Perioperative Medicine Summit

Evidence Based Perioperative Medical Care

Anemia & Bleeding Disorders

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Potential Topics

- Basic evaluation for bleeding diatheses
- Basic anemia management/blood conservation
- Jehovah's witnesses
- Von Willebrand disease
- Hemophilia and Other Rare Bleeding Disorders
- Sickle cell disease
- Hemolytic anemia
- Thrombocytopenia
- Others?

Screening for Bleeding Disorders

- Meta-analyses have clearly demonstrated the limited clinical utility of routine coagulation studies prior to surgery
  - Low yield
  - Poor correlation to bleeding outcomes
- Thorough history (including surgical & family history of bleeding) and exam are sufficient for screening of most patients
  - Exception: surgeries where even small amount of bleeding would be catastrophic (eg, intracranial)

Smetana GW, Macpherson DS. *Med Clin N Am*. 2003;87:7-40.
Apfelbaum JA et al. *Anesthesiology*. 2012;116(3):522-38.

Heritable Bleeding Disorders

- Some bleeding disorders have great phenotypic and heritability variance
  - Some heterozygotes bleed worse than those homozygous for an abnormal gene (factor XI deficiency)
  - De novo mutations are not uncommon (vWD)
  - Different mutations cause different heritability – autosomal dominant vs recessive (vWD)
- Some bleeding disorders only manifest with a surgical challenge
  - If family history is suspicious, don't neglect it because the patient has never had spontaneous bleeding

Heritable Bleeding Disorders

- Most common in North America is von Willebrand disease
- Most common in patients of Ashkenazi Jewish descent is factor XI deficiency (as much as 9% of that population)

Shpilberg O et al. *Blood*. 1995;85(2):429.

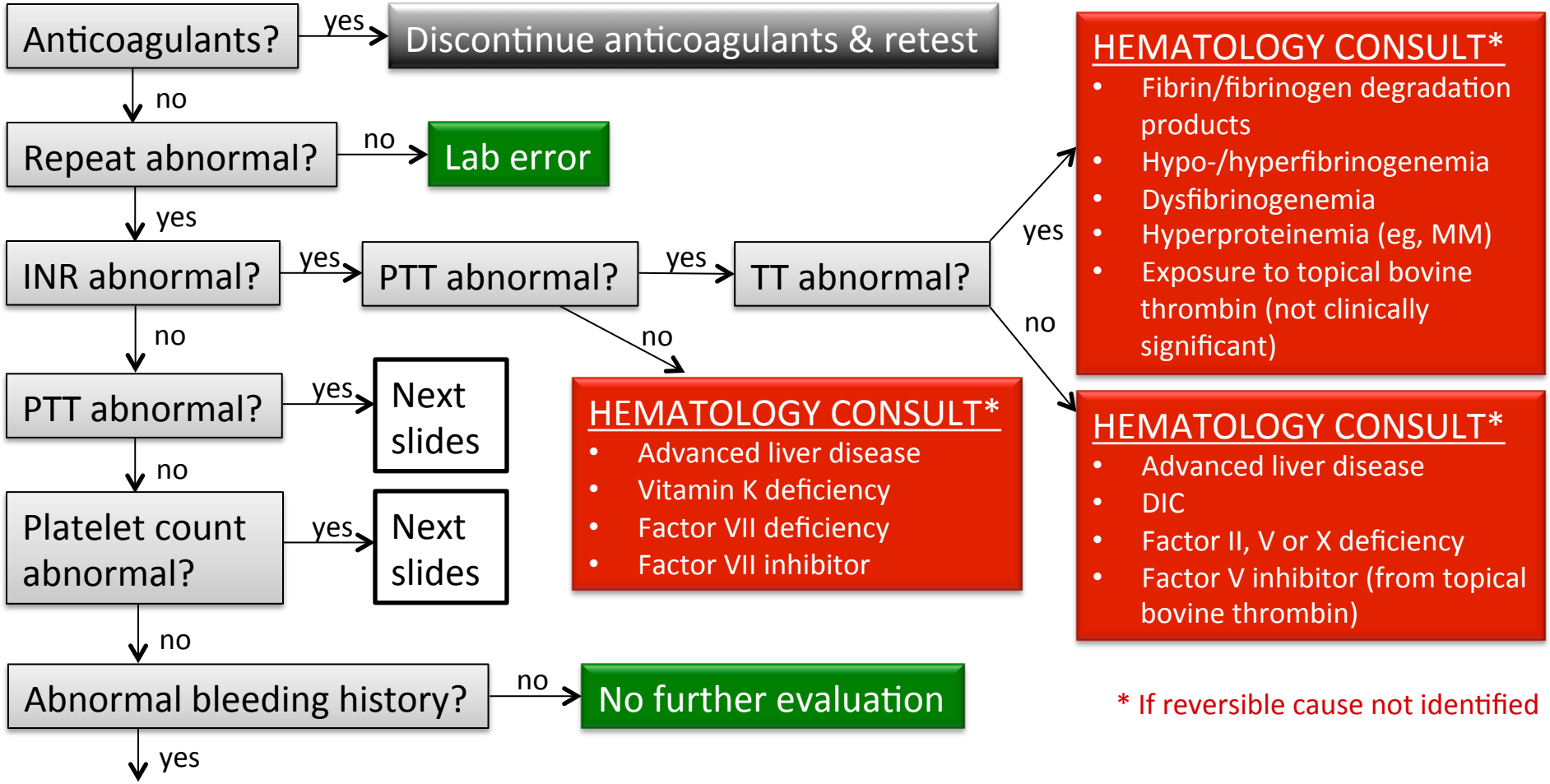
History of Bleeding

Requires laboratory evaluation which should begin with:

- PT/INR
- PTT
- Platelet count
- *Platelet function screening assay [eg, PFA-100®]?*
  - Some authors recommend this for screening even in asymptomatic patients if they have no prior history of surgery and are having neurosurgery, but one prospective study showed no change in outcomes
  - May also obtain this as part of initial evaluation if strong suspicion of von Willebrand disease (vWD) or other platelet function disorder

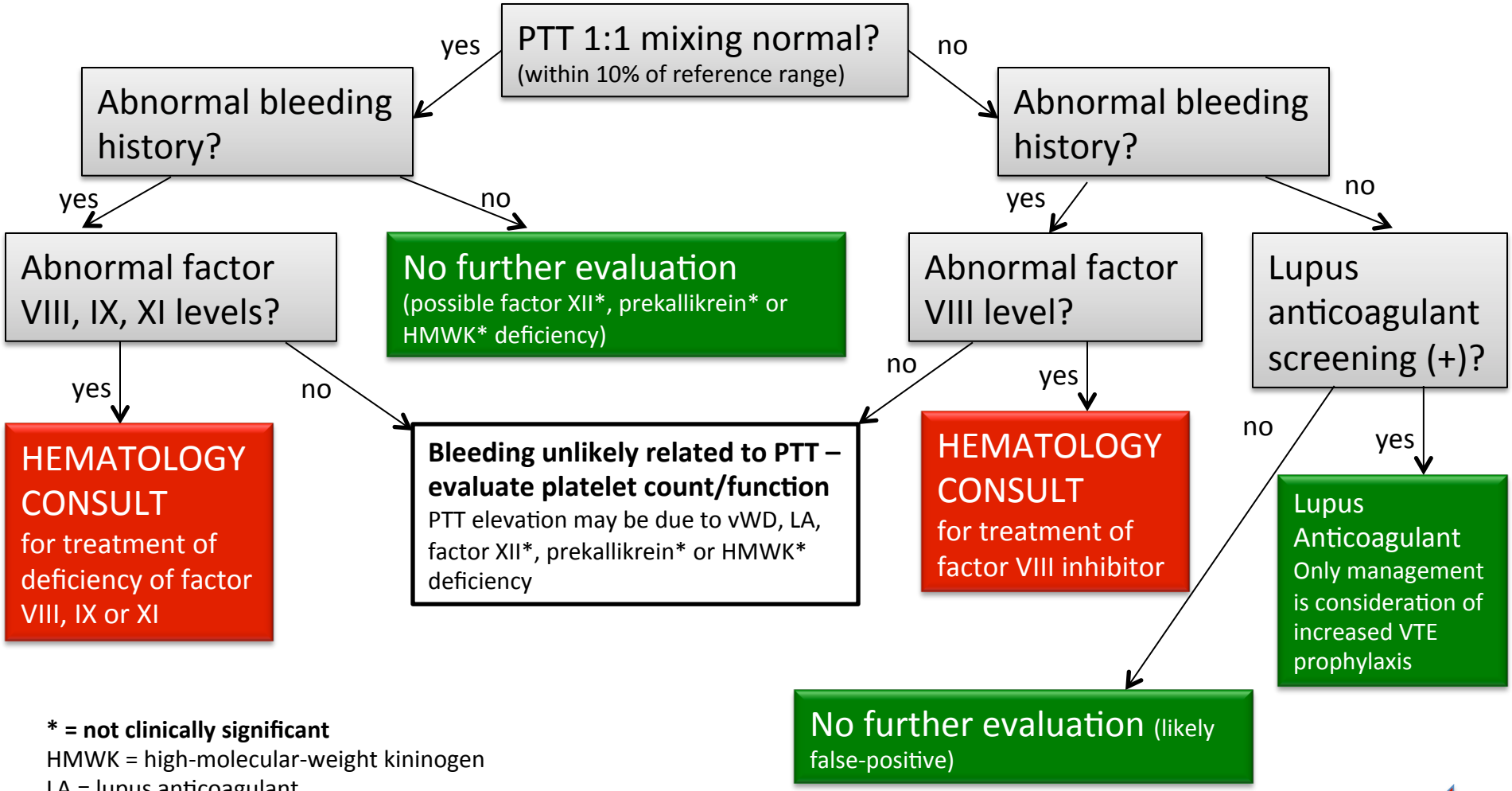
Chee YL et al. *Br J Haematol*. 2008;140:496-504.
Karger R et al. *ISRN Hematology*. 2012. Article ID 839242.

Abnormal Coagulation Evaluation



* If reversible cause not identified

Isolated PTT Elevation



*** = not clinically significant**
HMWK = high-molecular-weight kininogen
LA = lupus anticoagulant
vWD = von Willebrand disease

Adapted from Tcherniantchouk O et al. *Am J Hematol*. 2013;88:82–5.

Perioperative Anemia Treatment

- Correct nutritional deficiencies
- Optimize contributing/complicating chronic illnesses (eg, CKD, cardiovascular disease)
- Transfusion of red blood cells (RBCs)
- Erythropoiesis stimulating agents (ESAs)
- Empiric iron therapy

"Since no intervention is without risk, clinicians should avoid using these findings reported by Wu et al to justify interventions—use of transfusion, erythropoietic agents, iron supplementation—outside the research setting."
- Farjah F and Flum DR. *JAMA.* 2007;297(22):2525-2526.

Transfusion Risks

- Transfusion reactions
  - Transfusion-related acute lung injury (TRALI)
  - Acute hemolytic transfusion reaction (AHTR)
- Increased risk of infection (transfusion-related immunomodulation [TRIM])
- Volume overload (transfusion-associated circulatory overload [TACO])
- Increased allogeneic exposure
  - More difficulty with subsequent transfusion/ transplantation

Transfusion – Friend or Foe?

- Mortality & morbidity the same or better for restrictive (Hgb<8) vs liberal (Hgb<10) transfusion strategy[1]
  - TRICC trial – critical care (+ subanalysis of patients with CV disease)
  - FOCUS trial – hip fracture patients with CV disease or risk factors
  - TRACS trial – cardiac surgery patients
  - Orthopedic surgery[2]
- In CABG patients, predischarge nadir hemoglobin not associated with 30-day readmissions[3]

[1] Carson JL et al. Cochrane Database Syst Rev. 2012;4:CD002042.
[2] So-Osman C et al. *Blood Transfus. 2013;11(2):289-95.*
[3] Shehata N et al. *Transfusion.* 2013;53(8):1688-97.

RBC Transfusion Guidelines

- **American Association of Blood Banks[1]**
  - Hgb<7-8 for stable, asymptomatic patients
  - Hgb<8 for patients with underlying CV disease
    - Corroborated by recent study of postop MI patients[2]
- **American Society of Anesthesiology[3]**
  - Hgb<6 for anyone
  - Hgb>10 for noone
  - Hgb 6-10 – depends

[1] Carson JL et al. Ann Intern Med. 2012;157(1):49-58.
[2] Hollis RH et al. *JAMA Surg.* 2016;151(2):139-145.
[3] *Anesthesiology*. 2006;105(1):198-208.

Preventing Transfusion

- **Minimizing phlebotomy**
- **Iron**
  - No clear benefit alone unless patient is iron deficient or receiving ESA
- **Erythropoiesis stimulating agents (ESAs)[2]**
  - Reduce postoperative allogeneic transfusion[1]
  - Increase risk of venous thromboembolism (VTE)
  - FDA-approved for noncardiac, nonvascular surgery in patients with Hgb 10-13 g/dl but with warning to consider VTE prophylaxis
  - Concomitant iron therapy required

[1] Feagan BG et al. Ann Intern Med. 2000;133:845–54.
[2] Goodnough LJ et al. *Br J Anaesth*. 2011;106(1):13-22.

Preventing Transfusion

- **Preoperative Autologous Donation**
  - Combined with ESAs preoperatively reduces postoperative allogeneic transfusion
  - Results in large waste of autologous blood & increased preoperative anemia
  - Limited utility – large blood loss surgery with long (>3-4 weeks) lead-time in fairly healthy patient with high-likelihood for not tolerating or not accepting allogeneic blood
- **Cell Salvage**
  - Relatively limited utility – large blood loss in noncontaminated surgical field

Kumar A. *Cleve Clin J Med*. 2009;76(s4):112-8.

Jehovah's Witnesses

76 y/o WM with a PMH of CAD, HTN, DM2, HL, CVA, CKD3 & COPD who presents for evaluation before undergoing left reverse total shoulder replacement. He reports no symptoms other than his left shoulder pain and has had no recent hospitalizations or ER visits.

Early in the visit, the patient's wife informs you that you should be aware that the patient is a Jehovah's witness.

Now what do you do?

Lin ES et al. *Ochsner J*. 2012;12(1): 61–69.

Medical Care for Jehovah's Witnesses

- Obtain their specific advance directives
- Opposed to direct transfusion of blood products
  - Albumin, recombinant human erythropoietin (rhEPO), immunoglobulins, and factor concentrates are left to individuals to decide
- Do NOT assume the patient will refuse transfusion – always ask
  - Some may not be strict adherents to the religion
- Ask whether they will accept specific blood conservation methods

Lin ES et al. *Ochsner J*. 2012;12(1): 61–69.

Jehovah's Witness & ESAs

- Erythropoiesis-stimulating agents (ESAs) can be used to treat postoperative anemia
- Some Witnesses will not accept any blood product
- In the US, all commercially-available erythropoietin (EPO) is packaged in a small amount of human albumin (darbopoietin does come in an albumin-free version – must be specifically ordered)
- In other countries, albumin-free versions of EPO are available

Lin ES et al. *Ochsner J*. 2012;12(1): 61–69.

Other Blood Conservation for Jehovah's Witness Patients

- Cell salvage & acute normovolemic hemodilution
  - Most witnesses OK with this provided a completely closed system is used (this requires a device that maintains a closed circuit – not all RBC salvage systems do this)
- Preop autologous donation
  - Not OK because blood is not kept in continuous circuit with patient

Lin ES et al. *Ochsner J*. 2012;12(1): 61–69.

Other Blood Conservation for Jehovah's Witness Patients

- Deliberate intraop hypotension and hypothermia
  - Has shown promise but need to assure patient doesn't have other end-organ disease that would make this contraindicated
- Minimize phlebotomy
- Cautious use of antithrombotic agents

Lin ES et al. *Ochsner J*. 2012;12(1): 61–69.

Von Willebrand Disease

A 47 y/o WM presents for evaluation before undergoing laparoscopic hiatal hernia repair. At the start of your visit he reports that he has von Willebrand disease.

What would you do for further risk assessment and management from this point forward?

Treatment of Specific Bleeding Disorders

- Call hematology - you probably don't know what you're doing
- Patients may have incorrect information about what their actual bleeding disorder is
- Even if you are confident in the diagnosis, the management is individualized based on a patient's previous history
- **Need a specific plan from hematology covering the entire perioperative period**

Treatment: Von Willebrand Disease

- **DDAVP may be used for minor procedures in type 1 vWD**
  - *Based on prior response to test dose*
  - 0.3 mcg/kg IV or 300 mcg intranasally 30 min before procedure
  - May redose q12-24 hrs depending on bleeding risk
  - Tachyphylaxis occurs after >3 doses
  - **Decrease water intake and monitor for hyponatremia and volume overload**
- **Von Willebrand factor (vWF) concentrates for all others**
  - Most products are "impure" factor VIII concentrates that contain vWF in all multimers (e.g., Humate-P ©)
  - Dose: 30-60 units/kg IV 1 hr prior to surgery and repeated q12-24 hrs to maintain target vWF level
    - Minor surgery: vWF level >30 units/dl for 3-5 days postop
    - Major surgery: vWF level >50 units/dl for 7-14 days postop

Mannucci PM. *N Engl J Med*. 2004; 351:683-94.

Hemophilia

A 52 y/o WM is referred to you for preoperative evaluation before undergoing right total knee arthroplasty. He has a history of hemophilia A, but no recent problems.

What risk assessment and management would you perform for this patient?

Treatment of Specific Bleeding Disorders

- Call hematology - you probably don't know what you're doing
- Patients may have incorrect information about what their actual bleeding disorder is
- Even if you are confident in the diagnosis, the management is individualized based on a patient's previous history
- **Need a specific plan from hematology covering the entire perioperative period**

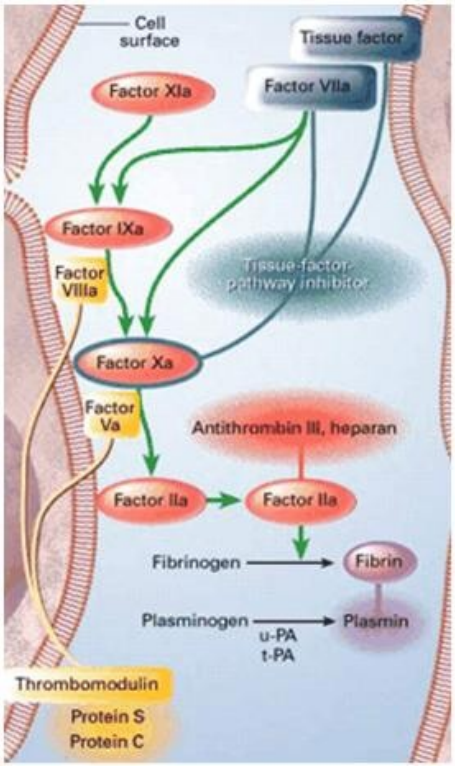
Treatment: Hemophilia A & B

- Dose factor VIII or IX as needed to maintain factor activity level 75-100% for 3 days after surgery and then 50% until healing complete
  - Need info on patient's factor VIII/IX response (what dose achieved 75-100% level)
  - Requires dosing/factor level measurement 1 hour prior to surgery and q8-12 hours initially
  - **Since therapy needed for prolonged period of time, consider placement of PICC**
- Recombinant Factor IX Fc Fusion Protein (ALPROLIX®) now available for hemophilia B – has longer half-life
- **Usually require postop admission, even for minor surgeries**

Kulkarni R. *Haemophilia*. 2013;19(1):2-10.

Treatment: Rarest of the Rare

- Factor XIII deficiency
  - Cryoprecipitate or factor XIII concentrates
- Other factor deficiencies
  - FFP at dose sufficient to achieve 50% of factor activity level
  - Redosing dependent on half-life of factor
- Factor inhibitors: recombinant factor VIIa
- Fibrinogen disorders: cryoprecipitate
- Other platelet function disorders: platelet transfusion (need HPA 1a-negative units for Glanzmann's thrombasthenia)



Coagulation Studies and Bleeding Risk

- INR and PTT abnormalities do not correlate well with bleeding risk[1]
- Patients with INR as high as 1.9 may have sufficient coagulation factors for effective hemostasis[2]
- No increased bleeding complications for percutaneous procedures performed with INR elevations as high as 2.7[3,4]

[1] Segal JB et al. *Transfusion*. 2005;45(9):1413-25.
[2] Deitcher SR. *Lancet*. 2002;359:47-8.
[3] McVay PA & Toy PT. *Transfusion*. 1991;31(2):164-71.
[4] Fisher NC & Mutimer DJ. *Intensive Care Med*. 1999;25(5):481-5.

FFP for Elevated INR

- FFP has an INR of 1.1-1.3
- In patients with mild elevations (PT 13-17 or INR≤1.7), significant change in INR is unlikely[1,2]
  - <1% normalize
  - Only 15% with >50% change in INR
- No data demonstrating improvement in bleeding complications with FFP use[3]
  - RCT of ICU patients with INR 1.5-3.0 needing trach, chest tube, CVAD or superficial abscess drainage showed no benefit from FFP[4]

[1] Abdel-Wahab OI et al. *Transfusion*. 2006;46(8):1279-85.
[2] Holland LL & Brooks JP. *Am J Clin Pathol*. 2006;126(1):133-9.
[3] Yang L et al. *Transfusion*. 2012;52(8):1673-86.
[4] Müller MC et al. *Transfusion*. 2015;55(1):26-35.

FFP Risks

- Same as for RBC transfusion except:
  - No hemolytic reactions
  - Thrombosis
  - 3-fold increase in risk of TRALI[1]
- Meta-analysis suggested increased mortality (not statistically significant)[1]

[1] Murad MH et al. *Transfusion*. 2010;50(6):1370-83.

Perioperative FFP Transfusion Guidelines

- **American Association of Blood Banks[1]**
  - Trauma patients with massive transfusion
  - Known specific, severe coagulation factor deficiencies
  - *Insufficient evidence to recommend for or against in patients with elevated INR (related to warfarin or not)*
- **American Society of Anesthesiology[2]**
  - **Excessive microvascular bleeding with PT >1.5x normal, INR >2, or aPTT >2x normal**
  - Excessive microvascular bleeding secondary to coagulation factor deficiency in patients transfused with more than one blood volume (approximately 70 ml/kg) and PT/INR & aPTT cannot be obtained in a timely fashion
  - Urgent reversal of warfarin therapy
  - Known coagulation factor deficiencies for which specific concentrates are unavailable
  - Heparin resistance (antithrombin III deficiency) in a patient requiring heparin

[1] Roback JD et al. *Transfusion*. 2010;50(6):1227-39.
[2] *Anesthesiology*. 2006;105(1):198-208.

Practical Approach

Collaborate with surgery & anesthesiology

- Bleeding risks with planned procedures
- Potential to handle bleeding complications expectantly (ie, give FFP only if bleeding problems occur)
- Degree of INR elevation & potential (or lack thereof) for FFP to reduce INR
- Risks of short-term delay for procedure to provide vitamin K and time for “gentler” reversal

Practical Approach

- Infusion should be started *on call* to the OR
  - Half-life of factor VII is 4 hours
- Starting dose of 10 cc/kg is usually sufficient
  - Each unit of FFP usually has 200-300 cc
- Check PT/INR/aPTT 20-30 minutes after completing transfusion

Stack G et al. Practical Guide to Transfusion Medicine, 2nd ed. AABB, 2007.

Thrombocytopenia

A 68 y/o AAF with a past medical history of MDS presents for evaluation before undergoing partial colectomy for early-stage colon cancer. She has been feeling well with no recent symptoms. Her exam is unremarkable.

Labs: WBC 3.9 (ANC 1400), Hgb 8.6, Plts 68k

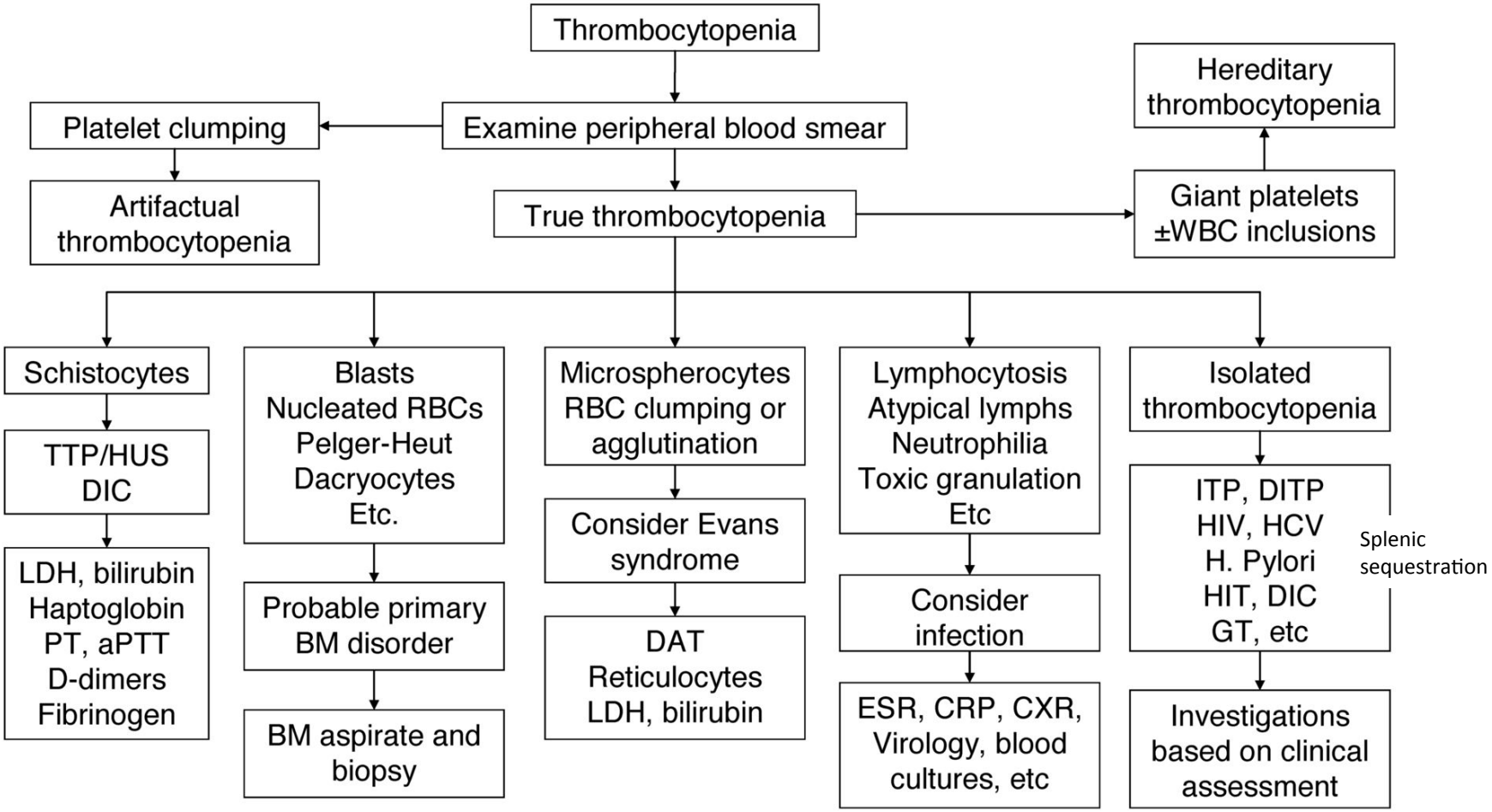
What risk management would you do?

Thrombocytopenia

- Relatively common finding in outpatient setting
- Most common causes in patients without significant organ dysfunction (eg, liver) or other hematologic abnormalities are:
  - Primary immune thrombocytopenia (ITP)
  - Drug-induced thrombocytopenia (DITP)
  - Gestational thrombocytopenia (GT)
- Risk of bleeding related to level:
  - <20k → excessive bleeding with low-risk surgery (CVAD placement)
  - <50k → excessive bleeding with most surgery or LP
  - <100k → bleeding risk with cardiac or neurosurgery

Kaufman RM et al. Platelet transfusion: a clinical practice guideline from the AABB. *Ann Intern Med.* 2015;162(3):205-13.

Algorithm for workup of thrombocytopenia based on observation of the peripheral blood film.



Stasi R. 2012 ASH Education Book. 1:191-7.

Mild Preoperative Thrombocytopenia

- Prognosis in nonoperative setting very good if platelet count within 100-150k over 6 month span
- For cardiac surgery patients, even mild thrombocytopenia carries increased risk of mortality

Rodeghiero F et al. *Blood*. 2009;113(11):2386–93.
Glance LG et al. *Anesthesiology*. 2014;120(1):62-75.

Platelet Transfusion

- Pooled platelets (“6-packs”) vs single-donor
  - Use single-donor for transplant candidates or severely immunosuppressed
- 1 unit raises platelet count ~20-30k
- Transfused platelet lifespan at least 3 days

Treatment: ITP

- Non-urgent surgery:
  - Prednisone 1 mg/kg/d PO for 1 week before surgery
- Urgent surgery:
  - IVIG 0.5-1 g/kg
- Emergency surgery or bleeding complications:
  - Platelet transfusion plus methylprednisolone 1 g IV

ASH 2011 Clinical Practice Guideline on the Evaluation and Management of Immune Thrombocytopenia (ITP)

Preoperative Thrombocytopenia

BOTTOM LINE

- Review previous labs and peripheral smear
- Would not delay surgery if all of the following are true:
  - Platelet count >100k & not significantly decreased from previous value
  - Noncardiac surgery
  - No liver disease, heparin exposure or HIV on history or exam
  - No history of bleeding
  - Peripheral smear is otherwise normal

Sickle Cell & Other Hemoglobinopathies

28 y/o AAF with sickle cell disease presents for evaluation before left total hip arthroplasty for AVN. She has acute pain crises 3-4 times per year but has not had one in 2 months. She had acute chest syndrome last year. She has a poor functional capacity related to hip pain, but reports no current symptoms other than this. Her exam is normal except for her arthritis.

Labs: Hgb 9.2 (baseline 9), otherwise normal

What unique risk assessment and risk modification would you do for this patient?

Sickle Cell & Other Hemoglobinopathies

- Collaborate with sickle cell expert[1]
- Assure that screening/health maintenance are up-to-date:
  - Vaccinations[1]
  - Echocardiogram to screen for pulmonary hypertension[2]
- Adequate pain control & avoid hypoxia
- Adequate hydration (hypotonic IV fluids if euvolemic)
- Continue hydroxyurea, if patient already on this

[1] Yawn BP et al. *JAMA*. 2014;312(10):1033-1048.
[2] Gladwin MT, Sacheva V. *J Am Coll Cardiol*. 2012;59(13):10.1016/j.jacc.2011.10.900.

Prophylactic Transfusion for HbSS

- Studies of benefit from prophylactic transfusion in sickle cell patients going for surgery are mixed
- Expert recommendations continue to recommend transfusion to achieve preop hemoglobin of ≥10 g/dl
  - Simple transfusion, not exchange transfusion
- Will likely need extra time to accomplish T&C

Yawn BP et al. *JAMA.* 2014;312(10):1033-1048.

Hemolytic Anemia

- Multiple different types of hemolytic anemia
- For most the keys are:
  - Avoid oxidative and other stressors (like pain, dehydration and hypoxia)
  - Avoid meds that may exacerbate hemolysis
  - Allow extra time for T&C (multiple previous transfusions make crossmatching more challenging)
    - If autoimmune hemolysis, may consider washed RBCs
  - Assure repletion of RBC vitamins/minerals – B12, folate, iron
- Best screening for acute hemolysis remains:
  - CBC
  - LDH + haptoglobin (if negative, rules out acute hemolysis)

G6PD Deficiency

- Avoid oxidative stressors
  - Pain control
  - Good hydration (normotonic IV fluids)
- May need admission for observation after outpatient procedures
  - Risk of hemolysis may extend up to a few days after surgery
  - Need close follow-up
- OK to use:
  - Benzodiazepines
  - Codeine/codeine derviatives
  - Propofol
  - Fentanyl
  - Ketamine

Class I	Severely deficient, chronic hemolytic anemia
Class II	1–10% residual activity
Class III	10–60% residual activity
Class IV	60–150%; normal activity
Class V	>150%; increased activity

Unsafe for Class I, II, and III	*Safe for Class II and III*
Acetanilid	Acetaminophen
Dapsone	Aminopyrine
Furazolidone	Ascorbic acid
Methylene blue	Aspirin
Nalidixic acid	Chloramphenicol
Naphthalene	Chloroquine
Niridazole	Colchicine
Nitrofurantoin	Diphenhydramine
Phenazopyridine	Isoniazid
Phenylhydrazine	L-DOPA
Primaquine	Menadione
Sulfacetamide	Paraaminobenzoic acid
Sulfamethoxazole	Phenacetin
Sulfanilamide	Phenytoin
Sulfapyridine	Probenecid
Thiazosulfone	Procainamide
Toluidine blue	Pyrimethamine
Trinitrotoluene	Quinidine
	Quinine
	Streptomycin
	Sulfamethoxpyridazine
	Sulfisoxazole
	Trimethoprim
	Tripelennamine
	Vitamin K

Elyassi AR, Rowshan HH. *Anesth Prog.* 2009;56(3):86-91.