Blood Stuff

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Case

• 40 y/o female who takes no medications but does report prolonged bleeding after tooth extraction and vaginal delivery presents for pre-operative evaluation prior to colectomy. PT/aPTT and platelet count are normal. What is the most likely diagnosis?
Hemostasis

- Vasospasm
- Platelet Plug (forms scaffold for fibrin plug)
  1.) Adherence (collagen, vWF, fibrinogen)
  2.) Activation- Gp IIb/IIIa receptor, helps to link platelets via fibrinogen
  3.) Granule release- APD, serotonin, PDGF, thromboxane A2
- Fibrin Plug
  - Accelerated on surface of platelets
Coagulation

- Delicate balance between coagulation, fibrinolysis, anticoagulation
- Pathway
  - IX $\rightarrow$ IXa (TF-VIIa)
  - X $\rightarrow$ Xa (IXa + VIIIa)
  - Prothrombin (II) $\rightarrow$ Thrombin (IIa) (Xa with Va)
  - Fibrinogen $\rightarrow$ Fibrin (thrombin)
  - X11a usually not involved in thrombin formation unless activated during sepsis, trauma, CPB
  - Each step regulated (will not go into today)
  - Factor IX is link between pathways
Pre-op Eval

- Personal or family hx of bleeding (during deliveries, surgery, tooth extractions, etc.)
- ASA, Plavix, NSAIDS, Vit E, herbs, etc.
- aPTT (most common)—will not pick up very rare VII deficiency
- PT—better predictor of bleeding at surgery if abnormal
- Bleeding time—not common
- CBC
Pre-Op Eval

• aPTT (intrinsic and common)
  – XII, PK, HK, XI, IX, VIII + X, V, Thrombin, Fibrinogen, Fibrin

• PT/INR (extrinsic and common)
  – VII + X, V, Thrombin, Fibrinogen, Fibrin
Clotting Factors

- Shortest t1/2
  - VII
- VIII NOT produced in liver (in endothelium)
- Lose V, VIII activity in PRBCs, not FFP
- FFP lasts 6 hours, immediate onset
- Vit K take about 6 hours to work
Pre-Op Eval

• Abnormal aPTT
  – If bleeding: VIII, IX, XI (VIII 9x more common, males)
  – Can have spontaneous development of VIII inhibitors (mix plasma with normal plasma, if corrects suggests deficiency, heparin affect excluded by adding heparin)
  – No bleeding: lupus anticoagulant, XII, PK, HK

• Abnormal PT/INR
  – VII
  – Mild defects in fibrinogen, II, X, V
Pre-Op Eval

• Abnormal aPTT/PT
  – Anticoagulants, DIC, liver disease, massive transfusion, vit. K deficiency

• Long bleeding time
  – Normal platelets: VWD, medications
  – Low platelets (<100,000)

• Platelet dysfunction usually causes mucosal bleeding, whereas coagulation abnormalities cause bleeding into joints
ACT?

• Activated clotting time
• Assess heparin anticoagulation
• Blood added to activator which stimulates intrinsic pathway, measures time for clot formation
• Device has two channels, one of which has heparinase
• Rapid
Pre-op Eval

• Bleeding disorder, normal PTT/PT, no meds
  – vWD, platelet disorders
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Platelet Count</th>
<th>Bleeding Time</th>
<th>PT/INR</th>
<th>aPTT</th>
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</table>
| vWD              | ******         | ↑             | ****** | 3/1/
| ITP              | ↓              | ↑             | ****** |       |
| HIT              | ↓              | ↑             | ****** |       |
| Hemophilia A/B   | ******         | ******        | ****** | ↑     |
| DIC              | ↓              | ↑             | ↑      | ↑     |
vWD

- Most common congenital bleeding disorder
  - 1% of population
- vWF links collagen fibrils and platelets and carries VIII
- Type I (AD), mild to mod quantitative deficiency
  - Can use DDAVP
- Type II, functional deficit
- Type III (AR), essentially absent
  - Also have very low VIII so may have bleeding similar to hemophiliacs
  - Need purified vWF or VIII concentrates
Acquired Surgical Bleeding

- Heparin
- LMWH
- Warfarin
- DTI
- ASA
- Plavix
- DIC, liver disease, massive transfusion, vit K deficiency
- Hespan (do not use more than 1-1.5 L a day)
Medications

• ASA/NSAIDS- increased bleeding time, stop 1 week prior to surgery
• Thienopyridine (plavix)- increased bleeding time, stop 5 days before surgery
• Abciximab, no tests affected
• Heparin, increased aPTT
• LMWH- can measure factor X activity
• Coumadin- PT/INR
• DTI- PT/PTT
Vitamin K Deficiency

• Green leafy vegetables, synthesized by intestinal bacteria
  – Body has 1 month stores
  – Classic patient on TPN, old, on abx, critically ill
  – Malnutrition (alcoholics)
  – Gastric bypass/malabsorption
Massive Transfusion

• 16% of blood volume of each PRBC U is citrate containing anticoagulant
  – Chelates ca++, mg++, and zinc so they cannot participate in coag
  – If replace 1.5 x patient’s blood volume in 24 hour period, massive amounts anti-coag (i.e. 70kg man, 7 L PRBCs, 1176 ml anticoagulant)+ dilutional effect
  – Give 1 U FFP for 4-6 PRBCs + 1 amp calcium
Heparin/Coumadin

- Binds to anti-thrombin III, inhibits IX, X, XI, II
- T1/2 1-2 hours, normalization of coagulation in 4 hours
  - Hold heparin for 4 hours prior to surgery
  - Only need PRBCs, FFP, platelets during time patient at risk if bleeding occurs on heparin
  - Rarely need protamine sulfate (can cause hypotension)
- Coumadin
  - Variable half lives of factors (4 hours-5 days)
  - 5 days to achieve anti-coag effect
  - 5 days to hold prior to surgery
  - Can bridge with heparin (4 hours, LMWH 12-24 hours)
Coumadin

- **Emergent Surgery**
  - Fully anticoagulated pt has about 10-15% normal activity of factors II, VII, IX, X
  - Need at least 50% activity to clot normally, thus would need 1.5 L FFP in short period time
  - Can give FFP, vitamin K, rFVIIa, whole body plasmaphoresis
    - rFVIIa 20-40 mcg/kg with 2 FFP, 90 if head bleed
    - rFVIIa directly activates IX and X
LMWH

• IIa and Xa, mostly Xa
• At therapeutic doses may only slightly prolong PT/PTT, thus cannot use these to r/o patient on these meds
• No immediate reversal agent, can try rFVIIa
• Takes 24 hours for complete elimination due to accumulation, with 2-4.5 hour t1/2
• Can accumulate in renal failure, obese patients (adipose tissues)
DTIs

• Argatroban
  – 0.5→2 hour elimination, only need short period of support for bleeding
ASA/PLAVIX

• ASA- Cox 1,2 inhibitor
  – Single 80 mg dose interferes with ALL platelets present at time drug given
  – Function will not be normal until ½ platelet pool recycled (10-14 days)

• Plavix- ADP receptor antagonist

• Vitamin E

• SSRIs

• Glycoprotein IIb/IIIa inhibitors
Platelet disorders

• Quantitative
  – Production- drugs, leukemia, aplastic anemia
  – Destruction- ITP, TTP-HUS, HIT, DIC
  – Sequestration- Splenomegaly, liver disease, lympho or myeloproliferative diseases

• Qualitative
  – Adhesion- vWD, uremia
  – Activation- antiplatelet agents
  – Granule release
ITP

• Platelet destruction

• Acute
  – Children, usually follows viral illness
  – Antibodies against viral antigens attack platelets
  – Usually resolves without treatment

• Chronic
  – Adult, autoimmune in etiology
  – Steroid of IVIG
  – Persistent bleeding or refractory to meds= splenectomy
HIT

• 20% pts have decreased platelets with heparin
• Antibodies recognize heparin bound to PF4 = aggregation/activation of platelets, platelets cleared by reticuloendothelial system (thrombocytopenia) and thrombosis (activation)
• Usually occurs 4-10 days after starting heparin
• Check HIT AB
• Need anticoagulation if evidence of thrombosis
Hypercoag

- Factor V Leiden (activated protein C resistance)
- Elevated homocysteine
- Prothrombin activating mutation
- Protein C/S deficiency
- Antithrombin deficiency
- HITT, P. vera, TTP, HUS, DIC, lupus anticoagulant
Blood Transfusion

• Whole blood
  – RBCs
  – Plasma
  – Platelets
  – Clotting Factors
  – WBCs
RBCs

- 200 ml red cells, 50 ml plasma, PCV 35-55%, store for 35-42 days
- Each unit raises PCV by 2 to 4%
- Lose factors V, VIII
- Can't be infused as rapidly as whole blood (viscosity)
- Usually indicated in Hb <7, usually not if >10
- No scientific basis for triggers
- Give based on symptoms, vital signs, tissue oxygenation, active cardiac disease, active bleeding
Leukoreduced RBCs

- Helps prevent immunomodulation, CMV/? Herpes transmission, febrile reactions (non-hemolytic), does NOT prevent GVHD
- 50-80% hematocrit
- Most blood products leukoreduced but not mandated by FDA
Gamma Irradiated Leukoreduced PRBCs

- Immunocompromised patients at risk for GVHD (90% mortality)
- Cross links DNA of donor T-cells
- Indicated for LBW infants, allogenic stem cell tx, congenital immunodeficiency, lymphoma, leukemia, ppl receiving HLA matched products
Washed RBCs

• Removes plasma, plasma proteins
  – To reduce allergic reactions
  – Usually does not prevent reactions in patients with IgA deficiency
  – Do not protect against GVHD
  – Usually not sufficiently leukoreduced
Platelets

- Each unit platelets raises count by 5-10K
- Pooled platelets “random donor”
- Apheresis platelets “single donor”
  - Apheresis platelets have more platelets
  - Takes 5-8 pooled platelet concentrates to get same amount as apheresis, thus exposes pt to 5-8 donors
- Non bleeding patients can tolerate 5,000-10,000 counts
- Recent studies show trigger should be 10,000 if stable, no active bleeding
- 50,000 if invasive procedure
- 100,000 for neurosurgery
Platelets

- Do not transfuse platelets in TTP and HIT → increased thrombosis
- Give platelets with DDAVP if uremic, can also use conjugated estrogens
FFP

• Acellular portion of blood
  – Proteins, colloids, nutrients, crystalloids, hormones, vitamins. Lots of albumin
  – Fibrinogen, XIII, VWF, VIII, II, VII, XI, X
  – Should not be used solely to expand volume or replace albumin
• Each unit raises factor levels by about 3%
• Dose of 10-15 ml/kg should result in normal levels for hemostasis
• Can be source of ATIII for heparin resistance
Cryoprecipitate

- VIII, VWF, fibrinogen, XIII
- Usually used to replace fibrinogen
Massive Transfusion

- Various definitions:
  - Replace entire volume in 24 hours
  - 50% volume in 3 hours
  - 10 U whole blood, 20 U PRBCs in 24 hours
  - 35% of original platelets and factors remain after 1 volume replaced

- Can get dilutional thrombocytopenia, coagulopathy. Monitor platelets, PT/PTT, fibrinogen
  - Keep platelets >50-60K, fibrinogen >100

- Hypocalcemia, hypomagnesaemia, depressed myocardial function and arrhythmias, hypothermia, hyperkalemia if prolonged storage
LABS

• Type and Screen
  – Slow
  – ABO and Rh
  – Also tested for alloantibodies (transfusions, previous pregnancies, etc.)
  – 30-45 minutes for test, 15-30 minutes to get crossed blood, longer to get blood if antibodies found
LABS

• Type and cross
  – Same as type and screen, but blood is tested against pt’s serum for compatibility

• Trauma blood is O, Rh + if males, postmenopausal females, O, Rh neg in females

• Platelets should, but do not need to be matched, if not use small volume. May contribute to platelet refractory state. Give rhogam.

• No compatibility testing for plasma, should be compatible with blood type. Rh compatibility not as important. Can give AB.

• For cryo ABO rec., but do not need ABO, Rh comp.
Complications

• AHTR
  – Fevers, chills, anxiety, shock, DIC, dyspnea, chest/back/flank pain, hemoglobinuria
  – CBC, coags, UA, Direct coombs, free plasma hb
  – Stop transfusion, NS, vasopressors, can give lasix, treat DIC, steroids, monitor cr
Complications

• Delayed hemolysis
  – 3-14 days post transfusion
  – Unexplained fevers
  – Caused by sensitization to minor antigens
Complications

• Febrile, non-hemolytic
  – Fevers, chills, rarely hypotension
  – Stop, give tylenol, order leukocyte reduced product
Complications

• Allergic
  – Urticaria, hives, rash, hypotension, shock
  – Antibodies to plasma proteins
  – Stop, give benadryl, steroids/epi if severe, pepcid, may restart if stabilizes
  – May need to use washed products
  – With complications always keep in mind that each unit is different
Complications

• TRALI
  – Thought to result from donor abs that attack recipient WBCs in pulm vasc.
  – Dyspnea, hypotension, bilat. Pulm. Infiltrates on CXR
  – Up to 4 hours post transfusion
  – Usually resolve in 4 days
  – Leading cause of transfusion related mortality
  – Ventilation and oxygen
Complications

• Transfusion related immunomodulation (TRIM)
  – Leukocytes = immunosuppression, can increase infectious complications post-op
Complications

• Infectious
  – All blood tested for syphilis, HbsAg, HIV1-2 antibodies, p24 antigen, HTLV I/II, Hep B core AB, HCV
  – Platelets have greater risk of bacterial contamination
  – Albumin heat treated, no risk of infection
References

- Sidebotham D. Cardiothoracic Critical Care. 2007.