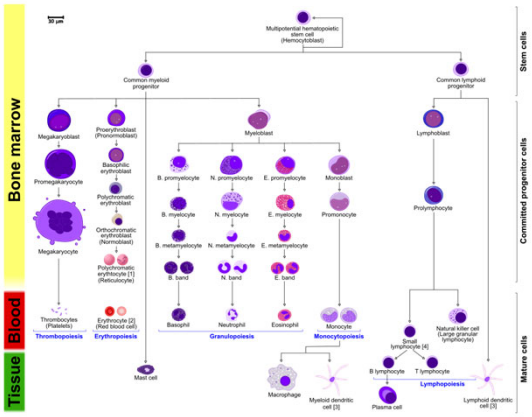
Iron Deficiency

Megakaryocytes and erythroblasts both share common precoursor myeloblast

Low iron detected by transferrin receptor-2, slowes proliferation, and bends towards megakaryocyte formation



Ferrucio, Blood, 2019

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Splenectomy

Can be surgial or function (sickle cell disease, immune dysregulation suchs as advanced AIDS or SLE)

Usually transient if surgical

Spleen "red pulp" has mutiple bapillary sinuses with macrophages that acts as a phagocytic filter.

Splenectomy decreases platelet clearance

Buzele, J of Vis Surg, 2016

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Reasonable to

- Recheck platelet count after acute illness
- Inflammatory markers
- Iron studies

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Clonal - MPN

- Pathologic activating marrow proliferative process
- Includes Essential Thrombocytosis, Polycythemia Vera, or prefibrotic Myelofibrosis, as well as MDS 5q-
- Markedly higher risk of large vessel thrombosis, as well as small vessel ischemia
- Splenomegaly is common, as is aVWD
- Suspect mutations include JAK2, CALR, and MPL
- Bone Marrow biopsy required to distinguish MPN type.
- Management based on risk factors, such as age, thrombosis history, mutation.

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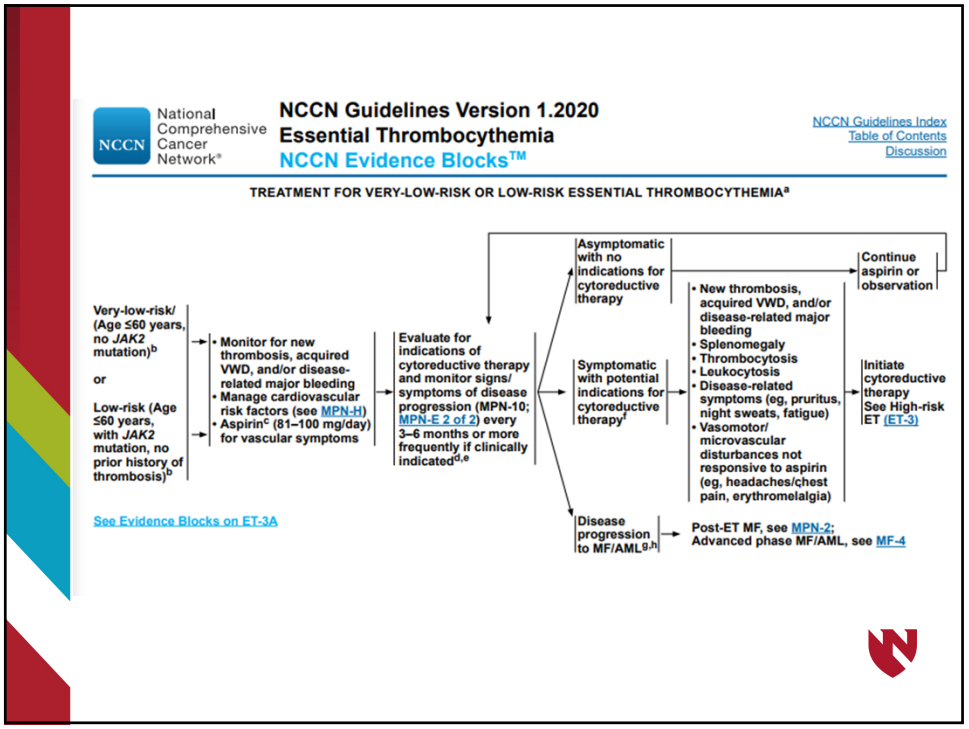

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Thrombocytopenia

Mild	< 150,000
Moderate	< 100,000
Severe	< 50,000
Symptomatic	< 20,000 – 30,000
Emergency	< 10,000

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Benign / Outpatient

- Pseudothrombocytopenia – Excessive platelet clumping causing light scatter suggestive of WBC. Use citrate.
- Liver disease
- Splenomegaly
- Infection
- HELLP / Preeclampsia / pregnancy
- Nutritional (Vit B12 / Copper / Folate)
- Artificial surfaces / shear
  - LVADs, Valves

- If these are stable, chronic, and mild, watching is appropriate.

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ITP

Immune/Idiopathic Thrombocytopenic Purpura

- Immune, peripheral destruction of circulating platelets
- May have antiplatelet Ab, or diagnosis of exclusion
- May be idiopathic or secondary
  - Drug induced
  - SLE / Antiphospholipid Antibodies
  - Hep C / HIV
  - H. Pylori
- NOT responsive to platelet transfusion
- May be severe (<10 is common acutely) or chronic and mild to moderate

- Treatments include steroids, TPO agonists, Rituximab, splenectomy.

ASH Guidelines, 2019

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Inpatient

Microangiopathic – assocaited with schistocytes

- DIC
- HUS
- TTP
- HIV-associated

- HIT
- ICU associated

Generally, will be multisystemic and ill

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Bleeding

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Patient 2

Ms. G is a 24 year old female presenting for annual follow-up. She has a history of heavy menstrual bleeding, improved on PO Iron and oral estrogen contraception, using IBP as needed for cramping. Also with history of depression, improved on fluoxetine. She reports that her coworkers (server) have noted increased bruising on her forearms.

CBC shows an unremarkable platelet count. PT / PTT are within normal range.

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Bleeding Types

- Injury/Surgery Related – Mild defects
- Mucocutaneous – Platelet Dysfunction
  - Petechae
  - Epistaxis, gingival bleeding
  - Menses
- Deep Tissues – Coagulation defects
  - Intraarticular
  - Intramuscular
- Delayed – Fibrinogen defects / Factor XIII

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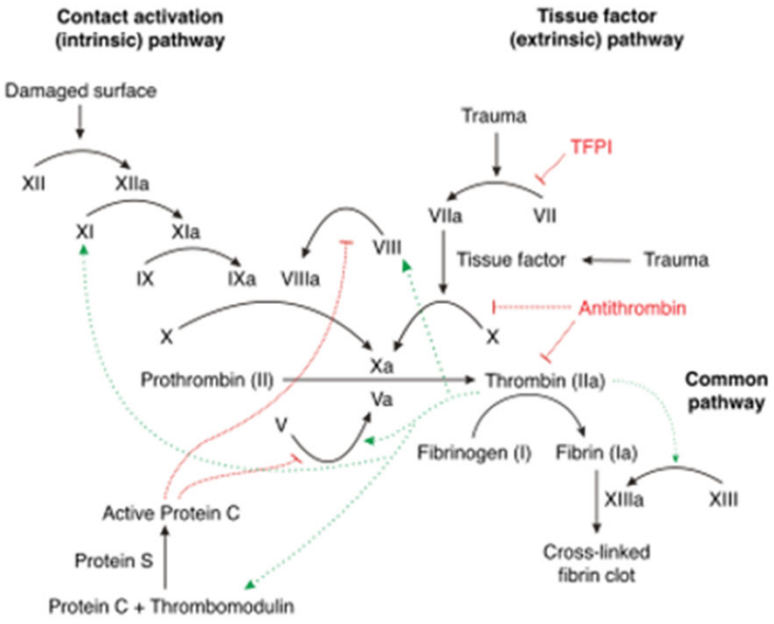

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ISTH

https://bleedingscore.certe.nl/

- Epistaxis- > 10min, < 5/year
- Cutaneous- 5 or more, petechaie, without trauma
- Cuts - > 10min, >1 bandaid
- Oral cavity- > 10min
- GI bleeding (not hemorroids)
- Hematuria
- Tooth Extraction
- Surgical bleeding per surgeon
- Menorrhagia – disruptive, q2hr, >7days
- Port-partum - > 6 weeks
- Muscle/joint outside of trauma
- CNS bleeding
- Other

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ISTH Bleeding Assessment

- Normal range is <4 in adult males, <6 in adult females and <3 in children
- Give a point back if tolerated 2x "challenges"

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Work-up

- CBC including platelet count, consider peripheral smear / platelet mean volume (small, large, dysmorphic platelets)
- PT/PTT
  - Prothrombin --> addition of tissue factor and Ca2+ to plasma
  - Active Partial Thromboplastin Time --> silica + Ca2+
- Consider von Willebrand's screen
  - Von Willebrand antigen
  - Von Willebrand R:Co
    - Ristocetin causes vWF platelet binding
  - Factor VIII level

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Hemophilia A

Inherited (66%) X-linked deficiency of Factor VIII
- Normal platelet function, normal PT, prolonged PTT
- You may diagnose these. 1/5000
- Carriers may have mild symptoms!

Mild – Factor level 6-30% -- generally no/few spontaneous bleeds, however may have excessive bleeding with procedures.
- Treatment may include DDAVP (intra nasal vs IV) if factor level corrects on trial. Can develop tachyphylaxis.

Moderate – Factor level 1-5% -- Postoperative/traumatic bleeding. Rare spontaneous bleeds
- Trial DDAVP for minor procedures, however generally require Factor VIII with procedures or significant spontaneous bleeds. Intermittent PPX

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Severe Hemophilia A

Factor levels generally =< 1%
Generally diagnosed perinatally with bleeding with heel pricks, circ, bruising with birth.
Frequent intraarticular bleeds, deep tissue bleeds, intracranial bleeds
- Often target joints with > 4 bleeds per 6 mo

Generational / Socioeconomic differences in outcomes after monoclonal purified / recombinant and ppx studies on QoL, joint changes
- Joint damage is still slowly progressive
- Hyaluronic acid, steroid injections, radionuclide/surgical synovectomy
- Joint replacement, may need revision given patient age

Prophylaxis should be considered standard of care with goal ABR < 3

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Treatment

Recombinant Factor VIII

- Each IU/kg infused raises Factor VIII level by 2%
- Half-life is ~8-12 hours
- Activity with Factor VIII

Now with extended life products

Product	Approval year	FVIII protein	Cell line	Mean half-life, hours	Comparator mean half-life (product)	Prophylaxis regimen
Kogenate® FS[26]	1993	Full length	BHK	13.7	–	25 IU/kg 3× per week
Helixate® FS[27]	1993	Full length	BHK	13.7	–	25 IU/kg 3× per week
Advate®[28]	2003	Full length	CHO	12.0	–	20–40 IU/kg every other day or every 3 days to maintain trough >1%
Moroctocog alfa (Xyntha®)[29]	2008	B-domain deleted	CHO	11.2	13.3 (Advate®)	30 IU/kg 3× per week
Turoctocog alfa (NovoEight®)[19–21]	2013	B-domain truncated	CHO	10.8	11 (Advate®)	20–50 IU/kg 3× per week or 20–40 IU/kg every other day
Simoctocog alfa (Nuwiq®)[32,33,35]	2015	Full length	HEK	17.1*	Bioequivalent (Kogenate® FS)	30–40 IU/kg every other day
Octocog alfa (Kovaltry®)[22–25]	2016	Full length	BHK	13.4	12.2 (Kogenate® FS)	20–40 IU/kg 2–3× per week
rVIII-single chain (Afstyla®)[37–39]	2016	B-domain and four amino-acids of a3 domain deleted	CHO	14.5	13.3 (Advate®)	20–50 IU/kg 2–3× per week

BHK: baby hamster kidney; CHO: Chinese hamster ovary; FS: sucrose-formulated; HEK: human embryonic kidney; IU: international unit.
*Median, lower/upper quartile: 13.7, 12.0/17.5.

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Hemophilia B

Similarly X-linked condition, however Factor IX affected, 1/30,000

Similarly mild (<30%) / mod (1-5%) / severe (<1%)

Treated with Factor IX (AlphaNine, BeneFIX, Ixinity)

-- Not DDAVP

- Longer half life 18-24 hours
- Factor XI dose rises 0.8-1% per UI/kg depending on product

Long acting agents may be dosed q7-10days ppx, q48h acute

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Hemophilia with inhibitor

Seen in 30% of hemophilia A severe patients, 5% in mild/mod, 3% Hemo B

Generally develops in childhood with Anti-FVIII (XI) inhib, decreased responsiveness to exogenous FVIII

- Phenotypically more morbid

Measured with Bethesda Units

Immune Tolerance Induction

- - If BU < 5, consider high dose of Factor (50IU/kg thrice weekly)
- - If BU 5-10, (consider 200UI/kg daily)

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Bypass agents

FEIBA – bypassing prothrombin complex (Factors II, IX, X, some FVII)

- Indicated in hemophilia A with inhibitor ppx or on demand
  - Also indicated for hemophilia with inhib B however NOT IDEAL as contains IX and may worsen inhib
    - Based on *clinical response* as no lab correlation to dosing.
    - Risk of thrombosis (arterial and venous) with higher doses

aFVII (NovoSeven) -- Activated Factor VII – for Hemo A/B with inhibitors

- Very short half-life, dosed 90mcg/kg q2hrs acutely, then 4-6 hours when stable.
- Not indicated for ppx

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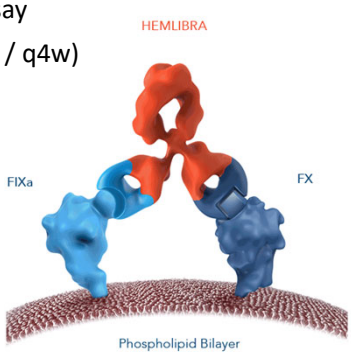
Emicizumab

- Bivalent antibody binding FIX + FX
- Initially used in F8 with inhibitor patients, now indicated in severe hemophilia A without inhibitor
- Activity cannot be assessed with FVIII assay
- Weekly 1.5mg/kg SQ dosing (can be q2w / q4w)



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Other factor Deficiencies

"Hemophilia C" Factor XI – AR with Factor XI < 15%, can be seen in some heterozygous. More common in AJ (8%?)

- Associated with increased fibrinolysis due to decreased thrombin-activatable fibrinolysis inhibitor

Bleeding type generally delayed after surgery/trauma
aPTT long, PT normal

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Other factors

Factor VII deficiency - AR, may be qualitative or quantitative

- Can be associated with other Vit K dependent proteins

Moderate (>5% activity) have mucocutaneous phenotype, severe (<1%) more like severe hemophilia

Prolonged PT, normal PTT

aFVII is commercially available (need a lower dose ~35UI/kg)

TXA also an option

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Factor X def – Stuart-Prower factor

- Rare, 1/500,000. AR.
- Similar phenotype to FVII def, however more Ob/gyn bleeding than in FVII def.
- Treated with plasma concentrated Factor X (Coagadex)

Factor XIII (fibrin stabilizing factor)

- Rarest 1/5mil. AR
- Delayed bleeding, umbilical cord bleeding, Ob/Gyn bleeding, miscarriages
- PT/PTT/fibrinog will be normal!

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Von Willebrand Disease

- The most common inherited bleeding disorder (0.6-1.3%)
- vWF needed for platelet adhesion with binding to collagen (vWF:CB) and platelet agglutination (vWF:RCo) as well as shepherd FVIII
- Blood group O lower levels

Table 1. Classification of von Willebrand Disease

Type	Description
1	Partial quantitative deficiency of VWF
2	Qualitative VWF defects
2A	Decreased VWF-dependent platelet adhesion with deficiency of HMW multimers
2B	Increased affinity for platelet GPIbα
2M	Decreased VWF-dependent platelet adhesion with a normal multimer distribution
2N	Decreased VWF binding affinity for FVIII
3	Virtually complete deficiency of VWF

FVIII, factor VIII; HMW, high-molecular-weight; VWF, von Willebrand factor.

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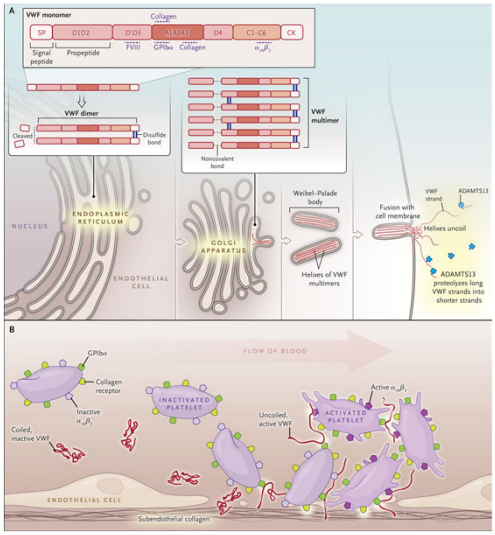

vWF found in endothelial cells, initially processed as monomers, however then form coiled-multimers that expand upon release from WP bodies, then either bind to collagen and platelets or are nom nom nomed by ADAMTS13

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Type 1

Auto Dom inheritance
Up to 70% of patients, symptoms generally mild mucocutaneous
Qualitative defect
Responds to DDAVP
Generally levels of FVIII and RCo increase during pregnancy.
Diagnostically,
FVIII mildly low, vWF antigen low, RCo activity low, ristocetin platelet function decreased or normal, normal multimers

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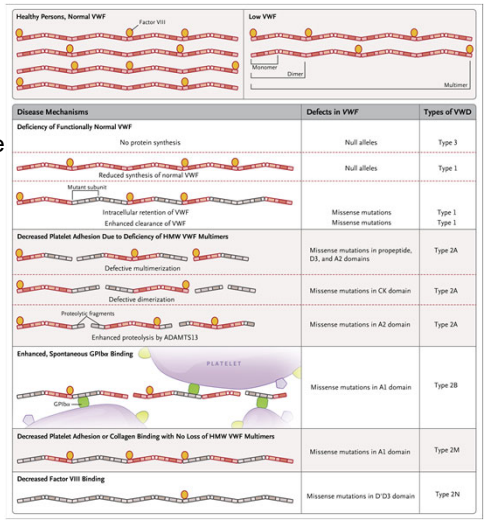
Type 2 - Defects

Type 2 A – Auto dom defect in multimerization

Type 2B – gain of function Increased GP1b binding so less free large multimers and plt consumtion, esp with stress.

Type 2M (Milwalkee) - loss of platelet binding.

Type 2N (Normandy) -- Loss of factor VIII binding.



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Type 3

It's just gone, man.
Rare, 1/1,000,000
Presents as severe hemophilia
Low factor VIII, absent vWF ag, RCa, RIPA, absent multimers.

Acquired von Willebrand's disease – Thrombocytosis > 1,000,000, cardiac bypass or LVAD, B-cell malignancy, drug induced (valproic acid). Labs similar to T1 / T3

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Treatment:

Type 1, type 2M (loss of plt binding) may respond to DDAVP. Can be intranasal in PRN, however surgical planning may need IV.
Consider intranasal estrogen for epistaxis, TXA
Type 2 A/B/N, Type 3 likely require FactorVIII-vWF concentrate "Humate-P"

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Acquired Factor Inhibitors

Classically Factor VIII

- Older adults, pregnant women, history of autoimmune disease
- Treatment depends on bleeding
  - Severe with BU <5 = high dose Factor VIII (ie 40UI/kg + (20UI/kg/BU)
  - Severe with BU >5 = FEIBA / aFVII
  - Not bleeding – Prednisone vs Cyclophosphamide
    - May resolve in a year

Prothrombin – Seen in APA with bleeding, treated with FFP

- Variable PT/PTT, needs prothrombin quant assay

Factor V – exposure to fibrin glue, may have significant bleeding

- Prolonged PT/PTT, normal thrombin time
- Tx with platelet transfusion, PLEX, IVIg, immunosuppressent

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Drugs

NSAIDs, ASA, P2Y12 inhibitors
SSRIs, Garlic
Vitamin K Inhibitor / Warfarin
Direct Oral Anticoagulants

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Now let's do some clots!

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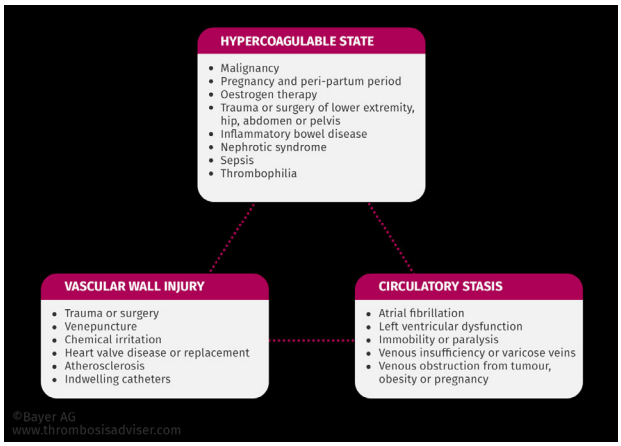

Thrombosis – Nester's Triad

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TABLE 1. Risk Factors Observed in 1231 Consecutive Patients Treated for Acute DVT and/or PE

Risk Factor	Patients (%)
Age ≥40 years	88.5
Obesity	37.8
History of venous thromboembolism	26.0
Cancer	22.3
Bed rest ≥5 days	12.0
Major surgery	11.2
Congestive heart failure	8.2
Varicose veins	5.8
Fracture (hip or leg)	3.7
Estrogen treatment	2.0
Stroke	1.8
Multiple trauma	1.1
Childbirth	1.1
Myocardial infarction	0.7
1 or more risks	96.3
2 or more risks	76.0
3 or more risks	39.0

cluded, in a recent review, that laparoscopic cholecystectomy is a low-risk procedure such that routine VTE prophylaxis is probably not justified.[19] But the decision regarding prophylaxis for laparoscopy should likely be made in the same manner as for conventional surgery, ie, customized for the

TABLE 2. Risk Factors for VTE

- Strong risk factors (odds ratio >10)
  - Fracture (hip or leg)
  - Hip or knee replacement
  - Major general surgery
  - Major trauma
  - Spinal cord injury
- Moderate risk factors (odds ratio 2–9)
  - Arthroscopic knee surgery
  - Central venous lines
  - Chemotherapy
  - Congestive heart or respiratory failure
  - Hormone replacement therapy
  - Malignancy
  - Oral contraceptive therapy
  - Paralytic stroke
  - Pregnancy/, postpartum
  - Previous venous thromboembolism
  - Thrombophilia
- Weak risk factors (odds ratio <2)
  - Bed rest >3 days
  - Immobility due to sitting (e.g. prolonged car or air travel)
  - Increasing age
  - Laparoscopic surgery (e.g. cholecystectomy)
  - Obesity
  - Pregnancy/, antepartum
  - Varicose veins

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Who needs indefinite?

No patients with first or recurrent VTE with strong temporary risk factors

- This may include patients with weak ongoing risk factors (including heterozygous thrombophilias)

Consider indefinite anticoagulation in 1st unprovoked if:

- Male (30-50% 10-year risk of recurrence)
- Older female (30% 10 year risk of recurrence)
- Obese
- Well tolerated and/or anxious
- Post thrombotic syndrome or pulmonary hypertension
- Positive D-dimer after holding anticoagulation 1 month
  - Risk models include Vienna, DASH, HERDOO, all of which use D-dimer

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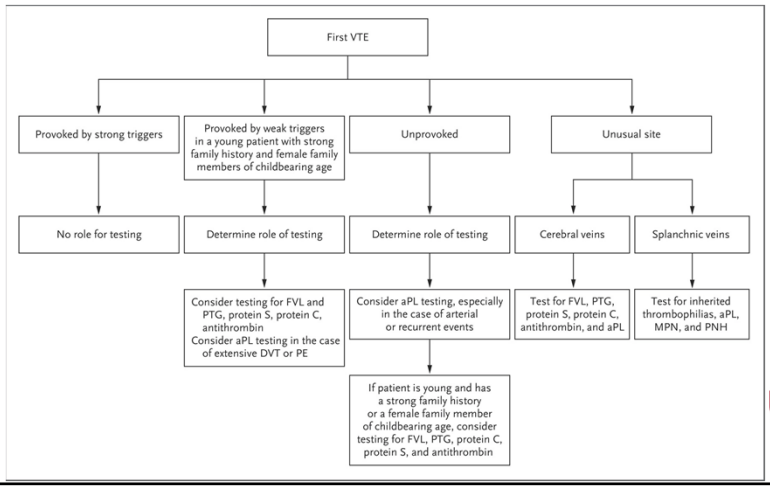
Who do we need to test?



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High risk thrombophilias (rare)

- Antithrombin deficiency - 1.8 % per year (95% CI 1.1-2.6%)
- Protein C deficiency - 1.5% per year (1.1-2.1%)
- Protein S deficiency - 1.9% per year (1.3-2.6%)

Moderate risk thrombophilia (common)

- Factor V Leiden - 0.5% per year (0.4-0.6%)
- Prothrombin gene mutation - 0.3% per year (0.2-0.5%)

Thrombophilias

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Acquired Thrombophilias

- Antiphospholipid Antibodies
  - Must be repeated 12 weeks later
  - Warfarin Preferred
- MPNs (esp JAK2+)
- Paroxysmal Nocturnal Hemoglobinuria
  - Clonal hemolytic anemia / marrow syndrome

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AGE APPROPRIATE CANCER SCREENING

SHOULD BE COMPLETED IN ALL PATIENTS WITH UNPROVOKED THROMBOSIS

EXTENSIVE TESTING (HEAD TO GROIN CT / BLIND TUMOR MARKERS) ARE NOT COST EFFECTIVE, BUT THROMBOSIS WITH ADDITIONAL SYMPTOMS MAY BE MORE AGGRESSIVELY INVESTIGATED

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Open for Questions

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