Coagulation Conundrums

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Disclosure

- I have nothing to disclose except
  - I do work for food
  - I promote giving Blood
Keep Blood in the Tubing
PVC-pipes

- Platelets Adequate number that work right
- Von Willebrand Factor (vWF)
- Clotting Factors
- Pipes - Intact and healthy endothelium
Clotting Process

- Break in vessel wall – smooth muscle contracts
- Platelets with (vWF) stick to collagen and Activate
- More platelets are attracted
- Clotting Factors activate to form Fibrin
- Clot contracts
**Procoagulation**

- Fibrinogen-Fibrin
- Prothrombin-Thrombin
- Factors V, VII, VIII, IX, X, XIII
- Tissue Factor
- Collagen
- vWF
- Activated Platelets
- Plasminogen Activator Inhibitor (PAI-1)
- Thrombin-Activatable Fibrinolysis Inhibitor (TAFI)

**Anticoagulation**

- Plasminogen
- Protein C, Protein S
- Thrombomodulin
- Heparin sulfate
- Antithrombin
- Tissue Plasminogen Activator (tPA)
- Tissue Factor Pathway Inhibitor (TFPI)
- Alpha-2-antiplasmin
- Nitric Oxide (NO)
- Prostacyclin

**Balance**

- **Clotting**
- **Bleeding**
Von Willebrand Factor - vWF

- Super glue of platelets to stick to damaged walls
- Stabilizes and transports Factor VIII
- Made by Endothelial Cells
- Most common genetic bleeding disorder
Endothelium

- Covers collagen, Tissue Factor (TF)
  - vWF
  - tPA
  - Nitric Oxide (NO)
  - Prostacyclin –Cox2 mediated
  - ADPase
  - TF Pathway Inhibitor (TFPI)
  - Heparin
  - Thrombomodulin – Binds free thrombin
Platelets

- Made in the bone marrow
- Thrombopoietin made in liver stimulates production
- Fragments of megacaryocytes
- No nucleus
- 67% in circulation
- 33% in spleen storage
- Life 8 – 10 days
Platelet Activation

Von Willibron Factor vWF

Collagen, Thrombin, TXA2 protease-activated receptor-1 (PAR-1)

Arachidonic acid

Cyclooxygenase COX1

TXA2 and ADP released, also PF4, Serotonin, Factor V

Increase cAMP inhibits activation

glycoprotein (GP) IIb/IIIa receptor

Fibrinogen, fibronectin attaches to other platelets
Activated Platelet

Von Willibron Factor vWF

Collagen, Thrombin, TXA2

Arachidonic acid

Cyclooxygenase COX1

TXA2 and ADP released, also PF4, Serotonin, Factor V

Increase cAMP inhibits activation

glycoprotein (GP) IIb/IIIa receptor

Fibrinogen/fibronectin attaches to other platelets
The Shape of Platelets

Flowing Platelets

Activated Platelets

Aggregated - Active Platelets

Courtesy of Helena Diagnostics
Clotting Cascade - Factors

**Intrinsic Pathway** – Inside the cut
Endothelial Injury

Test = aPTT
- XII to XII active
- XI to XI active
- IX to IX active
- VIII to VIII active

Calcium needed as co-factor

**Extrinsic Pathway** – outside the cut in the plasma

- Vitamin K - Liver dependant
- Test = PT
- VII to VII active + Tissue factor

**Common Pathway**
- X to X active with V present
- II Prothrombin to Thrombin
- I Fibrinogen to Fibrin
- XIII to XIII active stabilizer to crosslink fibrin

vWF stabilizes Factor VIII
Built in Clot Blockers and Busters

Intrinsic Pathway – Inside the cut Endothelial Injury

Test = aPTT
- XII to XII active
- XI to XI active
- IX to IX active
- VIII to VIII active

Common Pathway
- X to X active with V present
- II Prothromin to Thrombin
- I Fibrinogen to Fibrin

Liver made
- Protein S
- Protein C

Extrinsic Pathway – outside the cut in the plasma – Tissue Factor

Test = PT
- VII to VII active

Tissue Factor Pathway Inhibitor
- Antithrombin III

Plasminogen via t-PA/ PAI-1 to Plasmin
- Fibrin split products, D-Dimer
Built In Clot Blockers and Busters

Intrinsic Pathway – Inside the cut
Endothelial Injury
Test = aPTT
- XII to XII active
- XI to XI active
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Extrinsic Pathway – outside the cut in the plasma – Tissue Factor
Test = PT
- VII to VII active

Common Pathway
- X to X active with V present
- II Prothrombin to Thrombin
- I Fibrinogen to Fibrin

Heparin
Antithrombin III
Plasminogen via t-PA/PAI-1 to Plasmin
Fibrin split products, D-Dimer
Clotting too much

Clotting Too much – Thrombosis - Pulmonary Embolus, Deep Vein Thrombophlebitis, Stroke, Myocardial Infarction
Increased Clotting Presentation

Calf swelling, pain
  Deep Vein Thromboplebitis (DVT)
Chest Pain
  Pulmonary Embolus (PE)
  Myocardial Infarction, Angina
Atrial Fibrillation (Irregularly Irregular)
  Stroke, or Transient Ischemic Attacks (TIAs)
Fetal Loss
High Risk – post operative, pregnancy, cancer, surgery, congestive heart failure
Increased Risk of Clotting

History

- History of recurrent clots, PEs... consider genetic causes: protein S, C, or Antithrombin III deficient, Factor V Leiden, hyperhomocysteine, prothrombin 20210 mutation
- Pregnancy - Increased blood viscosity, fibrinogen and factor VIII. Post Partum - Hypercoaguable state
- Polycythemia vera - increased viscosity
- Prolonged Immobility – Travel, bed bound,
- Surgery – orthopedic
Increased Clotting History

- Smoking, Resent Surgery, Diabetes, Congestive Heart Failure, Cancer, Atrial Fibrillation are all high risk
- Autoimmune diseases such as systemic lupus erythematosis, and medications such as procainamide, chlorpromazine, and quinidine.
- Oral contraceptives – Estrogen
- Renal Failure
- Cancer
Bleeding History

1. Abnormal bleeding from the mucus membranes such as the mouth, nose or vagina suggests platelet defects or von Willebrand’s disease (vWD).

2. Abnormal bleeding into joint spaces and soft tissues implies a defect in the clotting factors.

3. Purpuric lesions are usually caused by vascular wall defects.
Bleeding History

- HX - History of melena, abdominal pain, Aspirin or non-steroidal anti-inflammatory agents (NSAIDs) use, past peptic ulcer disease, then consider GI bleeding, platelet dysfunction.

  - In females the menstrual history quantifying the amount of bloodloss, or possible pregnancy should be obtained.

  - History of alcohol abuse - consider liver disease.

  - Family history of blood cell or bleeding disorder: consider Hemophilia, von Willebrand Disease.
Bleeding History

- History of weight loss, Cancer, HIV, rheumatoid arthritis, thyroid disease, renal disease - then consider secondary cause

- History of fever and chills, cough, dyspnea, then consider Infection.

- History of prolonged bleeding after dental extractions, epistaxis, gum bleeding, easy bruising, then consider low or dysfunctional platelets.

- History of bleeding into joints, then consider hemophilia.

- History of Lupus - Lupus anticoagulant
PHYSICAL EXAM

GENERAL INSPECTION- clubbing in liver disease or lung cancer

- Skin- Hypothyroid, SLE, Bruises, lesions, petechiae or purpura in low platelets or vWF
- Weight - Loss in Cancer, HIV, Chronic disease

VITAL SIGNS- Pulse: Tachycardia from increased cardiac output

- Respirations: Tachypnea from decreased oxygen transport
- BP: Orthostatic if volume depleted
- SaO2 – Low in PE, ACS,
- Temp: Fever in infections and drug or transfusion reactions,
Physical Exam 2

- **HEENT** - Eye: Jaundice if hemolysis, pallor in palpebral conjunctiva
- **LUNG** - consider infection, lesion, rubs
- **CV** - new murmur or CHF, Listen for Bruits: carotid, femoral, aorta; JVD in PE, CHF,
- **ABDOMINAL** - Liver/spleen size, masses, tenderness, surgical scars
- **RECTAL** - Stool guaiac,
- **PELVIC/BREAST** - Uterine abnormality, Pap smear, Breast nodule
- **LYMPHNODES** - consider lymphoma, leukemia, infection, connective tissue disease
- **EXTR** - Homan’s or calf tenderness/swelling, Calf measurement, edema in CHF, Hepatic and Renal failure
- **NEURO** in suspected stroke
Platelet Problems or Von Willebrand Disease (vWD)
Clotting Factor Disorders

Hemarthrosis
Vascular Wall Defects

Purpura
Initial Lab work up- clotting

- CBC : WBC, RBC, Platelet counts
- Complete Metabolic Profile (Liver, Kidney)
- Cardiac Biomarkers – Troponin, CPK
- D-Dimer – DVT/PE
Best screening test for hypercoagulability?

- There is none!!
- Unprovoked clot is the first clue
- More that one suggests a genetic issue
Tests – Is Clotting going on

- D-Dimer elevation – from thrombolysis (break apart)
  - Also used to know when to stop Coumadin therapy
- Fibrin Split products
- Peripheral smear may show shistocytes (helmet cells)
Bleeding Test- PVC-Pipes

- Platelets – CBC platelet count
  - Do they work – PFA (Bleeding time)
- vWF – abnormal PFA and aPTT (Factor VIII depends of vWF) do vWF analysis
- Clotting Factors – PT and aPTT if either abnormal – do Mixing study – if corrects do Factor levels VIII, IX. If both PT and aPTT abnormal do TT Thrombin time
- CMP, UA (Renal or Hepatic causes)
- Pipes – Vasculitis C-Reative Protein, ESR, Biopsy
Tests to Order – Screen for Clotting ability

- **PT** - Prothrombin Time - +/- 2 of control = 11 - 16 sec. Extrinsic system monitor for coumadin therapy. INR is International Normalization Ratio, 1 is normal, 2-3 for Coumadin Therapy, 2.5 - 3.5 if heart valve.

- **aPTT** - activated Partial Thromboplastin Time - 25 - 38 sec. Intrinsic system. Used to monitor Heparin therapy (if abnormal do Factor analysis and consider vWD).

  - **Mixing Study** (add normal plasma to patient plasma re do PT and aPTT) – if PT or aPTT do not correct then there is an inhibitor present and not a factor deficiency.

- **TT** – Thrombin Time measures the common pathway
Coag Test Summary

<table>
<thead>
<tr>
<th>PT</th>
<th>aPTT</th>
<th>Differential diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged</td>
<td>Normal</td>
<td>Factor VII deficiency or inhibitor, vitamin k deficiency, liver disease, warfarin therapy</td>
</tr>
<tr>
<td>Normal</td>
<td>Prolonged</td>
<td>Factor VIII, IX, XI, XII deficiency or inhibitor; von Willebrand disease; lupus anticoagulant; heparin therapy</td>
</tr>
<tr>
<td>Prolonged</td>
<td>Prolonged</td>
<td>Prothrombin, fibrinogen, Factor V or X deficiency; liver disease; disseminated intravascular coagulation; combined heparin and warfarin therapy Need TT Thrombin Time</td>
</tr>
</tbody>
</table>
## Clotting Tests for bleeding

<table>
<thead>
<tr>
<th>Test/Disease</th>
<th>PT</th>
<th>aPTT</th>
<th>PFA</th>
<th>Platelet Ct</th>
</tr>
</thead>
<tbody>
<tr>
<td>vWD</td>
<td>Normal</td>
<td>Increased</td>
<td>Abnormal</td>
<td>Normal</td>
</tr>
<tr>
<td>Hemophilia A/B heparin, lupus</td>
<td>Normal</td>
<td>Increased</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>DIC</td>
<td>Increased</td>
<td>Increased</td>
<td>Abnormal</td>
<td>Low</td>
</tr>
<tr>
<td>Uremia</td>
<td>Normal</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Normal</td>
</tr>
<tr>
<td>Aspirin NSAIDs</td>
<td>Normal</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Normal</td>
</tr>
<tr>
<td>Early: Liver Dz Vit K def, F VII coumadin</td>
<td>Increased</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Late Liver Dz</td>
<td>Increased</td>
<td>Increased</td>
<td>Normal</td>
<td>Low</td>
</tr>
<tr>
<td>ITP, TTP, HUS, HIT</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Low</td>
</tr>
</tbody>
</table>
Tests to monitor therapy

- PT – INR Coumadin 2.0 – 3.0
- PTT – UF Heparin
- Factor Xa (Heparin) level – LMWH
- D-Dimer – can you stop anticoagulant?
- PFA – Antiplatelet working
- TEG – Thromboelastography – clot formation and lysis - Surgery
Bleeding Differential Diagnosis

- C - Cirrhosis/Liver Disease and Coumadin
- A - Aspirin and other NSAIDs
- L - Leukemia
- F - Factor Deficiency - Hemophilia
- D - Disseminated Intravascular Coagulation
- I - Idiopathic Thrombocytopenic Purpura (ITP)
- P - Platelet Deficiency (TTP, HUS, DIC, Heparin- HIT)
  - Platelet Dysfunction (vWD)
- S - Scurvy: Vitamin C Deficiency
PVC pipes

**Platelets**
- Not enough below 50,000 – production, destruction, sequestration
- Not working – ASA, NSAIDs, Uremia, Congenital
- **Von Willebrands Disease** - Type 1 most common

**Clotting Factors**
- Most common: VIII, IX
- Vitamin K Deficiency, Liver Disease

**Pipes** - Vasculitis, Scurvy, Ehlers-Danlos, Heritary Hemorrhagic Telangiectasias, Steroids
- Palpable Purpura – Sepsis, Meningococcemia, Henoch-Schonlein purpura, Drugs
Platelet Abnormalities: Abnormal Platelet Function

1. Acquired
   - Drugs (Aspirin, NSAIDs)
   - Diet (Omega 3 - Fish oil, chocolate, ...)
   - Uremia (renal failure)
   - Leukemia and Myeloproliferative Disorders
   - Mechanical (cardiopulmonary bypass)

2. Congenital
   - Bernard-Soulier (abnormal adhesion)
   - Glanzmann’s Thrombasthenia (abnormal aggregation)
   - Storage Pool Disease (abnormal release response)
   - Platelet-type von Willebrand’s Disease
Thrombocytopenia

Production
- Nutritional B12 or Folate Deficiency
- Congenital – Alports syndrome, Fanconi anemia, Wiscott-Aldrich syndrome
- Marrow damage – aplastic anemia, chemotherapy, drugs, maligancy – myeloma or leukemia, radiation, myelodysplasia

Destruction
- Immune – (Positive Platelet Associated Antibody test or HIT assay) ITP, Drug, HIV, SLE, HIT
- Non-Immune- DIC, TTP, Preeclampsia, HELLP syndrome Anti-phospholipid syndrome

Sequestration- Liver, spleen, marrow -myelofibrosis, cancer
Platelets - How Low Can you go?

- 150,000 - 350,000 cu/mm Normal
- 80 – 100 – need for surgery
- 40 – 50 for procedures like LP
- 10 – 40 – At risk if trauma or surgery
- < 10,000 spontaneous bleeding
- if > 1 million - Clotting too much
Thrombocytopenia Testing

- Liver Spleen size – Ultrasound or CT
- Bone Marrow Biopsy
- Platelet antibodies (direct and indirect)
- HIT assay if on heparin
- ADAMTS 13 (TTP)
- Blood smear (morphology)
- Antibody response to Escherichia coli O157:H7
ITP - Idiopathic Thrombocytopenic Purpura

- In children linked to viral infection
  - platelet-associated antibodies
  - 80% rapid remission, and does not recur
    - Treatment: steroids and IVIG
  - 10% to 20% develop chronic ITP
    - splenectomy works in 70%

- Adults linked to HIV and Hep C
  - 50% develop chronic ITP
  - Same treatments
TTP, HUS, DIC, get HEELP!

- **TTP** – Thrombotic Thrombocytopenia Purpura with ADAMTS-3 and big vWF
- **HUS** – Hemolytic Uremic Syndrome with E.Coli 0157:h7
- **DIC** – Disseminated Intravascular Coagulation – Sepsis, Burns, Trauma
- All of these need ICU/expert care: PUNT to Hematologist
HELLP- Pregnancy

- Hemolysis (high indirect Bilirubin, LDH)
- Elevated Liver Enzymes (AST, ALT)
- Low Platelets
- Severe preeclampsia (BP increased and proteinuria) increased maternal and fetal mortality
- 1 per 1000 pregnancies up to 20% with preeclampsia/eclampsia at 28 – 36 weeks gestation
- Rx Support and Deliver Baby
# Thrombocytopenia – Not HIT

<table>
<thead>
<tr>
<th>Issue/Disease</th>
<th>Acute ITP</th>
<th>Chronic ITP</th>
<th>TTP</th>
<th>HUS</th>
<th>DIC</th>
<th>HELLP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Children</td>
<td>Adults</td>
<td>Adults</td>
<td>Children</td>
<td>Any</td>
<td>Pregnant</td>
</tr>
<tr>
<td><strong>Cause</strong></td>
<td>Immune</td>
<td>Post viral</td>
<td>Immune HIV Hep C, SLE</td>
<td>ADAMTS-3 and big vWF</td>
<td>Infections E.Coli 0157:h7</td>
<td>Sepsis, Burns trauma</td>
</tr>
<tr>
<td><strong>PT/PTT</strong></td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>abnorm</td>
<td>+/-</td>
</tr>
<tr>
<td><strong>Fever</strong></td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>depends</td>
<td>+/-</td>
</tr>
<tr>
<td><strong>Hemolysis</strong>*</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td><strong>Organ failure</strong></td>
<td>no</td>
<td>no</td>
<td>CNS &gt; Renal</td>
<td>Renal &gt; CNS</td>
<td>All possible</td>
<td>Liver</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>None – IVIG, Steroids</td>
<td>Steroids Splenectomy</td>
<td>Plasma Exchange, No Plts</td>
<td>Support, No Plts</td>
<td>FFP, Cryo, platelets</td>
<td>Deliver (MgSO₄)</td>
</tr>
</tbody>
</table>

Hemolysis* - Microangiopathic: increased indirect Bilirubin/LDH/Shistocytes/Reticulocytes
Von Willebrand Disease

- Most common inherited bleeding disorder
- Found in approximately 1% of the population
- Most individuals are asymptomatic unless a significant bleeding event occurs
- Blood Group O individuals have significantly lower vWF than other groups (30% lower)
- vWF stabilizes Factor VIII so any decrease in vWF will increase aPTT and platelet function analysis will be abnormal
Von Willebrand Disease

- Measure vWF antigen (vWF:Ag)
  - How much protein is present?
- Measure vWF activity (Ristocetin Cofactor)
  - How well is the protein working?
- Measure Factor VIII activity
  - How well is vWF stabilizing Factor VIII?
- Evaluate pattern of von Willebrand multimers by electrophoresis
  - Important for classification of disease (6 types) and therapeutic management
- Treat most common cause with DDAVP
Hemophilia

- US 13,320 cases of hemophilia A (VIII) and 3,640 cases of hemophilia B (IX).
- Prolonged aPTT with a normal PT
- Bleeding into joints
- Treat with Recombinant Factor replacement (No longer plasma exposure)
- Three types of Hemophilia A – Genetic, vWD, Inhibitor to factor VIII acquired or developed
Renal Failure and clotting

- **Early stages of CKD** - Low protein C and antithrombin III, (anticlotting system) Increased fibrinogen, von Willebrand factor, factor VIII (pro thrombotic) Increased plasminogen activator inhibitor-1 (PAI-1), low tissue plasminogen activator (t-PA) So Clots stay

- **End stage CKD** - accumulating uremic toxins decrease platelet function, inhibiting their adhesion, aggregation and releasing platelet factors, such as serotonin or thromboxane A₂

- Damage to endothelial cells produce large amounts of prostacyclin (PGI₂) and nitric oxide (NO) inhibitor of platelet aggregation platelet adhesion.
Liver Disease

- The liver is THE site for coagulation factor synthesis (except Factor VIII)
- Liver failure leads to multi-factorial coagulopathy
  - Decreased coagulation factors
  - Decreased anti-coagulation factors
  - Decreased fibrinogen
  - Decreased platelets
  - Increased D-dimers (interfere with clot formation)
- Bleeding from liver failure is a major cause morbidity and mortality
- Give Vitamin K
Bleeding Therapy Summary

- Low platelets immune attack – Corticosteroids, splenectomy
- CKD – Dialysis, Renal transplant
- Low platelets – Transfuse platelets (not if HIT, TTP, HUS +\- ITP) thrombopoietin in future
- vWD – DDAVP
- Hemophilia A – Factor VIII, DDAVP
- DIC/Multiple clotting factors low – FFP or Cryo
- Liver Disease, Coumadin excess – Vitamin K
- HIT – Stop heparin and use non hepraniod
- Reverse heparin - protamine
Tests – Clotting too much recurrent DVT/PE

- Fasting homocysteine level/ MTHFR gene
- Factor V Leiden assay
- Protein S, C, antithrombin III assay
- Lupus anticoagulant
- Anticardiolipin antibodies
- Anti Beta-GPI antibodies
- Prothrombin 20210 mutation test
- Fibrinogen level
- HIT Assay if Heparin exposure
Hypercoagulability – PVC Pipes

- **Platelets**
  - Too many (over 1 million)
  - Overactive (HIT)

- **Von Willebrand Factor** – deficient ADAMTS13 (TTP) no breakdown, leaving big vWF = Clotting

- **Clotting Factors**
  - Anti-clotting factors deficient/ not working
  - Too many factors/triggers (Thrombin, Fibrinogen)

- **Pipes** – Stasis, surgery, injury, plaques,
Pregnancy and OCP Estrogen

- Increases in fibrinogen, vWF, and factors VII, VIII, and X; decreased protein S
- OCP + Smoking = increased platelet reactivity, mediated in part by increased thromboxane synthesis
- acquired activated protein C resistance
- protein S levels decrease
Cancer

- mucinous adenocarcinomas
- promyelocytic leukemia
- malignancies of lung, breast, GI, and any metastatic solid tumor

- Trousseau syndrome = migratory thrombophlebitis with noninfectious vegetations on the heart valves (marantic endocarditis)
Nephrotic Syndrome

- Decreased antithrombin and plasminogen (renal loss)
- Increased platelet activation and increased fibrinogen
- Increased renal vein thrombosis, DVT/PE
- Albumin below 2.0 g/dL
Heparin-induced thrombocytopenia (HIT)

- Due to an antibody against heparin
- Occurs in 1-3% of adult patients receiving heparin for 1 week or more. Heparin binds to platelet factor 4 (PF4), forming a highly reactive antigenic complex on the surface of platelets.
- An unexpected fall in platelet count occurring 4-14 days after heparin exposure.
- Platelet count usually falls by 50%.
- Mean platelet count 60,000 – 100,000/uL.
- Platelets become activated and induce clotting.
- Associated with thrombosis - 10-30% develop arterial or venous thromboses (usually DVTs or PEs).
- Of those forming a clot, 30% will die or require amputation.
- Platelet counts should be monitored while patient is on heparin therapy.
- HIT Assay.
- STOP all Heparin products (Flush, LMWH, Heparin) and give Direct Thrombin Inhibitor.
Who ya gonna Call?

Clot Busters

tPA (tissue Plasminogen Activator)
Fibrinolytics: Drug Clot Busters

tPA – reteplase, alteplase, tenecteplase

Intrinsic Pathway –
Inside the cut
Endothelial Injury

Test = aPTT

XII to XII active
XI to XI active
IX to IX active
VIII to VIII active

Extrinsic Pathway –
outside the cut in the plasma – Tissue
Throboplastin

Test = PT

VII to VII active

Common Pathway

X to X active with V present

II Prothrombin to Thrombin

I Fibrinogen to Fibrin

Plasminogen via t-PA to Plasmin

Fibrin split products, D-Dimer
Heparin

Intrinsic Pathway – Inside the cut Endothelial Injury
Test = aPTT
- XII to XII active
- XI to XI active
- IX to IX active
- VIII to VIII active

Extrinsic Pathway – outside the cut in the plasma – Tissue Factor
Test = PT
- VII to VII active

Common Pathway
- X to X active with V present
- II Prothrombin to Thrombin
- I Fibrinogen to Fibrin

Protamine reverses Heparin
Antithrombin III
LMW Heparin
Danaparoid, Fondaparinux

Intrinsic Pathway –
Inside the cut
Endothelial Injury

Test = aPTT
XII to XII active
XI to XI active
IX to IX active
VIII to VIII active

Common Pathway
X to X active with V present
II Prothromin to Thrombin
I Fibrinogen to Fibrin

LMWH

dalteparin – (Fragmin)
tinzapain – (Innohep, Logiparin)
enoxaparin (Lovenox, Clexane)

danaparoid – (Orgaran) good for HIT

fondaparinux – (Arixtra) direct Xa blocker, good for HIT

LMW Heparin
Danaparoid
Fondaparinux

Antithrombin III
Thrombin Inhibitors

Intrinsic Pathway –
Inside the cut
Endothelial Injury

Test = aPPT
- XII to XII active
- XI to XI active
- IX to IX active
- VIII to VIII active

Common Pathway
- X to X active with V present
- II Prothrombin to Thrombin
- I Fibrinogen to Fibrin

Bivalirudin – Angiomax
Lepirudin – Refludan
Argatroban –
Antithrombin III - Thrombate III
**Coumadin**

**Intrinsic Pathway** – Inside the cut
Endothelial Injury

Test = aPPT
- XII to XII active
- XI to XI active
- IX to IX active
- VIII to VIII active

**Extrinsic Pathway** – outside the cut in the plasma

Vitamin K - Liver dependant

Test = PT
- VII to VII active + III Tissue factor

**Common Pathway**

- X to X active with V present
- II Prothrombin to Thrombin
- I Fibrinogen to Fibrin

Coumadin blocks the liver - Vitamin K dependent factors

XIII to XIII active stabilizer to crosslink fibrin

Reverse with Vitamin K
Novel Oral Anticoagulants - Thrombin and Factor Xa inhibitors

NOACs

Intrinsic Pathway – Inside the cut
Endothelial Injury

Test = aPPT
- XII to XII active
- XI to XI active
- IX to IX active
- VIII to VIII active

Common Pathway
- X to X active with V present
- II Prothrombin to Thrombin
- I Fibrinogen to Fibrin

May replace Coumadin with fewer side effects. Risk of MI may be increased
Monitoring, cost, and reversal are issues

Apixaban
Rivaroxaban
Edoxaban

Dabigatran (DTI)
Platelet Activation Blockers

Von Willibrorn Factor vWF

Factor vWF

Aranchidonic acid

Collagen, Thrombin, TXA2

Cyclooxygenase COX

Aspirin, NSAIDS

Aranchidonic acid

TXA2 and ADP released

Endothelium

Vorapaxar – Zontivity- protease-activated receptor-1 (PAR-1 Thrombin) antagonist

Ticlopidine

Clopidogrel (Plavix)

Prasugrel (Effient)

Ticagrelor (Brilinta)

Increase cAMP inhibits activation

Dipyridamole (Persantine and Aggrenox – ASA combo)

glycoprotein (GP) IIb/IIIa receptor

Abciximab (ReoPro), Tirofiban (Aggrastat), and Eptifibatide (Integrelin).
Anti- Clotting Therapy

- **Antiplatelet to block Platelets** (MI and Stoke prevention)
  - Antiplatelet agents – aspirin or clopidogrel, or aspirin + dipyridamole New agents Prasugrel (Effient), Vorapaxar, and Ticagrelor
  - Dual drug for coronary stents

- **Anticoagulant for Clot prevention**- (DVT, PE, MI, AFib, Genetic....)
  - Heparin (Reversed with Protamine)
  - LMW Heparin and factor Xa blockers
  - Coumadin (Reversed with vitamin K)
  - Thrombin and F10a inhibitors: Oral and IV

- **Thrombolytics - To Bust Clots** (PE, MI, Thrombotic Stroke) tPA -

Emory University Physician Assistant Program
Clot Prevention

- Healthy diet
- Healthy weight
- Exercise
- No Smoking
- Alcohol in moderation
- Aspirin
- Statins
- LMWH for high risk

The **Double Coronary Bypass**.
From Vortex's menu: Beef Topped with two fried eggs, four slices of American cheese, and 5 slices of bacon, with two grilled cheese sandwiches replacing the buns.
Resources

- American Heart Association http://www.americanheart.org
- Thrombophilia Support http://www.fvleiden.org
- National Blood Clot Alliance http://www.stoptheclot.org/
- http://www.outcomes.umassmed.org/dvt/best_practice/
- Coumadin Rap https://www.youtube.com/watch?v=Mfk05IFfW48
- Thrombosis App