Hemophilia

Hemophilia is an x-linked recessive disorder characterized by a deficiency of Factor VIII (A) or IX (B), resulting in spontaneous hemorrhage and uncontrolled bleeding with trauma or surgery.

ANESTHETIC CONSIDERATIONS:

- Complications of inherited coagulopathy
  - Bleeding into enclosed spaces (joints, intracranial, pericardium, thorax, retinal)
  - High risk for perioperative bleeding
    - Avoid platelet-inhibiting agents
  - Perioperative factor replacement
    - Factor inhibitors may preclude use of factor replacement therapies necessitating use of PCCs/rFxVIIa
    - Thrombotic complications of PCCs/rFxVIIa
  - Caution with regional anesthesia and neuraxial techniques
- Consider preoperative hematology consultation

ANESTHETIC GOALS:

- Optimize factor activity and coagulation profile in perioperative period
- Minimize perioperative blood loss
  - Consider perioperative blood conservation

HISTORY

- Diagnosis, factor activity level, factor inhibitors
- Prior management for dental work, trauma
  - Response to DDAVP, Fx VIII concentrates, Fx VIIa
- Bleeding history
  - Easy bruising, bleeding, petechiae, mucosal bleeding, epistaxis, menorrhagia, hematuria, severe and prolonged bleeding after dental extraction, tonsillectomy, other surgery
  - Deep tissue bleeding, hemarthroses, intracranial bleeding

PHYSICAL

- GENERAL – bruising, petechiae
- Airway – active bleeding can cause airway hematoma
- MSK – joint swelling, deformity

INVESTIGATIONS

- CBC/D, x-match
- Lytes, urea, Cr
- Coagulation studies – INR, PTT, fibrinogen, factor levels, factor activity

OPTIMIZATION

- Consult Hematology
- Replace deficient coagulation factor and confirm levels within 2hrs preop
  - Hemophilia A – Fx VIII replacement
    - Fx VIII level must be 50-100% for major surgery
    - Initial infusion 50-60U/kg, then 25-30U/kg q8-12h to keep plasma Fx VIII level >50%
      - t1/2 of Fx VIII = 6hrs (peds), 12 hrs (adults)
      - Plasma Fx VIII level ↑s by 2% for each U/kg infused
      - Measure Fx VIII peak and trough levels to confirm appropriate dose and interval
    - Non-ortho procedures – continue Fx VIII replacement up to 2wks postop to avoid postop bleeding → disruption of wound healing
    - Bone/joint surgery – continue Fx VIII replacement 4-6wks
  - Hemophilia B – Fx IX replacement
    - Fx IX level must be 50-100% for major surgery
    - Initial infusion 100U/kg, then 50U/kg q12-24h to keep Fx IX level >50%
      - t1/2 of Fx IX = 18-24hrs
- Consider additional hemostatic agents
  - Hemophilia A
    - DDAVP, cryoprecipitate, TXA
    - If inhibitors present – PCCs or rFxVIIa
  - Hemophilia B
    - FFP
    - If inhibitors present – PCCs, rFxVIIa

ANESTHETIC OPTIONS

- **Local**
- **Regional**
  - Criteria for factor replacement for safe neuraxial technique in hemophilia A or B: 70-100%
  - Platelets – usual thresholds and stable platelet count (as long as factor level criteria met)
- **General**
  - Required if factor levels insufficient for regional anesthesia

ANESTHETIC SETUP

- **Drugs**
  - Antifibrinolytics (as infusion to continue postoperatively)
  - DDAVP available
  - Standard emergency drugs
- **Equipment**
  - CAS monitors (+/- others as dictated by procedure and comorbidities)
  - Large bore IV
  - Temperature probe, blood warmer, rapid infuser, cell salvage
  - Consider arterial line for sampling if frequent factor activity assays to be measured
  - Deficient factor replacement
  - X-match completed prior to OR (may be delays for antibody investigation)

MANAGEMENT OF ANESTHESIA

- **Induction**
  - Avoid airway trauma (risk hematoma/bleeding)
- **Maintenance**
  - Careful positioning in setting of hemarthroses
  - Monitor factor levels
  - Avoid conditions which will promote bleeding or inhibit coagulation – HTN, hypothermia, antiplatelet agents (eg: NSAIDs), anticoagulants
  - Avoid hypothermia
- **Emergence**
  - Ensure hemostasis achieved
  - Avoid airway trauma during extubation

DISPOSITION & MONITORING

- Factor activity assay on arrival in PARR
- Continue perioperative factor replacement based on procedure and severity of deficiency
  - General goals for factor activity:
    - 100% Day 1-3
    - 50-100% Day 4-7
    - 30 % Day 7-14

COMPLICATIONS

- **Major hemorrhage**

OBSTETRICS

- Female carriers may have ↑risk hemorrhage
  - ?Avoid neuraxial anesthesia
  - Ensure x-matched blood available
- 50% of the male children of heterozygous carriers for hemophilia A or B have hemophilia
  - May undergo trial of labor
  - Avoid fetal scalp electrodes and fetal scalp pH sampling
  - Avoid vacuum extraction and forceps delivery

PATHOPHYSIOLOGY OF HEMOPHILIA A

- Epidemiology
  - Represents 85% of all hemophilias
  - Prevalence: 1 in 5,000-10,000 males
- Genetics
  - Factor VIII gene located on X-chromosome
  - Hemophilia A is an x-linked recessive disorder
    - Inversion, major deletion, or missense mutation → severe hemophilia
    - Point mutation, or minor deletion → less severe hemophilia
  - Mutation can result in
    - Quantitative defect – ↓Fx VIII levels
    - Qualitative defect – ↓Fx VIII activity, N Fx VIII levels
  - Males carrying defective gene are diagnosed with hemophilia
  - Females carrying the defective gene are carriers
    - Females can be affected if random inactivation of one x-chromosome occurs (lyonization) or a single x chromosome is present (Turner's syndrome)
- Physiology
  - Fx VIII:C circulates bound to and protected by vWF
- Clinical presentation
  - Clinical severity of hemophilia A best correlated w/ Fx VIII activity level
  - Present with deep tissue bleeding (muscle, GI), hemarthrosis, hematuria, CNS bleeding
  - Female carriers would be expected to have Fx VIII activity level of 50%, however 10% of female carriers have Fx VIII activity < 30% due to lyonization → ↑risk of hemorrhage with surgery/trauma

Factor VIII activity	Severity	Clinical presentation	PTT
< 1% of normal	Severe hemophilia	Diagnosed in childhood	↑↑

(< 0.01 U/mL)	(most common)	Frequent spontaneous hemorrhages into joints, muscles, vital organs Progressive deforming arthropathy Tx – frequent Fx VIII replacement	
1-5% of normal	Moderate hemophilia	Increased risk of hemorrhage with surgery or trauma Less difficulty with spontaneous hemorrhage	↑
6-30% of normal	Mild hemophilia	May be undiagnosed into adult life Risk of excessive bleeding with major surgical procedures	↑

- Diagnosis
  - Coagulation studies – ↑PTT (INR normal)
  - Factor assays – ↓Fx VIII levels and/or ↓Fx VIII activity, with N levels of vWF, Fx IX and Fx XI
  - Genetics – defective Fx VIII gene on x-chromosome
- Management
  - Fx VIII plasma concentrate or recombinant Fx VIII
    - Target for Tx of spontaneous bleeding – Fx VIII level of 25%
    - Target for major surgery – Fx VIII level of 50-100% preop
  - DDAVP
    - Will ↑ levels of Fx VIII:C and vWF
    - Often effective in mild hemophilia A (Fx VIII:C levels >5%)
    - Dosing: 0.4mcg/kg in 50cc saline iv over 15-30min
    - Limitations: tachyphylaxis
  - Antifibrinolytics
    - Tranexamic acid/E-aminocaproic acid may be useful in dental procedures
    - Contraindicated in hemarthroses and hematuria

PATHOPHYSIOLOGY OF HEMOPHILIA B

- Epidemiology
  - Represents 14% of all hemophilias
  - Prevalence: 1 in 25,000-40,000 males
- Genetics
  - Factor IX gene located on X-chromosome
  - Hemophilia B is an x-linked recessive disorder

Factor IX activity	Severity	Clinical presentation	PTT
< 1% of normal	Severe hemophilia	Severe bleeding	↑↑
1-5% of normal	Moderate hemophilia	Increased risk of hemorrhage with surgery or trauma	↑
6-40% of normal	Mild hemophilia	May be undiagnosed into adult life Risk of excessive bleeding with major surgical procedures	↑

- Diagnosis
  - Coagulation studies – ↑PTT (INR normal)
  - Factor assays – ↓Fx IX levels and/or ↓Fx IX activity, with N levels of vWF, Fx VIII and Fx XI
  - Genetics – defective Fx VIII gene on x-chromosome
- Management
  - Fx VIII plasma concentrate or recombinant Fx IX
    - Target for Tx of spontaneous bleeding – Fx VIII level of 25%
    - Target for major surgery – Fx VIII level of 50-100% preop
  - FFP (cryoppt does not contain Fx IX)

ACQUIRED FACTOR INHIBITORS

- Epidemiology
  - Hemophilia A – up to 40% of patients with severe hemophilia A exposed to Fx VIII concentrate eventually develop circulating inhibitors to Fx VIII (as early as 10-14d after first exposure)
  - Hemophilia B – up to 5% of patients with severe hemophilia B develop Fx IX inhibitors
  - Acquired Fx VIII or Fx IX inhibitors – present with sudden onset severe spontaneous hemorrhage
- Diagnosis
  - Mixing study to screen for inhibitor
    - Mix patient plasma and normal plasma in 1:1 ratio and measure PTT
      - Fx deficiency – PTT shortens with mixing study
      - Fx deficiency + Fx VIII inhibitor – PTT does not shorten with mixing study
  - Quantify Fx activity level
  - Measure inhibitor titre (Bethesda assay – units of inhibitor/mL plasma)
    - Hemophilia A
      - High responders – titre >10-1000U/mL (typical of alloantibody, with marked inhibitor response after Fx replacement; levels cannot be neutralized by high-dose replacement therapy, and anamnestic response with repeat exposure to Fx replacement)
      - Low responders – titre <5-10U/mL (low levels of inhibitor despite repeated exposure to Fx replacement with no anamnestic response)
    - Hemophilia B
      - Modified Bethesda assay
    - Acquired autoAb to Fx VIII or IX

        - Modified Bethesday assay with inhibitor levels >1000 U/mL
- Management of Hemophilia A with inhibitors
    - Low responders
        - Fx VIII concentrates, with larger initial and maintenance doses as guided by Fx VIII levels
    - High responders
        - Use of Fx VIII concentrates not feasible
        - Activated prothrombin complex concentrates (Fx II, VII, IX, X; Autoplex, FEIBA)
            - Contain high levels of activated clotting fx → risk of DIC and major thromboembolism
        - Recombinant activated Fx VIIa (Novoseven)
            - Dose for Tx of active bleeding: 90-120mcg/kg iv q2-3h until hemostasis achieved
            - Labs will show ↓ in PTT, however this may not correlate w/ clinical hemostasis
            - Controls bleeding in 80% of cases
            - Risk of widespread or local thrombosis less than with PCCs
- Management of Hemophilia B with inhibitors or acquired autoantibody to Fx VIII or Fx IX
    - As for Hemophilia A with inhibitors

REFERENCES

- Anesthesia and Coexisting Disease p.419-421
- Barash p.397-398
- Miller p.1771
- Chestnut p. 953