I. Perioperative Management of Patients with Pediatric Sickle Cell Disease

Background

Beyond the first 6 months of life, hemoglobin A, a tetramer composed of 2 α- and 2 β-globin chains, is the predominant form of human hemoglobin. A single nucleotide substitution in the β-globin gene results in the replacement of glutamic acid with valine at the sixth amino acid position of the β-chain and imparts significant functional impairment and clinical sequelae in those who inherit the mutation.

Patients who are homozygous for the mutant sickle gene (β^s) and those heterozygous for the β^s gene who co-inherit a β^0 thalassemia deletion suffer a similarly severe phenotype and are classified as having sickle cell anemia (SCA). In contrast, most other compound heterozygotes, such as hemoglobin SC disease and sickle β^+ thalassemia, exhibit a mild to moderate clinical phenotype. Individuals with sickle cell trait are heterozygous for the mutant β^s gene at only one β-chain loci and typically have a benign clinical course in childhood.

Sickle cell disease (SCD) encompasses all sickle genotypes (except sickle trait) and is characterized by varying degrees of intracellular erythrocyte dehydration, irreversible polymerization of hemoglobin, and systemic oxidant stress. The resulting damage to red blood rheology and endothelial cell activation impairs blood flow through the microvasculature, resulting in ischemic tissue injury. Pediatric patients with SCD are at markedly increased risk for serious perioperative complications ranging from vaso-occlusive crisis (VOC) to acute chest syndrome (ACS) and stroke, among others. For this reason, pediatric patients with SCD are of great concern to pediatric anesthesiologists. VOC or acute pain crisis is the most common complication of SCD, characterized by recurrent episodes of severe pain that are usually

triggered by infection, dehydration, or hypoxemia. ACS is characterized by fever, respiratory symptoms, and pulmonary infiltrates on chest x-ray, that typically presents following infection, VOC, or after major surgeries.

Image: Comparison of Sickled Red Blood Cells and Normal Red Blood Cells

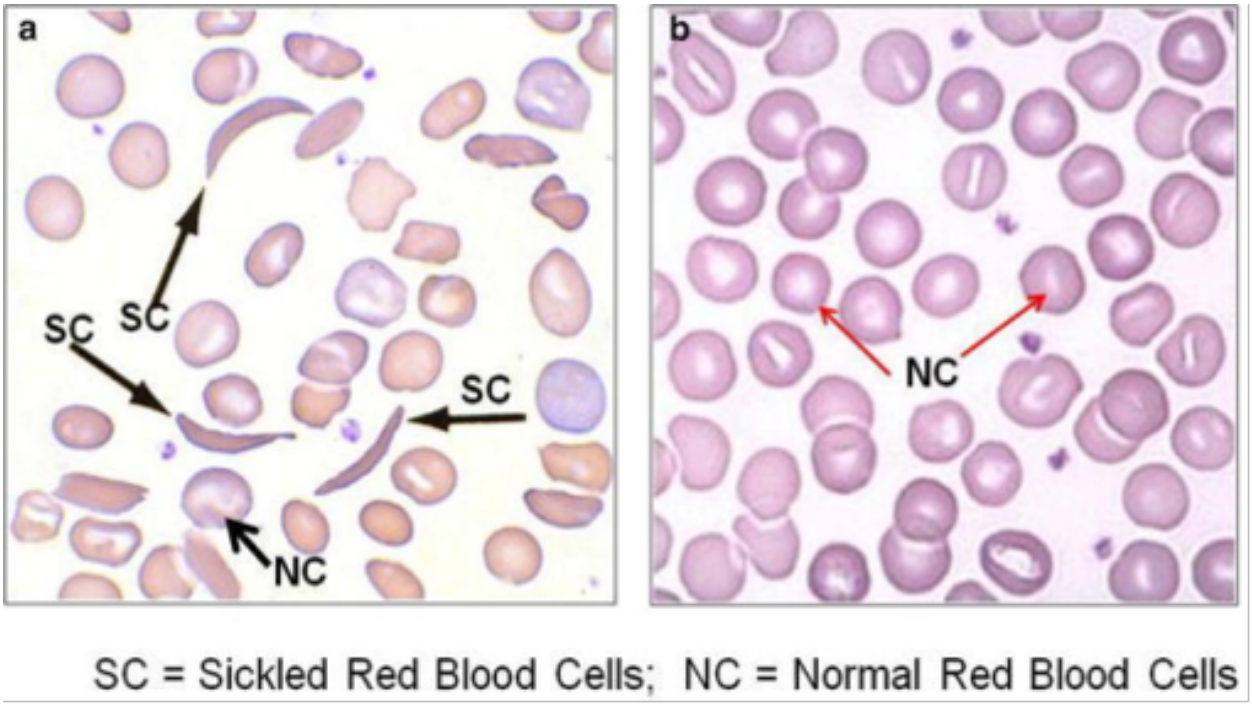

Fig 1: A figure of photomicrograph results for blood obtained from a person without and with sickle cell trait. (a) Sickled red blood cells (black arrowed) from a person with sickle cell trait under low oxygen tension. (b) Normal red blood cells (red arrowed) from a person with no sickle cells traitImages obtained from: https://openi.nlm.nih.gov/detailedresult?img=PMC4617725_13104_2015_1583_Fig1_HTML&query=sickle%20cell&it=xg&req=4&npos=2**. (a) Reprinted by CC0 1.0; (b) Reprinted by CC BY 4.0.**

Preoperative Considerations

- Identify and confirm hemoglobinopathies in pediatric patients with SCD via universal newborn screening, clinical history, hemoglobin electrophoresis, or genetic testing. In developed countries, many will

already be known from their hematology clinic affiliations where they receive longitudinal care.

- Evaluate for history of VOC, ACS, or stroke and resulting comorbidities such as cardiac disease, pulmonary disease, and pulmonary artery hypertension. Patients with frequent VOC or stroke, ACS, and advancing end-organ disease related to the hemoglobinopathy are considered high-risk patients.
- Common pediatric conditions such as upper respiratory tract infection, asthma, and obstructive sleep apnea have greater significance in children with SCA, and the presence of these conditions should be sought out.
- Review clinical history with pediatric hematology providers, along with results from any echocardiography, spirometry, central nervous system imaging and transcranial Doppler flow studies, hepatic and renal function tests, most recent complete blood count, and hemoglobin electrophoresis.
- Stratify patients as high-, medium-, or low-risk patients by virtue of their genotype, prior clinical trajectory, and nature of the planned surgical procedure.
- Evaluate use of disease-modifying therapies such as hydroxyurea therapy or chronic transfusion therapy. Be cognizant that children on chronic transfusion therapy are high risk and usually demonstrate frequent debilitating VOC, life-threatening stroke, or ACS.
- Review the proposed surgical procedure for which the patient is presenting. Surgical procedures can be classified as high-, medium-, or low-risk procedures, which we define in the table below. Surgical and procedural risk stratification is further delineated in the TAPS Trial (Howard et al., 2013) and the Cooperative Study of SCD (Koshy et al., 1995).

Procedure Risk	*Examples*
High	Neurosurgical, cardiovascular, and thoracic surgical procedures.
Medium	Cholecystectomy, splenectomy, tonsillectomy and adenoidectomy, cesarean section, liver biopsy, and most orthopedic procedures.
Low	Tympanostomy tube placement, insertion of vascular access devices, circumcision, hernia repair, most dental and eye procedures. Comment: Although infusion port placement is low risk, it is often used in high-risk patients to facilitate chronic transfusion therapy or venous access in the setting of recurrent hospitalizations.

- Restore and preserve normal intravascular volume, adequate oxygen-carrying capacity (as indicated by hemoglobin and hematocrit counts), and optimization of any SCD-related organ system dysfunction. Determine with the patient's hematologist, surgeon, and family whether the patient should be admitted the night before surgery for intravenous hydration, prophylactic red cell transfusion, and/or optimization of any recognized SCD-related organ system dysfunction.
- Assure preoperative hydration with intravenous fluids in the inpatient setting or through the administration of clear fluids by mouth until 2 hours before surgery. If possible, these patients should be scheduled for surgeries and procedures early in the day to minimize NPO times and avoid dehydration. In general, inpatient intravenous preoperative hydration should be used in medium- and high-risk patients undergoing medium- and high-risk procedures. Low-risk patients undergoing low-risk procedures can be hydrated preoperatively at home. Parents must be made aware of the importance of active oral hydration before procedures.
- Transfusion therapy can be administered as a simple transfusion (goal of hemoglobin 10 g/dL) or an exchange transfusion (goal of hemoglobin 10 g/dL and HbS% < 30).
- Prophylactic transfusion for pediatric patients with HbSS and HbSβ^0 undergoing low- and medium-risk procedures with a hemoglobin target of 10 g/dL% is a safe and efficacious standard of care. Preoperative prophylactic transfusion should be administered within 1 week of surgery with the simple transfusion goals outlined

above. Simple transfusion therapy is as effective as exchange transfusion for preventing SCA-related complications and is less likely than exchange transfusion to cause transfusion-related complications (especially alloimmunization and iron overload). Prophylactic transfusion of other sickle hemoglobin genotypes undergoing low-risk procedures is controversial and should be discussed on a case-by-case basis with the patient's hematology providers.

- Preoperative exchange transfusions are administered on a case-by-case basis but are generally reserved for patients undergoing high-risk neurosurgical and cardiothoracic procedures or high-risk patients undergoing moderate- and other high-risk procedures.

Intraoperative Considerations

- Minimize risk of hypoxemia and maintain oxygen saturation above 95%.
- Maintain hydration and volume status by estimating and replacing ongoing losses using isotonic solutions and colloid to maintain intravascular volume and a hematocrit of 27% to 30%. Note that excessive volume loading may exacerbate lung disease in general and ACS in particular.
- Arterial catheter insertion for longer and more invasive cases allows for serial measurement of hemoglobin and hematocrit concentration, acid-base balance, and serum lactate concentration in accordance with basic anesthesia practice.
- Estimate maximum allowable blood loss and transfuse to maintain a hemoglobin concentration between 9 and 10 g/dL in this population, as the propensity for stroke increases above hemoglobin concentrations of 11 g/dL in the acute setting.
- Monitor core body temperatures carefully as children with SCA are at increased risk for hypothermia, which can contribute to VOC.
- Use multi-modal analgesia with regional anesthetic blocks, acetaminophen, non-steroidal anti-inflammatory drugs, and titrate small doses of opioids.

- If a tourniquet is used as part of an orthopedic procedure, the limb should be completely exsanguinated before tourniquet inflation, and tourniquet use should be limited to the shortest feasible duration (preferably less than 1 hour).

Postoperative Considerations

- Collaborate with hematology providers, surgeons, and parents as to whether the patient is a candidate for outpatient surgery. Patients who are not should be admitted for hydration, pulmonary toilet, and postoperative analgesia.
- Be mindful that an uneventful intraoperative course does not guarantee a benign postoperative course. For practical purposes only, low-risk patients undergoing low-risk procedures are considered candidates for surgery on an outpatient basis, and there should be a low threshold for postoperative admission whenever there is a concern about outpatient management and/or follow-up.
- Consider pulmonary hygiene and pulmonary toilet with incentive spirometry in older children.
- Use analgesia with non-steroidal anti-inflammatory drugs, patient-controlled opioids, or peripheral nerve blocks.
- Monitor for hydration status, check for insensible losses, and maintain input versus output balance.
- The most common significant perioperative complication is VOC, which can progress rapidly to ACS or stroke.
- Use transfusion therapy either as simple transfusion or exchange transfusion to treat perioperative SCA complications. Other therapeutic considerations are listed in the table below:

Complication	*Management*
VOC	Intravenous hydration, oxygen, analgesia; follow hemoglobin and consider transfusion for symptomatic anemia or concerns for developing ACS; consult hematology.
ACS	Oxygen, pulmonary hygiene, ventilation support, bronchodilators ± inhaled corticosteroids, simple or exchange transfusion. Involve hematology and pediatric critical care medicine as appropriate.
Stroke	Prophylactic chronic transfusion therapy for children to reduce future incidence of stroke; new onset of stroke symptoms should be treated with aggressive exchange transfusion. Involve hematology, neurology, and pediatric critical care medicine as appropriate.
Acute Sequestration Crisis	Red blood cell transfusion, monitor hemoglobin, replace intravascular volume as these patients are hypovolemic due to blood loss into the spleen. Involve hematology and pediatric critical care medicine.
Aplastic Crisis	Red blood cell transfusion. Involve hematology practitioners.
Sepsis	Immunization against encapsulated bacteria, prophylactic penicillin for patients <5 years of age, prompt blood cultures and antibiotics for fever in patients with SCD. Involve hematology and pediatric critical care medicine as appropriate.

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II. Hip Fx: Fat embolism mgmt

Definition

Incidence/Mortality

Estimated to occur in 3-10% of orthopedic trauma patients. **Mortality is 10-20%**

Pathophysiology

Theory #1 (mechanical): large fat droplets are released into the venous system. These droplets are deposited in the pulmonary capillary beds and travel through arteriovenous shunts to the brain. Microvascular lodging of droplets produces local ischemia and inflammation, with concomitant release of inflammatory mediators, platelet aggregation, and vasoactive amines.

Theory #2 (biochemical): hormonal changes caused by trauma and/or sepsis induce systemic release of free fatty acids as chylomicrons. Acute-phase reactants, such as C-reactive proteins, cause chylomicrons to coalesce and create the physiologic reactions described above. The biochemical theory helps explain nontraumatic forms of fat embolism syndrome.

Diagnosis

History

Trauma to long bone/pelvis, recent orthopedic procedure, recent lipid infusion

Signs Under General Anesthesia

Clinical signs may include **hypoxia/increased A-a gradient**, **tachycardia**, and a **petechial rash on the *upper* portions of the body** (petechiae occur in only 20-50% of patients but are virtually diagnostic). Pulmonary compliance will likely decrease. PA pressures will rise and cardiac output will fall (although normally this information is not available). Delayed wake up may manifest. Mental status changes occur in awake patient, but are missed in patients under general anesthesia

There are **two classification schemes for diagnosis – Gurd and Schonfeld's**

Gurd's Diagnostic Criteria

Gurd's Diagnostic Criteria *Major Criteria*

- Respiratory insufficiency
- Cerebral involvement
- Petechial rash

Minor Criteria

- Tachycardia
- Fever
- Jaundice
- Retinal changes
- Renal changes

Laboratory Features

- **Microglobulinemia (required)**
- Thrombocytopenia
- Elevated ESR
- Anemia

One major and 4 minor criteria, plus fat microglobulinemia, must be present to formally diagnose fat embolism syndrome

Schonfeld Fat Embolism Syndrome Index

Schonfeld Fat Embolism Syndrome Index

- 5 points: petechial rash
- 4 points: diffuse alveolar infiltrates
- 3 points: hypoxemia (Pao2<70 mm Hg with an Fio2 100%)
- 1 point: confusion, fever, tachycardia, tachypnea

Note: **5 or more points are needed** to make a diagnosis

Workup

Labs

1. **ABG**: increase in pulmonary shunt fraction alveolar-to-arterial oxygen tension difference, especially if it occurs within 24-48 hours of a sentinel event; 2. **Hematocrit, platelet count, fibrinogen**: thrombocytopenia, anemia, and hypofibrinogenemia are indicative of fat embolism syndrome; 3. **Microglobulinemia is a *required* diagnostic test based on Gurd's criteria**. Note that urinary fat stains are not felt to be sensitive or specific enough for diagnosing fat embolism or for detecting a risk of it, and are thus not indicated

Imaging

1. **Chest radiography**: increasing diffuse **bilateral pulmonary infiltrates** within 24-48 hours of onset of clinical findings. 2. Noncontrast **head CT**: diffuse **white-matter petechial hemorrhages** consistent with microvascular injury. 3. Nuclear medicine ventilation/perfusion imaging of the lungs: Performed for suspicion of pulmonary embolus, the findings from this scan may be normal or may demonstrate subsegmental perfusion defects. 4. **Helical chest CT to rule out pulmonary embolism** 5. MRI: Scant data exist regarding MRI findings in patients with this syndrome; however, in one small patient group, multiple, nonconfluent, hyperintense lesions were seen on proton-density– and T2-weighted images. 6. Transcranial Doppler sonography: In

a small case study, 5 patients with trauma were monitored with intracranial Doppler sonography, 2 during intraoperative nailing of long bone fractures. Cerebral microembolic signals were detected as long as 4 days after injury. 7. **Transesophageal echocardiography (TEE)**: TEE may be of use in evaluating intraoperative release of marrow contents into the bloodstream during intramedullary reaming and nailing. The **density of the echogenic material passing through the right side of the heart correlates with the degree of reduction in arterial oxygen saturation**. Repeated showers of emboli have been noted to increase right heart and pulmonary artery pressures. Embolization of marrow contents through patent foramen ovale also has been noted. However, evidence of embolization by means of TEE is not correlated with the actual development of FES.

Procedures

Bronchoalveolar lavage (BAL) with staining of alveolar macrophages for fat (controversial)

BAL specimens have been evaluated in trauma patients and sickle cell patients with acute chest syndrome, and the results have been mixed. Lipid inclusions commonly appear in patients with traumatic and nontraumatic respiratory failure; the standard cut-off of 5% fat-containing macrophages in the BAL studies results in a low specificity for the test. Some authors suggest increasing the cut-off to 30% to improve specificity. Presently, using BAL to aid in the diagnosis or to predict the likelihood of fat embolism syndrome is controversial.

Treatment

“Supportive”, steroids don’t currently have a role in treatment (conflicting data)

III. Hemodialysis: Lab effects

Definition

The process of HD involves a dialyzer which contains semipermeable membrane with microscopic holes that allow only some substances to cross. Dialysate, also called dialysis fluid, is a solution of pure water, electrolytes and salts, such as bicarbonate and sodium, passes through one side of the membrane while blood from patients circulate through the other side of the membrane. Due to the difference in concentration, wastes will move through the semipermeable membrane to create an equal amount on both sides. Since there are different compositions of dialysate, electrolytes and other solutes can be manipulated to desired lab values. Dialysis can cause a decrease in osmolality due to removal of urea and other small solutes. HD also removes creatinine, potassium, phosphate, calcium, and magnesium, increase or decrease sodium, and change pH level by removing or infusing bicarbonate.

There are limited published data concerning the optimum medical management of the dialysis patient undergoing surgery. Dialysis patients have a higher perioperative mortality compared with patients without end-stage kidney disease (ESKD)

ROUTINE DIALYSIS PRIOR TO SURGER depending upon whether the patient is on hemodialysis or peritoneal dialysis.

- **Hemodialysis -** Hemodialysis patients should be dialyzed the day before surgery, if possible.
  If dialysis is provided the day of surgery, it is important to institute measures that avoid prolonged anticoagulation.
  The dialysis prescription is generally the same (or as close as possible to) the usual prescription for the individual patient. However, the patient's laboratory values (ie, serum potassium, calcium, and phosphorus) and the dialysate calcium and potassium concentration should be carefully reviewed and adjusted in order to use the dialysate potassium, calcium, and bicarbonate that will allow the patient to go to the operating room with normal or near-normal plasma concentrations.

The amount of ultrafiltration should be carefully adjusted to ensure that the patient is at or close to dry weight prior to surgery.

- **Peritoneal dialysis -** For peritoneal dialysis patients, some recommend increasing the amount of dialysis approximately a week before surgery. The dialysis time is increased in order to prevent under-dialysis postoperatively in the event that resumption of peritoneal dialysis is delayed (eg, due to an ileus or constipation). Patients who are on continuous ambulatory peritoneal dialysis (CAPD) add an additional exchange each day. Patients who are on automated peritoneal dialysis add one or two hours per day on the cycler. However, there are no published data to support this approach.

Similar to hemodialysis patients, peritoneal dialysis patients should be at their dry weight prior to surgery.

Hypotension secondary to vasodilation and negative inotropy with the use of induction and maintenance agents utilized for anesthesia frequently results in perioperative fluid loading to maintain hemodynamic stability.

Indications for dialysis — The major indications for urgent preoperative dialysis are hyperkalemia and volume overload.

Hyperkalemia — The potassium concentration that is acceptable for surgery depends on the urgency of the surgery. There are no guidelines that definitively state a maximum safe level of potassium prior to induction of anesthesia.

Elective surgery — For elective surgery, most anesthesiologists are prepared to induce a patient with a serum potassium level <5.5 mEq/L. The potassium concentration that is deemed acceptable for induction of individual patients may vary depending on chronicity of hyperkalemia, location of surgery (freestanding surgery center versus hospital operating room), and type of surgery. The type of surgery varies with respect to blood loss, fluid shifts, and acid-base disturbances, all which affect the rate of rise of the serum potassium concentration.

Hemodialysis can remove 25 to 50 mEq of potassium per hour, with variability based upon the initial serum potassium concentration, the dialyzer, the blood flood rate, and the potassium concentration of the bath . In general, two hours of hemodialysis will suffice to prepare a patient for surgery under most circumstances when K is >5.5.

Nonelective surgery — In general, the approach to hyperkalemic patients who require nonelective surgery is based upon the clinical setting. Important considerations include the anticipated degree of tissue damage and release of potassium during the operation, the urgency for surgery, and determination of whether it is safe to delay surgery for three to four hours while the patient is dialyzed.

All patients with an elevated serum potassium concentration should have a 12-lead electrocardiogram (ECG). Surgery with anesthesia in the face of chronic hyperkalemia (K <6) and no ECG changes is usually well tolerated by the majority of patients. Chronic dialysis patients often have an increased tolerance for hyperkalemia as ECG changes are frequently not seen until the serum potassium concentration exceeds 6.0 to 6.5 mEq/L .Changes in the ECG with hyperkalemia are thought to result from alterations in the transcellular potassium gradient rather than the absolute value of the serum potassium. Dialysis patients often have elevations in total body and intracellular potassium; as a result, the transcellular gradient may not be altered with moderate hyperkalemia, resulting in the absence of hyperkalemic changes on the ECG.

- If there are no ECG changes and the patient is otherwise stable, an individual with a serum potassium of 6.0 to 6.2 mEq/L should be able to safely undergo emergency surgery with close intraoperative monitoring by anesthesiologists . In such cases, hyperkalemia may be treated with medical (ie nondialytic therapies) if there is no functioning dialysis access.

    - If ECG features of hyperkalemia are present, we dialyze the patient. As noted above, two hours of hemodialysis is sufficient to reduce potassium. If dialysis **cannot** be performed prior to surgery, medical management should be initiated . However, even a short hemodialysis session would be preferred, if at all possible.
    - In a true emergency, life-threatening surgical situation, the operation is performed regardless of potassium level. Anesthesiologists will temporize with medical management of the hyperkalemia until a more definitive solution for electrolyte control can be initiated.

Volume overload — The optimal volume status prior to surgery is based in part upon estimates of anticipated fluid to be administered and/or lost during surgery. As a result, a discussion with the surgeon and anesthesiologist regarding perioperative volume status goals is desirable:

- If euvolemia or estimated dry weight is not achieved and/or the patient receives a large volume of fluid during surgery, hypervolemia and possibly pulmonary edema can occur in the immediate postoperative period, thereby necessitating dialysis.
- If too much fluid is removed, there is the risk of hypotension during anesthesia-induced systemic vasodilatation; this can cause many significant complications, including but not limited to thrombosis of the arteriovenous access.

Hemodialysis effects

Definition

Acute effects: hypotension (too much fluid removed), **“dialysis disequilibrium”** (rapid fluid/urea shifts resulting in cerebral edema – headache, nausea, can progress to convulsions and coma) hypercalcemia, *fever*, *arrhythmias* (due to *hypokalemia*) *bleeding* (due to heparinization.)

Chronic effects: hepatitis (B more common than C, due to frequent blood transfusions), **anemia**, infection/bacteremia, gastric emptying time increased.