Hemostasis

Tx of Thrombophilia

- Clot w/ Transient RFs: AC w/ INR 2-3 x3mo
- Clot w/ No Clear RFs: AC w/ INR 2-3 x6mo
- Clot w/ Fixed RFs, Recurrent, Life-Threatening: AC w/ INR 2-3 forever
- NB malignancy related thrombophilia is resistant to Coumadin hence use heparin products
- NB even after a pt completes recommended AC period above some continue AC but to a lower INR like 1.5-2
- NB consider IVC filter in not only those with AC contraindications but also those with recurrent DVT-PE

<table>
<tr><th></th><th colspan="2">Primary Hemostasis (immediate but temporary during first 12-24hrs)</th><th>Secondary Hemostasis (slow after 12-24hrs but durable)</th></tr>
<tr><td></td><td>Vessel
(vasoconstriction)</td><td>Platelet (clot)
Adhesion: GP Ib-IX-V on plts bind vWF and collagen in exposed endothelium forming a plt plug
Activation: Plts release ADP (inhibited by Plavix) and TXA2 (inhibited by Aspirin) which activate other plts (this process is inhibited by PGI2 & NO)
Aggregation: GP IIb-IIIa on plts crosslink w/ other GP IIb/IIIa on plts via fibrinogen (inhibited by Integrillin)</td><td>Coagulation (thrombus)
Intrinsic Pathway (12,11,9,8) w/ 12 activated by exposed endothelium = Activated Partial Thromboplastin Time (aPTT)
Extrinsic Pathway (3,7) w/ 3 released from injured cells = Prothrombin Time (PT) & International Normalizing Ration (INR)
Common Pathway (10/5,2,1) = Thrombin Time (TT)
12 (Hageman Factor)
↓
11
↓
9 3
↓ ↓
8 7
↓
10/5
↓
2 (Thrombin)
↓
1 (Fibrin aka Thrombus) w/ 13
↓
FSP/DD
All factors are made by liver
13 helps fibrin cross-link
Inhibitors
Antithrombin III (inhibits 12/11/9/10)
Protein S/C (inhibits 8/5)
Plasmin (breaks down 1)</td></tr>
<tr><td>Site</td><td colspan="2">Small Vessels</td><td>Large Vessels</td></tr>
<tr><td>Skin</td><td colspan="2">Petechiae (<2mm) vs Ecchymosis (2-10mm) vs Purpura (>10mm)
Entire Body
Non-Blanching Palpable
Dependent Parts of Body
Non-Blanching Non-Palpable</td><td>Hematoma
(unlike those to the left these change colors as heme is broken down)</td></tr>
<tr><td>Other Systems</td><td colspan="2"><u>Superficial Skin/Mucosa</u>
Epistaxis, Hemoptysis
GIB, Gingival Bleeding
Menometrorrhagia
GUB</td><td><u>Deep Tissue</u>
Intracranial Bleed
Hemarthrosis esp knee resulting in Arthropathy/Contractions
Intramuscular Bleed
Retroperitoneal Bleed</td></tr>
<tr><td>Bleeding</td><td colspan="2">Immediate after minor cuts</td><td>Delayed/Oozing after major cuts</td></tr>
<tr><td>Labs</td><td>None</td><td>1st Platelet Number & Smear
2nd Platelet Function Assay (PFA-100) which evaluates aggregation in presence of collagen and ADP
NB Bleeding Time (BT) (can increase w/ Quant/Qualit Plt, vWF, Capillary Wall problems, rarely done anymore)</td><td>1st: PT/aPTT
2nd: Fibrinogen/D-Dimer/FSP
3rd: Mixing Studies (used to determine if prolonged PT/aPTT is 2/2 factor deficiency or inhibitor, pt's plasma is mixed 1:1 w/ normal pooled plasma, if a factor deficiency then the deficient factor is restored to 50% which is enough to near normalize PT/aPTT, if an inhibitor is present then PT/aPTT will not normalize), Specific Factor Level, Specific Factor Activity (pt's plasma is mixed 1:1 w/ plasma completely deficient in the factor of interest, the difference in PT/aPTT tells how inactive the pt's plasma is)</td></tr>
</table>

Meds	Mechanical (refer to DVT-PE)	Antiplatelets **COX Inhibitors** • Aspirin (Aspirin) prevents platelet aggregation and activation by irreversibly inhibits cyclooxygenous (both COX-1 and 2) from converting arachidonic acids to prostaglandins particularly TXA_2 (pro-platelet) and unfortunately PGI_2 (anti-platelet) however TXA_2 inhibition > PGI_2 inhibition b/c PGI_2 is made by endothelial cells which have nuclei and thus are able to make more COX enzyme unlike TXA_2 which is made by platelets which lack nuclei and thus are unable to make more COX enzyme • dipyridamole (Persantine) similar to aspirin but decreases TXA2 by increasing cAMP not by enzyme inhibition • NB aspirin+dipyridamole (Aggrenox) • SEs: CNS (tinnitus), renal (resp alkalosis and metabolic acidosis), GI (ulcers), other (Reye's Syndrome) • NB other NSAIDs bind REVERSIBLY to COX therefore the effect is temporary and mild at best **ADP Inhibitors** • clopidrogrel (Plavix) prevents platelet activation and aggregation by irreversibly blocking ADP from binding receptors on platelets and irreversibly blocking fibrinogen from joining GPIIb/IIIa on different platelets • SEs: inhibits cytochrome P450 interfering w/ metabolism of many drugs (only w/ clopidogrel) • NB ticlopidine (Ticlid) no longer used b/c of r/o neutropenia and TTP **GPIIb/IIIa Inhibitors** • abciximab (Reopro), tirofiban (Aggrostat), eptifibatide (Integrillin) prevents platelet aggregation by blocking fibrinogen from joining GPIIb/IIIa on different platelets • Use: anti-platelet effect in ACS during PTCA • SEs: thrombocytopenia	Anticoagulants **warfarin (Coumadin)** • Mechanism: interferes w/ vitK carboxylation of glutamic acid residues of C,S,2,7,9,10 • NB both aPTT and PT/INR are elevated but PT is more sensitive • SEs: Skin (hemorrhagic bullae on breast, thighs, buttocks leading to skin necrosis when pt has Protein C/S deficiency), Ob (teratogenic), Other (many drug-drug interactions) **Heparins** (activates antithrombin III, fractionated so that only LMW molecules which have better anti-coagulations properties b/c more specific for Xa, less frequent dosing, more predictable effect hence you do not have to follow PTT, less SEs of HIT) • **Unfractionated Heparin (UFH)** • **Low Molecular Weight Heparin (LMWH):** enoxaparin (Lovenox), dalteparin (Fragmin), tinzaparin (Innohep) • **Factor Xa Inhibitor**: fondaparinux (Arixtra) IV, rivaroxaban (Xarelto) PO (new agent) **Direct Thrombin Inhibitor (DTI)** • argatroban (Argatroban) hepatically cleared • lepirudin (Refludan) renally cleared • bivalirubin (Angiomax) NB only used in PCI • dabigatran (Pradaxa) PO (new agent but increased r/o dyspepsia b/c it is prepared using acid) **tPA (activates plasmin)**
Hypo Hemostatic State	Vessel Damage (refer to Rheum notes)	Platelet Dysfunction <u>Qualitative Problems</u> Inherited • Von Willebrand Disease (AD/X) • Bernard-Soulier Syndrome (AR mutation of GP Ib-IX-V resulting in inability to bind vWF on exposed endothelium) = Giant Platelets • Glanzmann's Thrombasthenia (AR mutation of GP IIb-IIIa resulting in inability to bind crosslink with other plts via fibrinogen) Acquired • Multiple Myeloma (paraprotein coats	Hypocoagulable Elevated PT Nl aPTT: Heparin, Factor Deficiency/Inhibitors Elevated aPTT Nl PT: Factor Deficiency/Inhibitors Elevated PT/aPTT: Coumadin • **Classic Hemophilia A**: X-linked mutation of Factor 8, 1:5,000 male births, 40% have no +FHx suggesting high rate of germline mutations, Severe <1% vs Mod 1-5% vs Mild 5-30% activity, Tx: if mild bleeding/dz then SC DDAVP w/ goal Factor 8 activity of 40% vs if severe bleeding/dz then IV Factor 8 replacement w/ goal Factor 8 activity of 75%, NB ~15% of pts develop antibodies to the factor such that it is no longer effective hence the use of recombinant factors • **Christmas Hemophilia B**: X-linked mutation of

		platelets inhibiting their function) • Uremia 2/2 increased nitric oxide which inhibits plts, there is evidence that DDAVP and estrogens are helpful • Drugs (COX/ADP/GPIIb-IIIA Inhibitors, 4th generation penicillins aka Zosyn, etc) • Herbals (omega-3-FAs, garlic, onion, ginger, gingko, ginseng, etc) <u>Quantitative Problems</u> General • 150-100k No Risk at all • 100-50k Risk w/ Major Trauma or Major Surgery • 50-10k Risk w/ Minor Trauma or Minor Surgery/Procedures • <10k Risk of Spontaneous Bleeding • NB if a pts platelets have dropped considerably but still fall WNL (eg. 400k to 200k) still investigate Approach • r/o Psuedothrombocytopenia (0.1% of pts have antibodies to GPIIb/IIIa, the glycoprotein becomes exposed when platelets are exposed to EDTA, therefore when blood is drawn into EDTA tubes (lavender) there is agglutination and the platelets clumps look like leukocytes are counted as such (NB on the smear these platelets agglutinate around neutrophils aka satellitism, therefore recheck platelets in non-EDTA but still properly anticoagulated tubes like sodium citrate or heparin tubes or recheck freshly-shed non-anticoagulated blood) • Check CBC to determine if isolated thrombocytopenia (suggests increased destruction or other) vs multilineage involvement (suggests decreased production) get old records to see if acute or chronic • BM Bx (If increased destructive causes are ruled out and ITP is not likely b/c pt is older and thus you suspect decreased production then proceed with BM Bx) **Production Problem** (consider in pts given a dx of "ITP" but they have FHx and don't respond to ITP Tx) • **Alport's Syndrome** • **Fetchner's Syndrome** • **Epstein Syndrome** • **Sebastian Syndrome** • **May-Hegglin Anomaly** • **Wiskott-Aldrich Syndrome** • **Congenital Amegakaryocytic Thrombocytopenia** • **Thrombocytopenia with Absent Radius Syndrome** • **Amegakaryocytopenia with Radial-Ulnar Synostosis** **Increased Destruction**	Factor 9, just like A except less common (1/10 as common) and DDAVP does not work • **von Willibrand Dz** (refer) • **dys/hypofibrinogenemia** (dys = inherited excess of carbohydrate moieties, hypo = decreased amounts 2/2 liver disease or consumption, Dx: increased TT or Reptilase Time, Tx: cryo) • **Acquired Inhibition** (can be de novo against a specific factor aka auto-antibodies OR seen in hemophiliacs who have received factor replacement aka allo-antibodies, post-partum pts, pts w/ lymphoproliferative disorders, etc most commonly Factor 8, suggested by abrupt bleeding that does not correct after mixing, Tx: immunosuppressants) • **DIC** (refer) • **Primary Fibrinolysis** (2/2 prostate cancer or surgery, Mech: increased release of plasmin) • **Other Factor Deficiency** (aside from 8,9 others are very rare, 11, 10 (can be acquired w/ amyloidosis), 12, 13 (completely normal labs!!!)) • **Vit K Deficiency** (2/2 (1) poor intake of green leafy vegetables or use of TPN, (2) abx associated loss of enteric bacteria, (3) malabsorption, (4) poor storage 2/2 liver dz, (5) impaired fxn (not only coumadin but also cephalosporins), Dx: corrects after 1:1 mix w/ normal plasma, Tx: PO (best), SC (variable absorption), IV (r/o anaphylaxis) vitK) • **Liver Disease** ((1) deficiency of all coag factors, only clinical important when there is acute liver failure, Tx w/ FFP , (2) cholestasis interfering w/ vitK absorption, (3) hyperfibrinolysis, Tx w/ Cryo) NB follow PT not aPTT b/c it is more sensitive • **Meds** (above) • NB there are 3 diseases that have normal labs: certain vWD, Factor 13 deficiency, hyperfibrinolysis

		• **Immune/Idiopathic Thrombocytopenic Purpura (ITP)** • **Infections: HIV, HSV, EBV, HCV, CMV** • **Rheum: SLE, Antiphospholipid Syndrome, Sarcoid** • **Cancer: CLL, Lymphoma** • **Alloimmune: posttransfusion purpura** (1-2wks post-transfusion), **posttransplantation** • **Drugs: Quinine** (first documented), **Heparin** (most common), **GPIIa/IIIB Inhibitors** (most prominent newer member b/c occurs much faster and much more severe), **Sulfas, Vanc, Zyvox, AEDs, Tylenol, HCTZ, THE LIST IS RAPIDLY EXPANDING**, Usually ~1wk of exposure is needed to sensitize the patient (the big exception is abciximab which takes <24hrs), No specific tx other than discontinuing the drug but if acutely ill then consider steroids, platelet transfusions, IVIG, plasma exchange • **Infections: Ehrlichiosis, Babesiosis, RMSF** • **Vessel: Sepsis to DIC, HUS, TTP, vasculitis, any type of vessel damage, cavernous hemangioma** • **Obstetric Complications: gestational/isolated/incidental** (common (5-10%), mild (70-150k), asymptomatic to mother, neonate unaffected, occurring at during 3rd trimester, resolving following delivery, no other problems, pts might also have ITP where the thrombocytopenia is more severe and occurs earlier on like 1st trimester) vs **preeclampsia, eclampsia, HELLP** • **Blood that passes artificial surfaces: extracorporal cardiopulmonary bypass, CVVHD, IABP, Mechanical Valve** • **Splenic Sequestration from Hypersplenism:** splenomegaly 2/2 portal HTN, infiltrative process, Felty's Syndrome	
Hyper Hemostatic State • S/S: arterial or multiple / recurrent venous thrombi at a young age (<50yo) and at unusual locations (abdominal vessels = mesentery, renal vein, etc & CNS vessels = cavernous sinus, dural sinus etc), h/o pregnancy		Platelet Hyperfunction **Primary** • Malignancy (ET) **Secondary/Reactive** (usually don't have the other unusual symptoms noted in ET) • Transient (Acute Blood Loss, Rebound from Thrombocytopenia, Acute Infection, Acute Inflammation, Post-Op, Intense Exercise, etc) • Sustained (IDA, Asplenia, Malignancy, Chronic Infection, Chronic Inflammation, Drug Reaction, etc) • NB one of the APRs is thrombopoeitin hence any inflammatory state	Hypercoagulable aka Thrombophilia • **Hyperhomocysteinemia** (2.5x) measure fasting level, can be acquired (folate/VitB6/VitB12 deficiency, CRF, pernicious anemia, hypoTH) to inherited, Tx: lower to <10mmol/L with folate/VitB6/VitB12 supplements, NB studies are inconclusive if lowering homocysteine decreases thrombophilia risk • **APC Resistance aka Factor V Arg506Gln Mutation aka Factor V Leiden** (7-20x) Factor V is resistant to degradation by activated Protein C, 3% of the population!!! • **Prothrombin G20210A Mutation** (2.8x) increased prothrombin activity • **Protein C/S Deficiency** (10x) measure level, those w/ Protein C/S deficiency can get warfarin induced skin necrosis therefore always give heparin products first

loss, +FHx • Virchow's Triad of Hypercoagulable State: (1) Endothelial Damage, (2) Change in Blood Flow, (3) Thrombophilia / Thrombocytosis • NB even if a pt has an inherited RF 90% of these pts never have an event			• **Antithrombin III Deficiency** (25x) • **High Levels of Factor 8, 9, 11, Thrombin-Activatable Fibrinolysis Inhibitor, and Tissue Factor Pathway Inhibitor**: there are currently no labs that test for these levels • **Antiphospholipid Syndrome** (refer) • **Estrogen Hormones**: Obesity, OCP, HRT, Pregnancy, etc • **Malignancy**: all cancers but especially adenocarcinomas (lung, pancreatic, breast, ovarian, GU, lymphomas, CNS, etc) b/c they produce cysteine protease that activates Factor X resulting in migratory venous/arterial thrombi aka Trousseau's Syndrome • **Nephrotic Syndrome** (loss of antithrombin III) • **PNH** • **IBD** • **COPD** • **Age** • **Smoking** • **Prior Thrombotic Event** • High Risk Surgeries (intracranial, ortho, major vascular, bowel resection, gastric bypass, renal transplant, etc) (look at BUMC notes)

von Willebrand Disease (vWD)

Type	Mechanism (vWF found in Weibel-Palade bodies in endothelium while Factor 8 is made by liver) • (1) facilitates adherence of platelets to injured vessel walls • (2) stabilizes factor 8 in plasma increasing t1/2 5x	**Distribution** MOST COMMON INHERITED BLEEDING DISORDER affecting>0.1 % of the population!!!	**S/S** Primary and secondary hemostasis problems but variable in degree	**Dx** Increased BT and Abnormal Platelet Function Tests Increased aPTT and Decreased Factor 8		**Treatment**
				Quantitative Problem vWF:Ag Test (measures circulating vWF levels) vWF Multimer Analysis (uses electrophoresis to separate vWF into different sizes)	**Qualitative Problem** vWF:RCoF Test (functional assay that uses control platelets and the patient's vWF in the presence of the abx ristocetin cofactor to assess fxn of pt's vWF)	
I	AD	75%	Mild Sx	+	-	DDAVP (stimulates endothelial cells to make vWF, tachyphylaxis therefore only effective for 2d)
II	4 Types AD (A,B) AR (M,N)	20%	Mod Sx	-	++	Cryo (contains both vWF and Factor 8) NB DDAVP is contraindicated (the increased release of abnormal vWF causes increased destruction of platelets)
III	AR	5%	Severe Sx	+++	+++	Cryo NB DDAVP is contraindicated (same reason)

Antiphospholipid Syndrome

- Mech
  - Term used to describe the clinical relationship b/t hypercoagulable state and presence of antiphospholipid antibodies
- Etiology
  - Idiopathic
  - Rheumatologic Disorders (SLE, Sjogren's, etc)

- Infections (HIV, HCV, etc)
- Medications (same ones that produce lupus like syndrome)
- Malignancy (lymphoma)

- Diagnostic Criteria
  - (1) ≥1 Clinical Criteria
    - **Vessel Thrombosis** OR
      - Any type of vessel and of any size
        - Venous: DVT/PE, retinal vein occlusion, Budd-Chiari Syndrome, CNS sinuses
        - Arterial: premature CAD, CVA, renal artery thrombosis
        - "Catastrophic Anti Phospholipid Syndrome"
          - sudden thrombosis at multiple different sites resulting in infarction of multiple organs
          - anticoagulation is not enough in this syndrome, data suggests that steroids, cyclophosphamide, IVIG and plasmapharesis might be helpful
    - Pregnancy Morbidity
      - **≥3 consecutive abortions before 10wks** OR
        - NB abortion is nature's way of destroying a bad fetus therefore <3 is normal but when you have >3 and consecutive something wrong is going on
      - **≥1 fetal deaths after 10wks** OR
        - NB fetal death after 10wks is never normal b/c if there was something wrong with the fetus nature would have destroyed it early on
      - **≥1 premature (<34wks) birth NOT b/c of severe eclampsia or placental insufficiency**
        - NB pregnancy morbidity is not just 2/2 placental vessel thrombosis, it has been found that the antibodies noted below are actually trophotoxic
    - Other clinical features that are not part of diagnostic criteria and whose etiology is unclear
      - Migraine Headaches
      - Livedo Reticularis
      - Cardiac Murmurs
      - Chorea
      - Transverse Myelitis
  - (2) ≥1 Laboratory Evidence of **Antiphospholipid Antibodies on ≥2 occasions and ≥12wks apart (NB also elevated PTT and thrombocytopenia (these antibodies also bind to platelets resulting in thrombocytopenia which is more confusing b/c these pts are in a pro-coagulable state))**
    - **Anti-Cardiolipin**
      - Mechanism: exact mechanism is unclear but it is an antibody to mitochondrial phospholipids
      - NB 40% of APS pts have false positives to the VDRL test for syphilis b/c this test employs the use of cardiolipin as its reagent and these pts had anti-cardiolipin
    - **Lupus Anticoagulant via Russel Viper Venom Assay**
      - Mechanism: very confusing term b/c it is not specific to lupus and even though it increases the PTT test it actually is a pro-coagulant in vitro, exact mechanism is unclear but it is an antibody to phospholipids and it prolongs phospholipid dependent coagulation reactions
    - **Anti-Beta2-Glycoprotein**
      - Mechanism: unclear
    - Other
      - Hemolytic Anemia
      - Adrenal Insufficiency

- Therapy
  - Strategy is controversial in terms of when and what to treat with but there are some agreed upon recommendations:
    - Prophylactic anticoagulation is only indicated if the pt has had a h/o thrombosis
      - Lifelong Coumadin (INR 2-3) in the non-pregnant pt
      - ASA in the pregnant pt
      - NB hydroxychloroquine has been found to be helpful
    - Treatment
      - Difficult to use heparin b/c hard to monitor b/c PTT is already elevated thus you must monitor with a specific heparin assay

Heparin Induced Thrombocytopenia (HIT)

	Type I	Type II
Mechanism	Heparin directly stimulates platelet clumping	Heparin induces release of PF4 from endothelium and platelets ↓ Heparin–PF4 bind forming an immunogenic Ag ↓ Abs against Ag are created (variable depending on the genetics of the patient and molar ratio of Heparin-PF4 and sulphation grade of the specific Heparin) ↓

		ICs form and then bind to (1) endothelium causing injury and subsequent coagulation w/ macro/microvascular arterial/venous thrombosis and (2) platelets causing platelet activation and consumption w/ thrombocytopenia
S/S	Asymptomatic	Symptomatic Thrombocytopenia (bleeding) Arterial and Venous Thrombosis (this is actually more important than the thrombocytopenia, usually a worsening of thrombosis for which heparin was administered or may be a new site, arterial thrombosis specifically of the limbs/heart/brain seem to occur more commonly in pts w/ CVD while venous thrombosis specifically of the DVT/brain seem to occur more commonly in post-op pts) sometimes overt DIC, adrenal hemorrhage Skin Manifestations (allergic type reaction and skin necrosis)
RFs		Older Female Pt Post-Op esp from CV/Ortho Procedures UFH > LMWH Duration >1wk Concurrent Prothrombotic states Full Dose > Prophylactic Dose
Duration	Transitory resolving spontaneously	Resolves anywhere from days to months and requires cessation of heparin to do so
Incidence	20%	2% for UFH and much lower for LMWH
Onset	After 1-4d of heparin therapy	After 4-10d of heparin therapy (but can occur as early as <1d if pt has had prior exposure within the past few months b/c of amnestic response)
Platelets Nadir	100-150k	50-100k (but not as severe as other drug induced thrombocytopenias and thus the more common complication is thrombosis NOT bleeding unlike other drug induced thrombocytopenias)
Diagnosis		Combination of clinical likelihood (severity, recovery from drug withdrawal, onset of complications, exclusion of other causes, etc), functional tests and immunologic tests Typically if you suspect clinically then stop heparin and Tx as below and order Immunologic Test if + then confirm with Functional Test Clinical Likelihood • Sheridan Score, Greinacher Score Immunologic Tests (testing the presence of antibodies in pt) ~100% sensitive but ~50% specific • HIT Ab ELISA Functional Tests (testing the ability of pt's serum to activate platelets) ~50% sensitive but ~100% specific • Platelet Aggregation Test (PAT), 14C-Serotonin Release Assay (SRA), Heparin Induced Platelet Activation (HIPA), Flow Cytometry Assay (FCA)
Treatment	It used to be heparin was continued and pts were just observed but now since many of these pts are actually Type II it is recommended that heparin is discontinued	• Discontinue heparins (UFH, Heparin Flushes, LMWH, Factor Xa Inhibitors) ASAP • b/c these pts are still at risk for thrombosis use DTIs • even if you stop heparin products the antibodies are still floating around causing problems • if ongoing thrombotic problems consider thrombolytics, IVC filter, thrombectomy • do NOT give Coumadin during the acute phase and if you did then give vitK b/c risk of hemorrhagic necrotic bullae is much higher but once no longer acute (aka normal platelets) then pts need to be on Coumadin for 2-3 months • do NOT give platelets b/c can worsen thrombotic events • screen for lower extremity DVT
Other		Most common type of lawsuit in cardiothoracic surgery b/c high mortality if heparin is continued

Idiopathic Thrombocytopenic Purpura (ITP)

- Mechanism: autoantibodies to platelet resulting in premature clearance by the reticuloendothelial system
- NB some of these autoantibodies can also attack megakaryocytes impairing platelet production
- essentially a DOE as the test for antiplatelet glycoprotein autoantibodies aka "Platelet Associated Surface IgG Assay" has a sensitivity of ~55% and a specificity of 85% nevertheless still order but remember that it is a send out lab and takes weeks to come back
- typically seen in young females (always rule out HIV and HCV) but more elderly pts (>60yo) are being diagnosed and in this case a BM Bx is indicated to rule out MDS as MDS can present with an isolated thrombocytopenia
- Some very controversial studies suggest that ITP is associated w/ *Helicobacter pylori* infection and that eradication can lead to remission or improvement in the course of ITP
- 10% of pts have ITP + AIHI = Evan's Syndrome
- Treatment
    - Children (50%): M=F, plt<20, also accompanying eosinophilia/lymphocytosis, usually sudden onset esp after viral illness and there is a spontaneous remission rate of 75% within a few weeks therefore most argue not treating children but some do b/c kids are so active and you don't won't them getting a life threatening bleed (esp for some reason intracranial bleed)

- Young Adults (50%): F>M, plt 30-80, autoimmune process, usually insidious onset and there is a spontaneous remission rate of 5% therefore most argue treating and even when you do relapse often occurs therefore splenectomy and many other Tx are often needed
- If life threatening bleeding then…
  - Methylprednisolone 1g IV Qd x3d over 30min
  - IVIg 1g/kg IV Qd x3d
  - Platelet Transfusion
- If no life threatening bleeding then Tx if <30k otherwise just watch
  - First (~65% response rate)
    - Prednisone 1mg/kg/d PO tapered over 4-6wks
    - Anti-Rh(D) (RhoGam) Ig 75mcg/kg IV QD if Rh+ pts (essentially it just saturates spleen w/ Ig bound RBCs thus preventing the spleen from eating up platelets, the trade off is that you will have some anemia)
    - IVIg 1g/kg IV QD x3d (effect only lasts a few weeks therefore only used as a temporizing measure or bridge to splenectomy as very expensive like $25,000, NB the response to IVIg is highly predictive of response to splenectomy)
    - Immunosuppresants esp Cyclophosphamide, Cyclosporine, IFN
    - Anti-CD20 (Rituximab) (the idea is to kill B-cells that are making the auto-antibodies)
  - If refractory to above or recurrence (~80% response rate)
    - Splenectomy (75% effective, always wait for 4-6wks allowing for above treatments to act and making sure that spontaneous remission does not occur, give *Strept/Haemophilus/Neisseria* vaccinations prior to surgery)
    - Staphylococcal Protein A Immunoabsorption (essentially you run the pts blood thru a column which removes IC from blood but it is rarely used anymore)
    - Danazole (an attenuated male hormone that interferes w/ macrophages from eating platelets, 60% response in males but increasing response to about 80% in elderly females)
    - AGM-531 aka N-Plate (this is NOT thrombopoietin but similar in structure and thus stimulates platelet production the reason why you can't use actual CSF is b/c auto-antibodies actually form exogenous CSF and when you stop exogenous CSF these antibodies are still around and actually begin to bind endogenous platelet CSF)

Thrombotic Thrombocytopenic Purpura (TTP) & Hemolytic Uremic Syndrome (HUS)

- Mechanism: problem w/ ADAMTS-13 (a protease that cleaves vWF from multimers to unimers which have LESS of a tendency to adhere to platelets causing microcirculation aggregation so when there is a problem w/ ADAMTS-13 you have platelet aggregation) resulting in Triad: F + microangiopathic hemolytic Anemia + Thrombocytopenia ("FAT-RN")
  - **TTP** (addition of Neurologic problems – usually fluctuating MS from nl to abnl but MRI is always abnl, most common cause of M&M)
    - **Defective** ADAMTS-13
      - **Genetic Mutation of ADAMTS-13:** essentially ADAMTS-13 is unable to cleave multimers to unimers
      - **Inhibition of ADAMTS-13:** ADAMTS-13 is inhibited by neutralizing antibodies
  - **HUS** (addition of Renal problems – usually AKI but just sometimes hematuria/proteinuria without azotemia)
    - **Overwhelmed** ADAMTS-13
      - **Other (90%):** postpartum, metastatic cancer, post BM transplant, drug (various chemo, cyclosporine, ticlopidine)
      - **Infectious Diarrhea w/ EHEC-O157:H7 (10%):**
        - Epidemiology: found in uncooked beef (cow is the reservoir) and thus peak during summer season, <5yo, rural, usually outbreaks but sometimes sporadic, also unpasteurized apple juice and milk, raw alfalfa sprouts, contaminated swimming pools
        - Mechanism: Shiga-like toxin → dysentery 2/2 right sided colitis BUT also (1) stimulates production of more vWF multimers which overwhelms normal ADAMTS13 causing the triad and (2) acts on the globotriaosylceramide (Gb3) receptor on renal endothelium causing renal problems,
        - S/S: 20% of pts who develop bloody diarrhea develop HUS w/in 6d of onset of diarrhea
        - Tx: supportive NOT abx b/c releases more toxin creating worse HUS
- Labs
  - Normal Coags
  - ADAMTS13 activity assay (low (<5% = TTP/HUS vs 5-25% other disorders like DIC, liver dz, pregnancy, etc vs >25% nl)
  - ADAMTS13 inhibitor/antibody
- Tx (even if pt just has MAHA and thrombocytopenia alone this warrants Tx below, in general HUS less responsive that TTP)
  - Plasma-exchange Qd (90% remission rate) for >5d or >2d after normalization of labs, if not available than FFP, removes inhibitor/antibody and provides normal ADAMS-T13, 85% effective, primary Tx not below
  - Steroids and other immunosuppressants (cytoxan, rituxan, azathioprine, vincristine)
  - Splenectomy
  - RRT if renal problems
  - transfusion prn except plt b/c of the potential r/o additional microvascular occlusion

- NB don't use abx/anti-motility agents for infectious induced HUS
- Prognosis
  - 90% mortality if unTx 90%
  - Interestingly there is high r/o recurrence often occurring several years from first episode

Disseminated Intravascular Coagulation (DIC)

- Etiology
  - *tissue damage* (trauma, surgery, burns, et al which direct release of tissue factor)
  - *overwhelming infection* (sepsis (most common cause), Rickettsial infection, etc with release of endotoxin)
  - *malignancy* (any tumor that releases TNF)
    - liquid tumors esp APML = acute DIC
    - solid tumors esp Pancreatic Cancer (Trousseau's Syndrome w/ superficial migratory thrombophlebitis and DVT-PE) = chronic DIC
  - *obstetric complications* (fetal death, amniotic fluid embolism, abruption, eclampsia, et al)
  - *other* (peritovenous shunt used in chronic ascites, acute hemolytic transfusion reactions, PNH, rattle snake venom, heat stroke, et al)
- Pathogenesis (widespread microthrombosis vs widespread fibrinolysis)
  - (1) release enormous amounts of tissue factor which activates the extrinsic pathway → massive widespread coagulation → coagulation induces widespread platelet aggregation and agglutination (platelets)
  - (2) release enormous amounts of plasmin leading to fibrinolysis → Fibrin Degradation Products (FDPs) interfere with normal fibrin polymerization and platelet aggregation → the combination of increased fibrinolysis and impaired fibrin polymerization and thrombocytopenia leads to bleeding
  - Acute: presents as end organ ischemic damage and microangiopathic hemolytic anemia BUT bleeding also occurs as liver/BM cannot compensate quickly enough
  - Chronic: presents as end organ ischemic damage and microangiopathic hemolytic anemia BUT liver/BM is able to compensate for consumption of factors/platelets hence bleeding does not occur in chronic cases
  - End-Organ Damage: Renal, Liver, Resp, CNS
  - Other: *purpura fulminans* (large symmetric ecchymosis of the extremities but can occur anywhere w/ hemorrhagic bullae and gangrene) esp seen in meningococcemia sepsis

	Acute	Chronic
PT	↑	=
aPTT	↑	=
Thrombin	↑	=
Fibrinogen	↓	=
Platelet	↓	=
FDP aka Fibrin Degradation Products (FSP Flocculation and D-Dimer)	↑	↑
Hemolysis	↑	↑

- Treatment
  - Treat Underlying Process
  - Hemodynamic Support
  - Most pts do not require specific coagulopathic support b/c of its short duration or b/c it is not severe enough hence give FFP/Cryo/Plt only to pts who are bleeding, at high risk of bleeding, or require invasive procedures and plt<20, fibrinogen<50, INR>?, aPTT>?
  - Low Dose Heparin (only used in select chronic DIC pts)
  - Activate Protein C (Xigris) has both anticoagulant and anti-inflammatory effects, expensive so use in severe cases
  - Protein C Concentrate (?) in pts whose cause of DIC is due to protein C deficiency
  - 65% mortality