Bleeding and Thrombosis

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10-09-2017
Hemostasis

• Correct balance vital to life.

If blood clots in vessel = thrombosis

If blood fails to clot outside blood vessel = bleeding disorder
Key to diagnosis

- History
- History
- History
History 1

- **Bleeding history**
  - Epistaxis
  - Gingival hemorrhage
  - Mucosal Bleeding
  - Heavy Menses
  - Child birth
  - Easy bruisability
  - Bleeding following tooth extractions
  - Hematomas
  - Bleeding following surgery
  - Hemarthrosis

- **Drug history**
  - Aspirin
  - Warfarin
  - NSAIDS
  - B- Lactam antibiotics
  - Other antiplatelet agents
  - Other anticoagulants
  - Corticosteroids
  - Herbal medications
History 2

- Nutrition history
- Vit K deficiency
- Vit C deficiency
- Broad spectrum antibiotics

- Comorbidities
- Liver disease
- Renal disease

- Family history

- Physical Examination
## HEMOSTATIC DEFECTS

<table>
<thead>
<tr>
<th>Bleeding Problem</th>
<th>Platelet Disorder</th>
<th>Coagulation Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petechiae</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Bleeding Sites</td>
<td>Mucous Membrane</td>
<td>Deep Tissue</td>
</tr>
<tr>
<td>Time of onset of bleeding</td>
<td>Immediate</td>
<td>Delayed</td>
</tr>
<tr>
<td>Ecchymoses/Hematomas</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Hereditary

- Deficiency of coagulation factors
  - Hemophilia
  - Fibrinogen deficiency
  - Von Willebrand disease
- Platelet disorders
  - Glanzmann thrombasthenia
  - Bernard-Soulier syndrome
  - Platelet granule disorders
- Fibrinolytic disorders
  - Alpha 2 antiplasmin deficiency
  - PAI 1 deficiency
- Structural disorders
  - Hemorrhagic Telangiectasias
  - Ehler Danlos syndrome
Acquired

- Thrombocytopenias
- Liver disease
- Renal failure
- Vit K deficiency
- Acquired antibodies to coagulation factors
- DIC
- Drugs
- Vascular
Screening Parameters

bleeding disorder possible/likely

CBC/PBF/PFA
PT/APTT
FVIII (males)
FXIII

CBC, complete blood count; PBF, peripheral blood film; PFA, platelet function analyser; PT, prothrombin time; APTT, activated partial thromboplastin time
CBC/PBF:

- Platelet count, size and morphology
- Leukocyte morphology
- Other cytopenias
- Caution
  - Pseudothrombocytopenia
    (use citrate anticoagulated blood)
Platelets

- Responsible for primary haemostasis = bleeding time
- adhere to damaged vessel wall
- adhere to each other
- form a platelet plug
- platelet release reaction
Platelet function analyser (PFA)

- axis
subendothelium-
vWF-platelet
- platelet-platelet
interaction
Coagulation

- Cascade
- Series of inactive components converted to active components
- Prothrombin $\rightarrow$ Thrombin
  \[\text{Fibrinogen} \rightarrow \text{Fibrin}\]
“Classic” (Test Tube) Coagulation Cascade

Intrinsic Pathway

- Contact
  - XI
  - XIIa
  - Xla

Extrinsic Pathway

- Tissue Factor + VII
  - TF-VIIa

Common Pathway

- Prothrombin
  - X
  - Xla
  - VIIIa

- Thrombin
  - XIII
  - XIIIa

Since 1961

- Fibrinogen
- Fibrin (weak)
- Fibrin (strong)
"New" (in vivo) Coagulation Cascade

Tissue Factor + VII

PL

TF-VIIa

IX

IXa

PL Ca++

VIIIa

X

Prothrombin (II)

PL

Va

Xa

XIII

Thrombin (IIa)

Fibrinogen (I)

Fibrin (weak)

XIIIa

Fibrin (strong)
PT versus APTT

- FVIIa/TF
- FXa/FVa
- FIIa
- fibrin
- contact factors
  - FXIa
  - FIXa/FVIIIa
Case 1

- 35 yr woman
- epistaxis and bruising
- Plt: 5,000
- Refractory ITP (fails steroids)
- Splenectomy or Rituximab
ITP

• 1:20,000
• Antibodies against platelets, often against GPIIb/IIIa
• Dx: negative history, r/o all other causes:
  - vitamin B12, folate
  - blood smear (clumping?)
  - TSH (hypo?)
  - HIV
  (- ANA)
  - PT, PTT
  - bone marrow aspirate and biopsy: controversial
ITP - Therapy

- Guided by patient’s bleeding symptoms
- Treat when platelets < 30,000 or when bleeding
- Prednisone or high dose Dexamethasone
- IVIG total dose of 2 g/kg
- Anti-D antibody (WinRho) single dose
- N-plate, Eltrombopag, cyclophosphamide, azathioprine, danazol
Bleeding Caused by PLT Disorders

- Decreased production
  - nutritional
  - B12/folate deficiency
  - congenital
  - Alport's syndrome
  - Fanconi's anemia
  - May-Hegglin anomaly

- sequestration
  - marrow damage
  - Aplastic anemia
  - cytotoxic
  - Malignancy
  - Myelofibrosis

- increased destruction
  - Immune-Med.
    - ITP
  - Drug-induced
    - Systemic-SLE/HIV

- Non-Immune
  - DIC
  - TTP
  - Antiphospholipid

- hemodilution
  - massive transfusion
  - Cardiopulmonary bypass
Case 2

- 30 yr man
- Lifelong epistaxis + easy bruising
- Tooth extraction – bleeding for several days
- Adopted
- Hbg 13.0; MCV 78; PLT 250,000
- PT 12 sec; APTT 40 sec; TCT normal
- Platelet aggregation study normal

A: von Willebrand’s disease
(Glanzmann, mild hemophilia A or B, dysfibrinogenemia)
von Willeband’s disease

- Prevalence: 1% of population
- Bruising – mucosal (nose, gums, menstrual, tonsillectomy, tooth extraction)

- Dx: ↓ von Willebrand factor activity
  ↓ factor VIII
  ↑ bleeding time, PFA100
  von Willebrand factor multimers

  - type 1: quantitative. 90% of cases (all multimers present, but decreased)
  - type 2: qualitative (missing large multimers). 2A, 2B, 2N, platelet type
  - type 3: severe 1 (all multimers missing)

Rx:
  - type 1: DDAVP (0.3 μg/kg) i.v., s.c., or intranasal
  - type 2: Humate P (= factor VIII concentrate with vWf) Cryo
Case 3

• 10 yr boy
• Chronic bruising and hematoma
• PLT: 225,000
• PT 12.5 sec, INR 1.2, APTT 68 sec, APTT mixing study 33 sec
• FVIII: 1%

A: Hemophilia A
Hemophilia

- = bleeding into muscles and joints
- Second most common CONGENITAL bleeding disorder after vWF Deficiency
- Factor VIII concentrates (recombinant or plasma derived)
- Desmopressin for mild case (type A)
- Avoid ASA
- Phys.therapy/ortho care/joint replacement
Case 4

- 32 yr man; hematemesis x 2 h
- Strict vegetarian diet x 4 weeks for weight control and abstained from alcohol for same period of time
- PE: pale, spleen 3 cm enlarged; liver not palpable
- Hbg 8.0; MCV 85; WBC 10; PLT 75,000
- PT 28 sec; APTT 50 sec; fibrinogen 165 mg/dL
- Albumin 2.0; AST 75; ALT 45
- PT 1:1 mix: 12 sec; aPTT 1:1 mix: 30 sec

Q: Dx?  
A: chronic liver disease
Case 5

- 56 yo man
- Severe postoperative bleeding after hernia operation
- Hematothorax after central venous support

A: Acquired hemophilia A caused by high titer FVIII-autoantibodies
Acquired bleeding disorders

• Recent onset, not lifelong and no family history.

• May be generalized bleeding or localized problem.

• Lab approach
  – Check inhibitor (mixing study)
  – Bethesda assay
Case 6

- 61 yr man
- ICU admission for urosepsis and multiple wounds
- Spontaneous bleeding and oozing from IV sites and wounds
- Digital ischemia and gangrene
- WBC 16,300, Hb 9.8, PLT 87,000; PT 18 sec; APTT 46 sec; fibrinogen 123; D- Dimer 5,600.

A: Disseminated intravascular coagulation (DIC)
DIC

• Breakdown of hemostatic balance

• Simultaneous bleeding and microvascular thrombosis

• Life threatening condition

• Causes: 1 sepsis 2 obstetric 3 malignancy
  assume sepsis and treat for this if uncertain
  consider giving plasma and platelets if needed
Take Home message

• Take **HISTROY**
  – Identifying potential hemostatic problems.
  – Eliminate the need for lab screening tests

• Majority of hemorrhagic problems can be identified by simple screening.

• Avoid aspirin and NSAIDs
Thrombosis

- Blood in vessels should be fluid

- Thrombosis is blood coagulation inside a vessel

- Not to be confused with appropriate coagulation when blood escapes a vessel, failure of coagulation in this situation leads to bleeding
Thrombosis

• Thrombosis can occur in
  – arterial circulation: high pressure: platelet rich
  – venous circulation: low pressure fibrin rich
Arterial thrombosis

- Coronary circulation = myocardial infarction
- Cerebral circulation = CVA/ stroke
- Peripheral circulation = peripheral vascular disease: claudication, rest pain, gangrene
Arterial thrombosis

- Risk factors for atherosclerosis:
  - Smoking
  - Hypertension
  - Diabetes
  - Hyperlipidaemia
  - Obesity / sedentary lifestyle
  - Stress / type A personality
Arterial thrombosis

- Myocardial infarction: diagnosis
  History, ECG, cardiac enzymes

- CVA: history and examination, CT scan/
  MRI scan

- Peripheral vascular disease: history and
  examination, ultrasound, angiogram
Rudolf Virchow

- German physician
- Graduated in medicine 1843
- Presented work on thrombosis 1845
- Described leukemia, pulmonary embolism, etc
- 1858 published ‘Cellular Pathology’

Virchow’s Triad

- Stasis of blood flow
- Hypercoagulability
- Endothelial injury
Risk Factors: Virchow’s Triad

• **Stasis**
  - Immobility
  - Congestive failure

• **Injury**
  - Surgery (especially major orthopedic and pelvic)
  - Trauma
  - Presence of venous catheter

• **Thrombophilia**
  - Malignancy
  - Obesity
  - Pregnancy
  - Oral contraceptives
  - Hyperviscosity
  - Nephrotic syndrome
  - Inflammatory bowel disease
  - Antiphospholipid syndrome
  - Inherited thrombophilia
Venous thromboembolism (VTE)

- Deep venous thrombosis
  - Swollen, warm, tender leg

- Pulmonary embolus
  - Pleuritic chest pain, breathlessness, cyanosis, death

“Pulmonary embolus is not a disease. It is a complication of DVT.” Ken Moser MD
<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
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<tbody>
<tr>
<td>Clinical signs or symptoms of deep-vein thrombosis</td>
<td>3.0</td>
</tr>
<tr>
<td>Alternative diagnosis less likely than pulmonary embolism</td>
<td>3.0</td>
</tr>
<tr>
<td>Heart rate &gt;100 beats/min</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization or surgery in the previous 4 wk</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous venous thromboembolism</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1.0</td>
</tr>
<tr>
<td>Active cancer</td>
<td>1.0</td>
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* A total score of 4.0 or lower indicates that pulmonary embolism is unlikely, and a score higher than 4.0 indicates that pulmonary embolism is likely. This table was adapted with permission from Wells et al.⁸
Diagnosis of VTE

• D-Dimer

• DVT: compression ultrasound
  Venography

• Pulmonary embolus: CT scan
  CT pulmonary angiogram
  V/Q (ventilation/perfusion) scan
Screening For A Hypercoaguuble State

- Causes: genetic
  - Factor V Leiden (5%)
  - PT20210A (3%)
  - Antithrombin deficiency
  - Protein C deficiency
  - Protein S deficiency
# Thrombophilia

<table>
<thead>
<tr>
<th></th>
<th>venous</th>
<th>arterial</th>
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<tbody>
<tr>
<td>Protein S deficiency</td>
<td>yes</td>
<td>yes</td>
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<tr>
<td>protein C def.</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>AT III def.</td>
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<td>yes</td>
</tr>
<tr>
<td>factor V Leiden</td>
<td>yes</td>
<td><strong>no</strong></td>
</tr>
<tr>
<td>prothrombin 20210</td>
<td>yes</td>
<td><strong>no</strong></td>
</tr>
<tr>
<td>homocysteinemia</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>MTHFR polymorphism</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>antiphospholipid antibodies</td>
<td>yes</td>
<td>yes</td>
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Treatment of VTE

• Treatment

• Initial
  Low molecular weight heparin, sc weight adjusted dose

• Then
  oral warfarin for 3-6 months
Venous thrombosis

• Prevention

• Thromboprophylaxis
  – Heprain or LMWH
  – TED stockings
  – early mobilization and good hydration
Case 7

- 21 yr woman
- SOB, CP post airline flight
- On OCPs
- Mother: thrombophlebitis x 2 postpartum.
- Sister: sudden death postpartum
- PE: Alert, mildly anxious
- T 101, HR 105, RR 18
- RLE edema and redness
- Lungs clear to auscultation
- D-dimer 2,000

Q: Which diagnostic study should be done next?
Factor V Leiden

- Prevalence: 2 - 15% (western world)
- RR for 1st DVT/PE:
  - heterozygotes: 3 - 8
  - homozygotes: 80
  - heterozygotes + pill: 30-50
- Diagnosis: coagulation test (APC resistance) or genetic test
- Not associated with arterial clots (except for selected patients)
Prothrombin 20210 polymorphism

- Prevalence: 2.3 % (normal population)
- Mild risk factor for 1st DVT/PE: RR 2.8
- Risk for recurrence of DVT/PE: not increased
- Associated with elevated prothrombin levels
- Not associated with arterial thrombosis
Case 8

- 47 yr man
- DVT after 3 h airplane flight
- FH: uncle with DVT after hip arthroplasty, grandfather stroke age 68
- Thrombophilia w/u negative

Q: How long to anticoagulate?

A: 3 months
Treatment

- Enoxaparin 1mg/kg sq every 12 hours for 5 days
- Warfarin started day 1 at 5 mg a day
- CBC on day 3-5 and INR every day if inpatient
- May stop enoxaparin after 5 days if INR > 2.0
- Warfarin continued to keep INR at 2.5 (2.0-3.0 range) for 3 months
# DVT/PE: Anticoagulation – how long?

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<tbody>
<tr>
<td>1.</td>
<td>after transient risk factors</td>
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<tr>
<td>2.</td>
<td>Idiopathic DVT/PE:</td>
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<tr>
<td></td>
<td>- Factor V Leiden, hetero</td>
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<tr>
<td></td>
<td>- Prothrombin 20210 mutation:</td>
</tr>
<tr>
<td></td>
<td>- Protein C or protein S deficiency</td>
</tr>
<tr>
<td></td>
<td>- ATIII deficiency:</td>
</tr>
<tr>
<td></td>
<td>- homozygote factor V Leiden:</td>
</tr>
<tr>
<td></td>
<td>- Factor V Leiden + prothrombin 20210 mutation:</td>
</tr>
<tr>
<td></td>
<td>- APLA syndrome:</td>
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<tr>
<td></td>
<td>- Tumor</td>
</tr>
<tr>
<td>3.</td>
<td>Recurrent DVT/PE</td>
</tr>
</tbody>
</table>
Case 9

27 yr woman
- SLE
- 2 DVTs, now 3rd
- PT 12.5 sce
- APTT 43.3 sec; does not correct with 1:1 mix

Q: Cause of prolonged APTT?

A: Antiphospholipid syndrome
Antiphospholipid antibodies

I) antibody test (ELISA)
   - anticardiolipin
   - anti-β2-glycoprotein I

II) functional test
   - lupus anticoagulant (inhibitor)
Lupus anticoagulant

1) Screening test (aPTT, dRVVT, KCT, Silica clot time) – prolonged

2) Normal plasma mixing study – does not correct

3) Confirm (mix with excess of phospholipids) – corrects
   - hexagonal phospholipid test
   - platelet neutralization procedure (PNP)
Aspirin

• Inhibits cyclo-oxygenase irreversibly
• Act for lifetime of platelet, 7-10 days
• Inhibits thromboxane formation and hence platelet aggregation
• Used in arterial thrombosis, 75-300 mg od

• Clopidogrel similar, but inhibits ADP induced platelet aggregation
Heparin

- Glycoaminoglycan
- Binds to antithrombin and increases its activity
- Indirect thrombin inhibitor

- Monitor with APTT, aim ratio 1.8-2.8
- Given by continuous infusion
Low molecular weight heparin

- Smaller molecule, less variation in dose and renally excreted
- Once daily, weight-adjusted dose given subcutaneously
- Used for treatment and prophylaxis
Warfarin

- Orally active
- Prevents synthesis of active factors II, VII, IX and X
- Antagonist of vitamin K
- Long half life (36 hours)
- Prolongs the prothrombin time (Monitor INR)
- Individual variation in dose
- Usual target range 2-3
Direct Oral Anticoagulants

- Oral anti-IIa and anti-Xa inhibitors
- Dabigatran, Rivaroxaban, Apixaban
- For DVT/ PE and AF
- Equivalent to warfarin INR 2-3, but daily or BID, no monitoring
- Cant assay easily or reverse!
Indication of Inferior vena caval filter placement

- Carefully selected patients at high risk for venous thromboembolism in whom is a contraindication to, or a failure of, anticoagulant therapy
VTE – Prevention Underutilized

- Most common cause of preventable death in hospitalized patients

- AHRQ: VTE prevention is number 1 priority to improve safety in hospitals
VTE Consequences

- Leg swelling, discomfort (DVT)
- Dyspnea, chest pain, hemoptysis, hypoxemia (PE)
- Extended hospital LOS
- Fatal PE (RV failure)
- ≥3 months of anticoagulant treatment
- Postphlebitic syndrome
- Chronic thromboembolic pulmonary HTN (~4%)

VTE Prevention

• Targets one or two legs of Virchow’s triad:
  – Mechanical prophylaxis (stasis)
    • Elastic compression stockings
    • Sequential compression devices
  – Pharmacological prophylaxis (hypercoagulability)
    • Unfractionated heparin
    • Low-molecular-weight heparins
    • Direct anticoagulants
Take Home Message

• Pathogenesis: Virchow’s triad
• Arterial vs Venous Thrombi
• Provoked versus Unprovoked (VTE)
• DVT and PE are the same disease
• Assigning pretest probability for VTE is an essential step in diagnosis
• DVT & PE Diagnosis
• VTE Treatment
• Always consider VTE prophylaxis in inpatients
Questions?

Comments?