Sickle-Cell Disease

A genetic hemoglobinopathy in which sickle-shaped erythrocytes cause both chronic hemolysis and vaso-occlusive crises

ANESTHETIC CONSIDERATIONS:

- Chronic hemolytic anemia
  - Chronic RBC transfusion and its complications (alloimmunization, iron overload, viral transmission)
- Multisystem disease with end-organ dysfunction
  - Brain → CVA (25%)
  - Heart → ↑ CO, cardiomegaly, LVH, AMI without coronary disease
  - Lung → pHTN (20-40%), OSA (20% of children with sickle-cell disease)
  - Kidney → CRF, nephrogenic DI
- Potential for perioperative exacerbations of vaso-occlusive crises
  - Acute pain crisis
  - Acute chest syndrome (ACS)
- Pre-operative optimization → consider pre-operative transfusion
- Medications
  - Immunosuppressants, antineoplastics (e.g. hydroxyurea, 5-aza-2'-deoxycytidine)
- Opioid tolerance

ANESTHETIC GOALS:

- Avoid precipitants of sickle cell crisis
  - Hypoxia
  - Vascular Stasis
  - Hypothermia
  - Hypovolemia / hypotension
  - Acidosis
- Optimize perioperative pain control

HISTORY

- Look for evidence and extent of end-organ damage:
  - Focus on lung, kidney and brain pathology
  - Investigations, recent hospitalizations and symptom patterns will give some indication of severity of sickle-cell disease
- Acute Painful Crises (formerly Sickle Cell Crises) predictors of postoperative sickle-cell complications
  - Increased age, organ failure, pregnancy, co-existing infection, recent cluster of ACS episodes and African haplotype (see table in Pathophysiology)
- Risk stratification based on procedure (% risk of sickle-cell disease events)
  - Tonsillectomy 0%
  - Hip surgery 2.9%
  - Myringotomy 3.9%
  - Intra-abdominal surgery 7.8%
  - Cholecystectomy 10-20%
  - Cesarean section and hysterectomy 16.9%
  - D&C 18.6%
- Clinical Features of sickle-cell disease (see table in Pathophysiology)
  - Vaso-occlusive Crisis (or Pain Crisis)
  - CVA
  - Cardiovascular
    - Chronic anemia → ↑ CO and cardiomegaly (but no specific CMO)
    - Myocardial infarction in absence of CAD
  - Pulmonary
    - Acute Chest Syndrome
    - Airway hyper-reactivity
    - Restrictive Lung Disease
  - GU
    - Chronic renal insufficiency (5-20%)
    - ARF
    - Nephrogenic DI (Sickling in the vasa rectae presumably interferes with countercurrent exchange in the inner medulla, thereby leading to impairment of free water reabsorption and polyuria)
    - Priapism
  - GI
    - Cholelithiasis (70%)
  - Hematological
    - Hemolytic anemia
    - Acute aplastic anemia
    - Splenic crisis
  - Chronic infections

PHYSICAL

- **GENERAL**
  - On physical exam look for signs of end-organ damage in keeping with above

- **HEENT**
  - A/W exam (OSA association with difficult airway)
- **RESP**
  - Signs of lung pathology including pulmonary HTN and cor pulmonale
- **CVS**
  - Extent of hypertension and fluid status secondary to CRF
- **CNS**
  - Psychiatric issues, seizure activity, developmental delay, or focal neurological sequelae of CVA

INVESTIGATIONS

- **Labs**
  - CBC to assess extent of anemia (Hb S levels not recommended)
  - Crossmatch and further antibody and antigen testing
  - BUN / Cr & urinalysis including dipstick for proteinuria and signs of infection
  - SaO_2, ABG
- **Imaging**
  - CXR for extent of lung disease (interstitial fibrosis) or infection – consider PFTs (obstructive or restrictive pattern)
  - Others in keeping with pathology: LFTs, ECG, ECHO, neuroradiology, etc.

OPTIMIZATION

- Hematology consultation (Uptodate)
  - **Hydroxyurea** – proven efficacy
    - Ribonuclease reductase inhibitor
    - Causes increase in Hemoglobin F (protective against acute painful crises)
    - May also increase nitric oxide (see below)
  - **Erythropoietin**
    - Increases Hb F, controversial efficacy
    - Added if hydroxyurea has no effect
  - **Inhaled nitric oxide**
    - Particularly useful in acute chest syndrome
    - Low concentrations of NO may or may not increase oxygen affinity of sickle erythrocytes
    - NO may reduce the adhesion of sickle erythrocytes to the pulmonary endothelium
  - **Magnesium** (0.6 mEq/kg per day of magnesium pidolate)
    - Preliminary reports show promise by reducing the number of dense sickle erythrocytes likely by increasing cell volume
  - **Anticoagulation** (self administered heparin reduced hospital visits)
  - **Poloxamer 188** - artificial nonionic surfactant that reduces sickle erythrocyte adherence to the endothelium
  - **Hematopoietic cell transplantation** – limited experience
  - Stroke Prevention trial (STOP, J Pediatr 2001)
    - Chronic transfusion (i.e. not preoperative transfusion) vs. observation reduced risk of stroke, acute chest syndrome episodes, and acute painful crises in those with abnormal transcranial Doppler
- Ensure patient euvolemic
- Treat infections
- Pre-operative transfusion (see table below)
  - Rationale: dilution of sickle cells with normal erythrocytes and inhibition of intrinsic hematopoiesis with normal RBCs (thus inhibiting generation of sickle capable RBCs) will decrease incidence of perioperative sickle-cell disease complications
  - Consider transfusion in 3 situations:
    - To improve O_2 carrying capacity and as blood volume replacement during an aplastic or splenic sequestration crisis
    - To provide protection from imminent danger during acute chest syndrome or septicemia
    - To improve rheologic properties of blood and prevent initial or recurrent cerebral thrombosis, to prevent recurrent priapism, and to reduce perioperative complications
  - National Preoperative Transfusion in sickle-cell disease Study Group (NEJM 1995)
    - No difference between aggressive exchange transfusion (target Hb S < 30%) versus conservative transfusion (Hb > 100) in terms of serious complications (ACS, VOC)
    - Aggressive transfusion group had higher rate of transfusion related complications

Table 5. Guidelines for the use of Perioperative Prophylactic Erythrocyte Transfusion

Transfusion goal	Low perioperative	Moderate perioperative	High perioperative	Uncomplicated Pain	Severe ACS
Hematocrit of 30%	Not Indicated	May be beneficial	May be beneficial	Not indicated	Reduces hypoxemia
Hemoglobin S <30%	Not indicated	Not Indicated	May not be Indicated	Not indicated	Reduces hypoxemia

An individualized assessment of patient risk should be based on a synthesis of factors outlined in the text. Prophylactic transfusion is of potential benefit in moderate and high- risk cases, but the efficacy has not been clearly demonstrated by a randomized trial. The efficacy of pre-emptive transfusion therefore remains controversial. The use of transfusion for mild cases of acute chest syndrome is unclear, although transfusion in severe cases improves arterial oxygenation. The role of exchange transfusion versus simple transfusion for relief of severe hypoxia in acute chest syndrome is unclear. Extended cross matching for E, C and K antigens decreases alloimmunization.

ANESTHETIC OPTIONS

- Concern of increased complications with regional / neuraxial anesthesia: no evidence in small studies
- TEA may be useful adjunct for post-operative pain management

- Only low-risk patients should be considered for outpatient surgery

ANESTHETIC SETUP

- **Drugs**
  - Emergency drugs
- **Equipment**
  - Measure oxygen saturation in multiple areas
  - CAS monitors + 5 lead ECG
  - Temperature
  - Consider art line (if sampling needed)
  - Consider invasive monitoring

MANAGEMENT OF ANESTHESIA

- **Induction**
  - Anesthetic goals: avoid hypoxia, hypercarbia, acidosis, hypothermia, vascular stasis, dehydration, catecholamine release (triggers VOC)
- **Maintenance**
  - Tourniquet use controversial - best to avoid
  - Avoid over-transfusion (Hb < 100)
- **Emergence**
  - Aggressive pain control: Ketorolac good choice for opioid sparing
  - Incentive spirometry / chest physio
  - Only low risk patients should be considered for outpatient procedures

DISPOSITION & MONITORING

- Overnight monitoring to r/o crisis precipitated by surgery

COMPLICATIONS

- Vaso-occlusive crisis
  - AKA Acute Painful Episode (or sickle cell crisis)
  - Precipitated by: cold, dehydration, stress, menses, alcohol, OSA but majority have no identifiable causes
  - Episodes can affect any area of body → bone pain, abdominal pain
  - Often accompanied by objective clinical signs: fever, swelling, tenderness, nausea and vomiting
  - Treatment
    - Consider adjuvant regional anesthesia
    - Acetaminophen / NSAIDs
    - Opioids
    - Adequate hydration, temperature
    - RBC transfusion not required for uncomplicated pain crisis
- Acute chest syndrome
  - Most frequently reported cause of death in adults, and is a risk factor for early mortality
  - Working definition of ACS
    - Presence of a new pulmonary infiltrate, involving at least one complete lung segment (not atelectasis)
    - Chest pain
    - Temperature > 38.5ºC
    - Tachypnea, wheezing, or cough
  - Labs
    - Leukocytosis
    - Thrombocytopenia or thrombocytosis
    - Falling hemoglobin concentration
    - Elevations in lactate dehydrogenase and bilirubin levels
  - Causes
    - Unknown cause: 46%
    - Pulmonary infarction:16% (in-situ thrombosis due to intravascular sickling and occlusion in the microvasculature)
    - Fat embolism, with or without infection: 9% (have bone pain and neurologic symptoms)
    - Chlamydophila (formerly Chlamydia) pneumoniae infection: 7%
    - Mycoplasma pneumoniae infection: 7%
    - Viral infection: 6% (e.g. respiratory syncytial virus, parvovirus, rhinovirus)
    - Mixed infection: 4%
    - Other pathogens: 1%
  - Treatment
    - Supportive
    - Antibiotics for community acquired and atypical pathogens
    - Maintain PaO_2 of 70-100 mmHg
    - Judicious use of opioids
    - Bronchodilators (if evidence of wheezing)

Table 2. Predictors of Postoperative Complications

Predictors of Postoperative SCD complications
• Type of surgical procedure-Low, moderate or high risk
• Increased age-Associated with disease progression
• Frequency of recent complications-Current activity of disease state
• Hospitalization-Marker of disease severity
• Temporal clustering of ACS-Progression of lung disease
• Abnormal lung fields on radiograph-Evidence of sickle chronic lung disease
• Pregnancy-Increased risk of maternal complications
• Pre-existing infection-Triggering agent for ACS
• Haplotype-African haplotypes have more severe disease than the Asian haplotype

Low-risk surgical procedures include minor procedures such as inguinal hernia repair or extremity surgeries. Moderate risk procedures include more invasive interventions such as intra-abdominal operations, while high-risk events include intracranial and intrathoracic procedures.

ACS = acute chest syndrome; SCD = sickle cell disease.

        - Hydrate to euvolemia (can cause pulmonary edema in overhydration in combination with opioids)
        - Simple transfusion (leukocyte depleted, match C, E, and Kell antigens) – careful not to excessively increase HCT and blood viscosity exacerbating vaso-occlusion
        - Exchange transfusion (use in setting of progressive infiltrates and refractory hypoxemia) – Hb S to < 30% and HCT = 30%
        - Anticoagulation not recommended unless thromboembolism identified
        - Incentive spirometry
        - Inhaled NO – undergoing clinical trials
- Most common sickle cell related causes of death
    - Infection — 48 percent
    - Stroke — 10 percent
    - Complications of therapy — 7 percent
    - Splenic sequestration — 7 percent
    - Thromboembolism — 5 percent
    - Renal failure — 4 percent
    - Pulmonary hypertension — 3 percent

PATHOPHYSIOLOGY

- Genetic hemoglobinopathy characterized by vaso-occlusion and hemolysis
    - Normal adult Hb consists of 2 α subunits and 2 β (βA) subunits
    - Sickle cell gene on chromosome 11 (βS)
    - Sickle cell disease is homozygous for βS → α/α, βS/βS
    - Sickle cell trait (SCT) is heterozygous at β locus → α/α, βS/βA
    - Results in:
        - Increased membrane permeability to electrolytes → hemolysis
        - Distortion of erythrocytes → sickling with certain triggers
        - Rightward shift of Hb dissociation curve
    - Disease is of medium severity in SCT and most severe in sickle-cell disease
- **Sickling mechanisms**
    - Traditional polymerization theory of Hb S
    - Multiple pathway model
        - Leukocyte / endothelium interaction with inflammation
        - Activation of macrophage tissue factor → activates platelets, coagulation and endothelial cells
        - Clinical dehydration or activation of endothelial cells and platelets elevates levels of thrombospondin or vWF to mediate RBC adhesion to endothelium
        - Regional hypoxia releases endothelial cell P-selectin to enhance adhesion of sickle cells (including heterocellular interactions with platelets and neutrophils)
- **Clinical Manifestations**

Table 1. Clinical Features of Sickle Cell Disease

Complication	Features
Neurological	
Pain crisis	Occurs in >70% of patients
Stroke	10% of children; subclinical microvascular occlusion in ≈20%. Cause of >20% deaths.
Proliferative retinopathy	50% of SC adults; rare in SS homozygotes
Peripheral neuropathy	Unusual complication
Chronic pain syndrome	A small subset of patients
Pulmonary	
Acute Chest Syndrome	Occurs in 40% of patients; mortality rate of 1.1% for children and 4.8% for adults.
Airway hyperreactivity	35% of children
Restrictive lung disease	10–15% of patients
Genitourinary	
Hyposthenuria	Nocturnal enuresis not a sensitive predictor
Chronic renal insufficiency	Present in 5–20% of adults
Urinary tract infection	Increased incidence; may trigger ACS
Priapism	10–40% of men
Pregnancy	Probable increased incidence of obstetrical complications, increased incidence of VOC
Gastrointestinal	
Cholelithiasis	Up to 70% of adults
Liver disease	Viral hepatitis from transfusion in up to 10% of adults. Liver failure <2%.
Dyspepsia	Mucosal ischemia, rather than increased acid production, is thought to be the cause. Reflux is not a complication of SCD.
Hematological	
Hemolytic anemia	Typical baseline hemoglobin levels are 6–9 g/dl in SS disease, higher in SC disease and Arab phenotype.
Acute aplastic anemia	Parvovirus B19 infections trigger acute severe exacerbations of anemia
Splenic enlargement/fibrosis	Less affected: SC disease, Arab haplotype
Orthopedic	
Osteonecrosis	Up to 50% of adults
Osteomyelitis	Salmonella and *Staphylococcus aureus* are commonest pathogens.
Dactylitis	Early onset is a marker of disease severity
Vascular	
Leg ulcers	20% of SS adults; rare in SC disease
Immunological	
Immune dysfunction	Increased susceptibility to infections
Erythrocyte auto/alloimmunization	Increased incidence of transfusion
Hemolytic transfusion reactions	Alloimmunization

ACS = acute chest syndrome; SCD = sickle cell disease; SS = patients homozygous for hemoglobin S; VOC = vasoocclusive crisis.

REFERENCES

- Bunn HF. Pathogenesis and treatment of sickle cell disease. N Engl J Med 1997; 337: 762–9.
- New England Journal of Medicine. 340(13):1021-1030, April 1, 1999.
- N Engl J Med 1995 Jul 27;333(4):206-13
- Sickle Cell Disease and Anesthesia. Anesthesiology 2004; 101:766–85 (source of tables)
- Uptodate 14.3
- J Pediatr 2001 Dec;139(6):785-9
- Barash