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Review Article

Perioperative Management of Sickle Cell Disease

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Abstract. Over 30 million people worldwide have sickle cell disease (SCD). Emergent and non-emergent surgical procedures in SCD have been associated with relatively increased risks of peri-operative mortality, vaso-occlusive (painful) crisis, acute chest syndrome, post-operative infections, congestive heart failure, cerebrovascular accident and acute kidney injury. Pre-operative assessment must include a careful review of the patient's known crisis triggers, baseline hematologic profile, usual transfusion requirements, pre-existing organ dysfunction and opioid use. Use of preoperative blood transfusions should be selective and decisions individualized based on the baseline hemoglobin, surgical procedure and anticipated volume of blood loss. Intra- and post-operative management should focus on minimizing hypoxia, hypothermia, acidosis, and intravascular volume depletion. Pre- and post-operative incentive spirometry use should be encouraged.

Keywords: Sickle cell disease, Perioperative management, Transfusion, Surgical procedures.

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Introduction. Over 30 million people worldwide, from 163 countries, have sickle cell disease (SCD), with the highest concentration of the disease among persons of African, Middle Eastern, and Central Indian ancestry.[1-3] SCD patients undergo emergent and elective surgical procedures for SCD complications and for surgical indications common to the general population. **Table 1** lists the most common surgical procedures carried out in SCD patients. Surgeries in the SCD population are associated with higher peri-operative complication rates. We briefly review the epidemiology and pathophysiology of SCD and discuss the major issues in the peri-operative management of SCD patients.

Ideally, peri-operative care of the SCD patient must be a collaborative effort between the surgeon, anesthetist, recovery room staff, primary care physician, and a consulting hematologist experienced in the management of SCD. Unfortunately, in many areas of the world, services from such expert hematologists are not available. It is essential therefore for all physicians who care for SCD patients to become familiar with the perioperative management of SCD patients. This review is therefore directed towards the global audience of generalist physicians, surgeons, anesthetists, nurses, and intensivists involved in the peri-operative management of SCD patients.

Table 1. Common surgical procedures in sickle cell disease.

Abdominal	
	Cholecystectomy
	Splenectomy
	Appendectomy
Cardiac	
	Cardiopulmonary Bypass
	Valve and congenital defect repairs
	Pulmonary Thrombectomy
Genitourinary	
	Cystoscopy
	Transurethral Resection
ENT	
	Tonsillectomy
	Pressure-equalizer tube insertions
Neurosurgery	
	Intracerebral aneurysm ablation
Obstetric & Gynecologic	
	Cesarean Section
	Hysterectomy
	Dilation and Curettage
	Tubal Ligation
Orthopedic Procedures	
	Hip Arthroplasty
	Drainage of bone infections
Vascular	
	Insertion of Indwelling Vascular Access Lines

Genetics of Sickle Cell Disease. The normal adult hemoglobin, Hemoglobin A (HbA), is formed by two α and two β globin chains ($\alpha_2\beta_2$), clustered on chromosomes 16 and 11. The sickle hemoglobin mutation (Hb S) results from a single amino acid substitution of valine for glutamic acid in the 6th position of the β globin chain.[4] The sickle cell gene evolved independently in sub-Saharan Africa, the Arabian Peninsula and Central India.[2] Several other hemoglobin gene variants have emerged in different populations from spontaneous mutations. These are either structural variants resulting from changes in the amino acid sequence or thalassemias that lower or abolish globin chain production. Homozygous inheritance of the sickle cell gene (Hb SS) or co-inheritance of the sickle cell gene with another mutated hemoglobin gene variant results in SCD.[1-7] The compound heterozygotes include a combination of HbS with hemoglobin gene variants such as Hemoglobin C (Hb SC), Hemoglobin D (Hb SD), Hemoglobin E (Hb SE), Hemoglobin O Arab (Hb SO Arab) or with beta thalassemia (Hb Sβa thal). A combination of HbS with the normal hemoglobin A results in the carrier state (Sickle Cell trait), Hb AS, which is not considered sickle cell disease.[2] Globally the homozygous Hb SS, also called Sickle Cell Anemia, is the most common sickle cell genotype.[1,3-6]

The various sickle cell disease states differ in the percent HbS concentration (**Table 2**).[8] This results in considerable heterogeneity in the phenotypic manifestations of sickle cell disease, including the baseline hemoglobin level. Overall, the most severe manifestations are seen in the homozygous Hb SS and Hb Sβ^0 thal genotypes.

Pathophysiology. The hallmark of sickle cell disease is recurrent vaso-occlusion. It is now apparent that complex and dynamic mechanisms underlie the vaso-occlusive process, of which Hb S polymerization plays an essential role.[9-15] Hemoglobin deoxygenation in SCD leads to sickling of the RBCs as a result of Hb S polymerization. The process of polymerization is triggered and/or enhanced by hypoxia, vascular stasis, infection, inflammation, increased blood viscosity, vasoconstriction, dehydration, hypotension, stress, cold temperature, acidosis, and decreased flow.[9,10] There is RBC clumping, endothelial damage, and inflammatory response with release of mediators that up-regulate cell adhesion molecules on the endothelial cells. These lead to adhesion of sickled cells to the vascular

Table 2. Percent Hb S concentration in selected major Sickle Cell genotypes.

Genotype	# Hb S	% other Hemoglobins	Hb (g/dL)
Hb SS	>90%	Hb A 0% Hb A2 <3.5% Hb F <10%	6-9
Hb Sβ0 thal	>80%	Hb A2 >3.5% Hb F <20%	7-9
Hb Sβ+ thal	>60%	Hb A 10-30% Hb A2 >3.5% Hb F <20%	9-12
Hb SC	50%	Hb C 45% Hb A2 <3.5% HbF ≤1.0	9-14

endothelium, fibrin deposition and microvascular occlusion. Neutrophils, monocytes, invariant natural killer T (iNKT) cells, other leukocytes, and platelets are activated and participate in the vascular occlusion. The vascular occlusion delays flow, further enhancing deoxygenation of the affected red blood cells, leading to worsening polymerization. The resulting ischemia creates a feedback loop of deteriorating endothelial activation. These changes occur in multiple vascular beds resulting in multisystem involvement. The half-life of the sickled red cells is markedly reduced from the normal 120 days to 10 to 12 days, resulting in a chronic hemolytic anemia, with its attendant hyper-proliferative bone marrow and hyperdynamic circulation, even at baseline.[4,16,17]

Surgical Complications. Historically, surgical procedures in sickle cell patients have been associated with relatively increased risks of peri-operative mortality, vaso-occlusive (painful) crisis, acute chest syndrome, post-operative infections, and congestive heart failure.[18-29] Careful pre-operative assessment and judicious peri-operative management are critical in mitigating these risks.

Pre-Operative Assessment and Interventions. The goals of pre-operative assessment are to ensure that the patient is medically optimized for the intended surgical procedure, estimate the risk of peri-operative complications, and plan for the optimal management of anticipated peri-operative complications. Sickle cell disease must be appreciated as a multisystem disease that affects almost all organs.[30]

Currently, none of the generally available surgical risk calculators have been validated for patients with sickle cell disease.[31-33] Risk estimates obtained using these surgical risk calculators, while helpful, must be presumed to underestimate the overall peri-operative risk in SCD patients.

During the pre-operative assessment one must ascertain the sickle cell genotype, frequency of crisis and the date of patient's last crisis, average length of hospital stay during painful crisis, known triggers for crisis, baseline level of activity, baseline opioid use, steady-state hemoglobin and hematocrit, reticulocyte count, and WBC count, as well as history of blood transfusions. A sample pre-operative data abstraction form is attached as Supplementary Appendix 1. The severity of pre-existing cardiac and pulmonary complications of SCD need to be ascertained in the pre-operative assessment. **Table 3** lists selected known cardiac and pulmonary complications in SCD patients. Routine pre-operative cardiac echography in all SCD undergoing general anesthesia is unnecessary and will likely not impact the peri-operative management in most patients. Nonetheless, given the relatively large amounts of fluids administered to SCD patients, cardiac echo may be useful to ascertain the extent of cardiac dysfunction in patients with prior history of heart failure, poor functional status or with dyspnea at baseline. In resource-poor countries (where obtaining cardiac echography may not be readily accessible), patients who develop breathlessness, fatigue or palpitations and have to stop when walking at their own pace on a level ground or when climbing a flight of stairs must be presumed to have significant cardiac or pulmonary dysfunction. Inability to perform these tasks will correspond to class III or higher on the New York Heart Association heart failure classification,[35] or less than 4 metabolic equivalents functional activity level.[34] Extreme caution must be used in decisions

Table 3. Cardiac and Pulmonary Complications in Sickle Cell disease.

Cardiac	Congestive Heart Failure	
	Cardiomegaly	
	Cardiomyopathy	
	Mitral Valve Prolapse	
	Hypertension	
	EKG Abnormalities	
		Left Ventricular Hypertrophy
		Right Ventricular Hypertrophy
		First degree A-V Block
	Cardiac Hemosiderosis	
Pulmonary	Atelectasis	
	Acute Chest Syndrome	
		Pulmonary Embolism
		Fat Embolism
		Pneumonia
	Pulmonary Hypertension	
	Plastic Bronchitis	
	Reactive airway disease	
	Restrictive lung disease	
	Chronic Sickle Cell Lung Disease	

about the volume of fluid administration in such patients.

Special steps should be taken during the peri-operative process to avoid triggering a sickle cell crisis. Common triggers of the acute crisis include anxiety, emotional stress, infection, dehydration, acidosis, hypoxia, vascular stasis and increased blood viscosity.[9,11] Adequate counseling, including education of patient about the procedure and awareness of patient's special considerations, can significantly assuage the emotional stress and anxiety about the surgical procedure. If needed, anxiolytics can be used cautiously.

Intracellular dehydration is a known trigger for Hb S polymerization.[9-11] Whenever possible, prolonged pre-operative fasting must be avoided. Patients should be encouraged to drink clear fluids up until 2-4 hours before surgery. For patients undergoing moderate or major procedures, intravenous hydration must be used. Supplement 2 lists the composition, osmolarity and pH of commonly used solutions. Normal saline (9g/dl of sodium chloride contains 154 milliequivalents of sodium, pH of 5.5, osmolarity of 308 milliosmoles per liter) is acidic and increases the viscosity of the blood.[36] Hypotonic fluids, in theory, decrease RBC sickling and are preferred.[37-39] Excessive fluid loading is associated with pulmonary edema and can precipitate acute chest syndrome and thus needs to be avoided.[40,41] Exactly how much fluid should be given is unknown.[42] Standard maintenance amounts may be used in most patients and the intravenous infusion rate must be significantly reduced once the patient resumes oral intake. Changes in daily weights and input/output data may help guide the fluid management decisions.

Hypoxia is the most important trigger of sickle cell crisis and needs to be avoided.[9-14,43] However, routine use of oxygen supplementation is not advisable as its potential harm far exceeds its benefits.[44-46] To identify those in need of supplemental oxygen, oxygen monitoring in the perioperative period must be considered mandatory in all patients. Pulse oximetry does not correlate well with arterial oxygen tension in some SCD patients.[47] It is therefore important that arterial blood gas confirmation is obtained in hypoxic patients.

The use of incentive spirometry has been shown to decrease the incidence of atelectasis and acute chest syndrome in hospitalized patients.[40,48,49] Accordingly, use of incentive spirometry before and after the procedure needs to be strongly encouraged. Given the relatively high frequency of acute chest syndrome following high risk (intracranial, cardiovascular, and intrathoracic) procedures and the need to monitor arterial blood gases during its management, establishing baseline blood gas values in such patients is advised. Routine assessment of baseline pulmonary function tests is not needed.[50,51]

The role of routine pre-operative blood transfusions, either simple RBC transfusion or exchange transfusion, remains controversial.[27-29,52-68] Theoretically, transfusion will reduce the percent HbS concentration and improve tissue oxygen delivery. However, transfusion increases the blood viscosity and thereby increases the risk of Hb polymerization.[55,56] There is a net benefit of increased tissue oxygen delivery over increased viscosity when the transfused hemoglobin level is kept at or just below 10g/dl.[55,56] However, no increase in perioperative complications has been observed in centers that do not routinely offer preoperative transfusion, or in countries with low availability of blood for routine preoperative transfusion.[54] Also, transfusion is associated with increased risks of alloimmunization, iron overload and may be associated with increased risk of infections.

The largest cohort study of surgery in SCD patients, the Cooperative Study of Sickle Cell Disease, found beneficial effects of preoperative transfusion in Hb SC patients for all surgical procedures.[27] For Hb SS patients, peri-operative transfusion was associated with a lower rate of SCD-related postoperative complications in patients undergoing low-risk procedures (such as inguinal hernia repair, myringotomy, dilatation and curettage, and surgeries on eyes, skin, and nose). However, there was no association between transfusion and sickle-related postoperative complications among patients who had moderate risk procedures (throat, neck, spine, proximal extremities, hip replacement, genitourinary system, and intra-abdominal).[27]

Using a target hemoglobin level of 10g/dl, the Preoperative Transfusion in Sickle Cell Disease study Group performed a multicenter, randomized controlled trial and found conservative, simple RBC transfusion was equally effective as exchange transfusion (maintaining hemoglobin at 10g/dl and HbS level of 30% or less) in preventing

peri-operative complications.[58] However, the study did not have a comparable group without blood transfusion. Also, transfusion was associated with increased rates of allo-immunization.

Recently, the Transfusion Alternatives Preoperatively In Sickle Cell Disease (TAPS) study,[53] a multicenter randomized trial of 67 Hb SS and Hb $S\beta^0$ thal patients, found a reduction in clinically important complications in the transfused patients undergoing medium risk procedures (15% vs. 39%, p=0.02). In contrast, preoperative transfusion was associated with a higher rate of post-operative complications in a matched prospective study of 40 patients undergoing laparoscopic cholecystectomy for cholelithiasis in Saudi Arabia (25% vs. 0%, p=0.007).[59]

Tables 4 and **5** summarize the findings of published original studies on pre-operative transfusions.[27-29,53,57-68] A systematic review and meta-analysis of the randomized and observational studies found no difference in perioperative mortality, vascular, or non-vascular perioperative complications between those treated with preoperative transfusion versus no transfusion strategy.[52] This review notwithstanding, the current consensus in the United States is "to bring the hemoglobin level to 10 g/dl prior to undergoing a surgical procedure involving general anesthesia" in patients with Hb SS or $S\beta^0$ thal.[56]

Based on the current aggregate data, it is fair to advocate that transfusion decisions need to be selective and individualized based on the type of SCD, the baseline hemoglobin, the baseline cardiopulmonary reserve, and the risk of the surgical procedure. If a decision to transfuse is made, phenotypically matched blood must be used to minimize the risk of alloimmunization. For those with hemoglobin levels less than 9 g/dl, simple RBC transfusion is equally efficacious compared to exchange transfusion. For those with high baseline hemoglobin (above 9 g/dl), perhaps exchange (or partial exchange) transfusion, rather than simple transfusion, should be used to avoid raising the hemoglobin level above 10g/dl.

Cold weather and skin chilling are known precipitants of the crisis in some sickle cell patients.[9,10] It has been hypothesized that hypothermia leads to exaggerated reflex vasoconstriction, increased capillary transit time, red cell sludging, and may lead to shunting of blood from the bone marrow.[15,69,70] Accordingly, thermoregulation has been strongly recommended in the perioperative care of SCD patients. Warm intravenous fluids are advised. Many centers fearfully avoid hypothermia, even in cardiac surgery, in sickle cell patients. To date, there are no known reports of peri-operative hypothermia as a contributory cause of perioperative vaso-occlusive crisis. In vitro, there is delayed RBC sickling and slowing of polymerization with hypothermia. Indeed, hypothermic cardiopulmonary bypass, including cold crystalloid cardioplegia and systemic hypothermia, have been and continue to be successfully used in cardiac surgery in sickle cell patients at one major center without any significant adverse effects.[54,71] This center's protocol meticulously avoids hypoxia, acidosis, hypotension, and dehydration in these patients. It has been suggested that the level of anesthesia needed for cardiopulmonary bypass impairs thermoregulatory vasoconstriction, the presumed mechanism of hypothermia-induced sickling.[25,54]

Anesthetic Agents. In general, anesthetic techniques used in SCD patients must minimize exposure to hypoxemia, hypercapnia, acidosis, hypothermia, and hypovolemia during surgery. Care with positioning is important to minimize venous stasis. Respiratory depressants are avoided. Intubations are usually performed after paralysis with a short-acting agent. During induction, steps are taken to avoid breath holding, laryngeal spasm and struggling. A variety of anesthetic agents have been used successfully and the choice of a specific

Table 4. Randomized control trials.

Year	Author	Size	Intervention	Comparison	Genotype	Main Findings
2013	Howard et al.[53]	70	Simple RBC transfusion	No transfusion	SS, Sβ0thal	High SCD-related complications in the no transfusion group
2002	Al-Jaouni et al.[62]	369	Simple or partial exchange	No transfusion	SS	Increased complication rates in the transfused group
1995	Vichinsky et al.[58]	604	Exchange transfusion	Conservative Transfusion	SS	No difference in post-operative SCD-related complications

Table 5. Observational studies

Year	Author	Size	Study Description	Genotype	Main Findings
2013	Amar et al.[63]	14	Retrospective review. Simple or exchange transfusion versus no transfusion	SS	No benefit from routine pre-op transfusion
2011	Aziz et al.[61]	40	Retrospective review. Simple or exchange transfusion versus no transfusion	??	No difference between exchange ad conservative transfusion. Lowest rate in the no transfusion group.
2009	Marulanda et al.[64]	23	Aggressive versus simple transfusion	SS	Both were effective. Lowest complication rate in the aggressive transfusion group.
2008	Al-Samak et al.[59]	85	Simple versus exchange versus no transfusion	SS	Complication rates of 22.2% in the exchange, 9.5% in simple transfusion, and 4.34% in the no transfusion group
2008	Augier et al.[65]	29	Restrospective review. Transfusion rate of 32%	79% were SS	50% complication rate for the transfusion group and 27% for the no transfusion group
2005	Buck et al.[29]	114	Exchange versus top up transfusion	SS, SC, SB thal	No difference
2005	Fu et al.[67]	28	Retrospectve review of minor elective procedures. No pre-operative transfusion in 85% of patients.	SS	No acute chest syndrome. Fever and/or transient pain in 15% of patients.
2003	Wali et al.[60]	39	Conservative versus aggressive transfusion	SS, SC. SB thal	No difference
1998	Neumayr et al.[68]	92	Retrospective review. Transfusion versus no transfusion.	SC	No difference for minor procedures. Higher complication rates for abdominal procedures in the no transfusion group.
1997	Haberkem et al.[28]	364	Exchange vrs Simple transfusion versus no transfusion	SS/ $S\beta^0$ thal	No difference
1995	Koshy et al.[27]	717	Cohort study. Transfusion (simple or exchange) versus no transfusion	SS, SC, Sβ thal	SC – transfusion gp had lower rates of complications. SS – no difference for intermediate risk procedures
1993	Bhattacharyya et al.[66]	22	Retrospective review. Exchange versus sequential transfusion	SS, SB thal	No difference
1993	Griffin and Buchanan.[57]	54	No pre-op transfusion	?	No increase in complication rates (compared to reported rates from other centers)

study, the use of halothane for anesthesia was associated with the lowest risk of perioperative atelectasis (25%) as compared with isoflurane (83%) or enflurane (59%).[72] The choice of agent used had no effect on SCD-related morbidity.

The relative safety of general anesthesia compared to regional anesthesia in SCD patients is unclear. SCD related complications were more frequent in those who received regional anesthesia compared with those who received general anesthesia in the Cooperative Study of Sickle Cell Disease.[27] However, there was no adjustment for potential confounding by the effect of obstetric procedures, for which regional procedures were more often used. Similarly, regional procedures were often used for sicker patients who were considered too high a risk for general anesthesia. Other studies have failed to confirm such an association between regional anesthesia and increased complications.[73,74] Theoretically, in regional anesthesia there is regional hypoperfusion, venous stasis, and lack of control of ventilation. There is a redistribution of blood flow with increase in capillary and venous oxygen tension in the blocked region, and compensatory vasoconstriction in the non-blocked area with resultant fall in oxygen.

Surgical Procedures. The uses of laparoscopic procedures have significantly shortened hospital stay. Among SCD patients, laparoscopic cholecystectomy and laparoscopic splenectomy are preferred compared to open cholecystectomy or splenectomy. In many centers, it has been associated with significant reductions in post-operative complications.[75-77] In one center, however, laparoscopic surgery did not decrease the risk of developing ACS.[78]

The use of an arterial tourniquet in SCD patients is controversial. It is dogma that application of arterial tourniquet creates ideal conditions for sickling from the stasis, hypoxia, and acidosis distal to the tourniquet. As such, SCD has long been considered a contraindication to tourniquet use.[79] This dogma is now being questioned.[80-83] Tourniquets have been used successfully in SCD patients with acceptable or no complications, while paying "meticulous attention to preoperative preparation and intraoperative management".[83] It has been postulated that the acute acidotic environment induced by the tourniquet application alters endothelium-RBC membrane interactions, promote systemic vasodilatation, and "alter a host of other biochemical reactions" that on balance may not promote sickling.[83] No randomized studies have been conducted. A review of the rather limited published reports suggests that tourniquets may be used with relative safety in most patients with sickle cell disease with proper perioperative management.[84]

Radiological Contrast. Contrast imaging studies are often needed in cardiac and neurologic surgeries. Hyperosmolar contrast media can induce RBC dehydration, polymerization and sickling, with a resultant sickle crisis.[85] Isotonic media have no such deleterious effects.[86] Accordingly, it is recommended that low osmolar or isotonic contrast media be used in sickle cell disease patients.[86] Radiologic contrast should be avoided in SCD patients with renal failure.

Postoperative Care.

Pain control. An important issue in the perioperative management of sickle cell disease patients is adequate pain control. Nonpharmacologic measures, including music, relaxation, heat or ice packs, may be used as adjuncts to pharmacologic pain management.[56] The patient's self-report, in addition to the vital signs, needs to be incorporated in adjusting pain medications. Many adult SCD patients in the US have had multiple exposures to opioids, are often opioid-tolerant, and tend to require large doses of opiates for adequate pain control.[56,87] If known, patients' opioid doses used for management of their painful crises can serve as a guide to post-operative pain management. A combination of long-acting opioids and a short-acting opioid for breakthrough pain often provides adequate relief. Alternatively, continuous administration of pain medications, through the use of patient-controlled analgesia pumps, may be used. Morphine and hydromorphone are the major opioid agonists used for severe pain management in sickle cell patients in the post-operative period. These drugs have no ceiling effect. However, they can cause severe sedation and respiratory depression. Hence, doses should be discontinued or skipped in patients with a respiratory rate less than 10 and in those with severe sedation.

Acute chest syndrome. Sickle cell patients are at risk for acute chest syndrome in the immediate post-operative period. Excessive administration of IV fluids, as well as respiratory sedation from the use of opioid medications and adjuvants, potentiate this risk.[40] Maintaining adequate ventilation is the best preventive measure. Pre and post-operative use of incentive spirometry is strongly advised. The role of prophylactic CPAP in the immediate post-operative period has yet to be evaluated. Fluid administration should not exceed one and one-half (1.5) times the patient's maintenance requirements.[40,56]

Prompt recognition of acute chest syndrome is important. By definition, acute chest syndrome is the presence of a new pulmonary infiltrates with chest pain, tachypnea, hypoxia, dyspnea, cough, fever, or leukocytosis.[30,40,56] However, not all the cardinal signs and symptoms may be present initially. The spectrum of presentation may range from mild, where hypoxia is minimal, to severe acute respiratory distress. Management consists of ensuring adequate ventilation, including the use of mechanical ventilation in severe cases, oxygen administration, bronchodilators (even in the absence of wheezing), antibiotics, moderate use of analgesia, and judicious hydration.[56] Simple blood transfusion or exchange transfusion in severe cases can accelerate the resolution. The use of steroids, particularly in adult patients, is controversial.[56] The use of nitric oxide or other vasodilators (calcium channel blockers, prostacyclin), and the nonionic surfactant poloxamer 188, is currently undergoing clinical trials.[56]

Deep vein thrombosis prophylaxis. Sickle cell disease is a hypercoagulable state.[88-90] Current evidence suggests increased platelet and coagulation activation, even at the patient's basal

state. SCD patients have low circulating levels of anticoagulant proteins C and S, moderate thrombocytosis, decreased platelet thrombospondin-1 content, and increased levels of markers of platelet activation.[88-90] Adequate deep vein thrombosis prophylaxis must be instituted after all major surgeries until the patients are sufficiently ambulatory.

Post-operative fever. Post-operative fever is a common complication of many major surgical procedures in the general population, with estimates ranging from 14% to 91% depending on the type of procedure.[91,92] Major traumatic surgeries are associated with higher risks of postoperative fever. Highest fever rates are observed after major orthopedic procedures.[91] Interleukin – 6 is an important driver of this response. Fever tends to be non-infectious in etiology if it occurs within the intra-operative period or in the first 48-hours. Other non-infectious causes include administration of blood products, heparin, and other medications. Infections account for most fevers occurring after the second postoperative day.[91,92]

Reported rates of post-operative fever among SCD patients are comparable to rates for non-SCD patients.[27,93,94] However, because of the higher rates of functional asplenia in SCD patients, they are more susceptible to invasive bacterial infections from encapsulated organisms such as Streptococcus pneumonia and Hemophilus influenza. These infections can be overwhelming if therapy is delayed. Fortunately, immunization with pneumococcal and Hemophilus influenza vaccinations have significantly decreased these risks in many countries. Nonetheless, the occurrence of post-operative fever in SCD requires careful clinical and laboratory evaluation. The extent of diagnostic work-up must be guided by the history and physical examination findings. Fever occurring after 48 hours must be managed as infectious in origin until proven otherwise. Common causes of infection include urinary tract infections, pneumonia, intravascular catheter-related infections, surgical site infections, and/or infected prosthesis. Viral infections from transfused blood products are now rare and tend to occur after 4 weeks.[92]

Conclusions. In conclusion, pre-operative assessment of SCD patients undergoing emergent or non-emergent surgery must include a careful review of the patient's known crisis triggers, baseline hematologic profile, standard transfusion requirements, pre-existing organ dysfunction and opioid use. Use of preoperative blood transfusions should be selective, and decisions must be individualized based on the baseline hemoglobin, surgical procedure and anticipated volume of blood loss. Intra- and post-operative management should focus on minimizing hypoxia, hypothermia, acidosis, and intravascular volume depletion. Excessive administration of IV fluids, as well as respiratory sedation from the use of opioid medications and adjuvants, potentiate the risk of acute chest syndrome. Use of pre- and post-operative incentive spirometry should be strongly encouraged. Arterial tourniquets and hypothermic cardiopulmonary bypass have been safely used in SCD patients at some centers.

Take Home Points:

1. Surgical procedures in SCD have been associated with relatively increased risks of peri-operative mortality, vaso-occlusive (painful) crisis, acute chest syndrome, post-operative infections, congestive heart failure and acute kidney injury.
2. Use of preoperative blood transfusions should be selective.
3. Intra- and post-operative management should focus on minimizing hypoxia, hypothermia, acidosis, and intravascular volume depletion.
4. Pre- and post-operative use of incentive spirometry decreases the risk of acute chest syndrome.
5. Use of arterial tourniquets and hypothermic cardiopulmonary bypass in SCD patients, though controversial, have been safely utilized at some centers.

References:

1. Modell B, Darlison MW, Moorthie S, Blencowe H, Petrou M, Lawn J. Epidemiologic methods in community genetics and model global database of congenital disorders. 2016 (in Press).
2. Tsaras G, Owusu-Ansah A, Boateng FO, Amoateng-Adjepong Y. Complications associated with sickle cell trait: a brief narrative review. The American Journal of Medicine, 2009; 122(6): 507-512. https://doi.org/10.1016/j.amjmed.2008.12.020 PMid:19393983
3. Piel FB, Hay SI, Gupta S, Weatherall DJ, Williams TN. Global burden of sickle cell anaemia in children under five, 2010–2050: modelling based on demographics, excess mortality, and

interventions. PLoS Medicine. 2013 Jul 16;10(7):e1001484.
4. Ashley-Koch A, Yang Q, Olney R S. Sickle hemoglobin (Hb S) allele and sickle cell disease: a HuGE review. American Journal of Epidemiology 2000; 151(9): 839-845. https://doi.org/10.1093/oxfordjournals.aje.a010288 PMid:10791557
5. Steinberg MH, Rodgers GP. Pathophysiology of sickle cell disease: role of cellular and genetic modifiers. Seminars in Hematology 2001; 38 (4): 299-306. https://doi.org/10.1016/S0037-1963(01)90023-X
6. Hassell K L. Population estimates of sickle cell disease in the US. American Journal of Preventive Medicine 2010; 38(4): S512-S521.
7. Shafer FE, Lorey F, Cunningham GC, et al. Newborn screening for sickle cell disease: 4 years of experience from California's newborn screening program. Journal of Pediatric Hematology/Oncology 1996; 18(1): 36-41. https://doi.org/10.1097/00043426-199602000-00007 PMid:8556368
8. National Heart, Lung, and Blood Institute. Evidence-based management of sickle cell disease: expert panel report, 2014. Washington, DC: National Institutes of Health. 2014.
9. Noguchi CT, Schechter AN, Rodgers GP. Sickle cell disease pathophysiology. Baillière's Clinical Haematology 1993; 6(1): 57-91. https://doi.org/10.1016/S0950-3536(05)80066-6
10. Kato GJ, Hebbel RP, Steinberg MH, Gladwin MT. Vasculopathy in sickle cell disease: Biology, pathophysiology, genetics, translational medicine, and new research directions. American Journal of Hematology 2009; 84(9): 618-625. https://doi.org/10.1002/ajh.21475 PMid:19610078 PMCid:PMC3209715
11. Manwani D, Frenette PS. Vaso-occlusion in sickle cell disease: pathophysiology and novel targeted therapies. Blood 2013; 122(24): 3892-3898. https://doi.org/10.1182/blood-2013-05-498311 PMid:24052549 PMCid:PMC3854110
12. Chirico EN, Pialoux V. Role of oxidative stress in the pathogenesis of sickle cell disease. IUBMB life 2012; 64(1): 72-80. https://doi.org/10.1002/iub.584 PMid:22131167
13. Kassim AA, DeBaun MR. Sickle cell disease, vasculopathy, and therapeutics. Annual Review of Medicine 2013; 64: 451-466. https://doi.org/10.1146/annurev-med-120611-143127 PMid:23190149
14. Frenette PS. Sickle cell vaso-occlusion: multistep and multicellular paradigm. Current Opinion in Hematology 2002; 9(2): 101-106. https://doi.org/10.1097/00062752-200203000-00003 PMid:11844991
15. Kaul DK, Finnegan E, Barabino GA. Sickle red cell–endothelium interactions. Microcirculation 2009; 16(1): 97-111. https://doi.org/10.1080/10739680802279394 PMid:18720225 PMCid:PMC3059190
16. McCurdy PR, Sherman AS. Irreversibly sickled cells and red cell survival in sickle cell anemia: a study with both DF32P and 51CR. The American Journal of Medicine 1978; 64(2): 253-258. https://doi.org/10.1016/0002-9343(78)90053-0
17. Eadie GS, Brown IW, Analytical review: red blood cell survival studies. Blood 1953; 8(12): 1110-1136. PMid:13105714
18. Holzmann L, Finn H, Lichtman HC, Harmel MH. Anesthesia in patients with sickle cell disease: a review of 112 cases. Anesthesia & Analgesia 1969; 48(4): 566-572. https://doi.org/10.1213/00000539-196907000-00013
19. Patterson RH, Wilson H, Diggs LW. Sickle-Cell Anemia: a Surgical Problem. II. Further Observation on the Surgical Implications of Sickle-Cell Anemia. Surgery 1950; 28(2): 393-402. PMid:15442815
20. Browne RA. Anaesthesia in patients with sickle-cell anaemia. British Journal of Anaesthesia 1965; 37(3): 181-188. https://doi.org/10.1093/bja/37.3.181 PMid:14277955
21. Shapiro ND, Poe MF. Sickle-cell disease: an anesthesiological problem. Anesthesiology 1955; 16(5): 771. https://doi.org/10.1097/00000542-195509000-00017
22. Oduro KA. Anaesthesia and sickle cell haemoglobin. British Journal of Anaesthesia 1973; 45(1):123. https://doi.org/10.1093/bja/45.1.123-a PMid:4696431
23. Oduro KA, Searle JF. Anaesthesia in sickle-cell states: a plea for simplicity. British Medical Journal 1972; 4(5840): 596-8. https://doi.org/10.1136/bmj.4.5840.596
24. Searle JF. Anaesthesia in sickle cell states. Anaesthesia 1973; 28(1): 48-58. https://doi.org/10.1111/j.1365-2044.1973.tb00284.x PMid:4568880
25. Firth PG, Head CA. Sickle cell disease and anesthesia. Anesthesiology 2004;101: 766-786. https://doi.org/10.1097/00000542-200409000-00027
26. Vichinsky EP, Neumayr LD, Haberkern C, et al. The perioperative complication rate of orthopedic surgery in sickle cell disease: report of the National Sickle Cell Surgery Study Group. American Journal of Hematology 1999, 62(3), 129-138. https://doi.org/10.1002/(SICI)1096-8652(199911)62:3<129::AID-AJH1>3.0.CO;2-J
27. Koshy M, Weiner SJ, Miller ST, et al. Surgery and anesthesia in sickle cell disease. Cooperative Study of Sickle Cell Diseases. Blood 1995; 86(10): 3676-3684. PMid:7579333
28. Haberkern CM, Neumayr LD, Orringer EP, et al. Cholecystectomy in sickle cell anemia patients: perioperative outcome of 364 cases from the National Preoperative Transfusion Study. Blood 1997; 89(5):1533-1542. PMid:9057634
29. Buck J, Davies SC. Surgery in sickle cell disease. Hematology/Oncology clinics of North America 2005; 19(5): 897-902. https://doi.org/10.1016/j.hoc.2005.07.004 PMid:16214650
30. Ballas SK, Lieff S, Benjamin LJ, et al. Definitions of the phenotypic manifestations of sickle cell disease. Am J Hematol. 2010 Jan;85(1):6-13 PMid:19902523 PMCid:PMC5046828
31. Gupta PK, Gupta H, Sundaram A, Kaushik M, Fang X, Miller WJ, Esterbrooks DJ, Hunter CB, Pipinos II, Johanning JM, Lynch TG. Development and validation of a risk calculator for prediction of cardiac risk after surgery. Circulation. 2011 Jan 1: CIRCULATIONAHA-110.
32. Bilimoria KY, Liu Y, Paruch JL, Zhou L, Kmiecik TE, Ko CY, Cohen ME. Development and evaluation of the universal ACS NSQIP surgical risk calculator: a decision aid and informed consent tool for patients and surgeons. Journal of the American College of Surgeons. 2013 Nov 1;217(5):833-42. https://doi.org/10.1016/j.jamcollsurg.2013.07.385 PMid:24055383 PMCid:PMC3805776
33. Ford MK, Beattie WS, Wijeysundera DN. Systematic review: prediction of perioperative cardiac complications and mortality by the revised cardiac risk index. Annals of Internal Medicine. 2010 Jan 5;152(1):26-35. https://doi.org/10.7326/0003-4819-152-1-201001050-00007 PMid:20048269
34. Jette M, Sidney K, Blümchen G. Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. Clinical Cardiology. 1990 Aug 1;13(8):555-65. https://doi.org/10.1002/clc.4960130809 PMid:2204507
35. Kubo SH, Schulman S, Starling RC, Jessup M, Wentworth D, Burkhoff D. Development and validation of a patient questionnaire to determine New York Heart Association classification. Journal of Cardiac Failure. 2004 Jun 1;10(3):228-35. https://doi.org/10.1016/j.cardfail.2003.10.005 PMid:15190533
36. Coran AG, Ballantine TV, Horwitz DL, Herman CM. The effect of crystalloid resuscitation in hemorrhagic shock on acid-base balance: A comparison between normal saline and Ringer's lactate solutions. Surgery 1971;, 69(6): 874-880. PMid:5578448
37. Guy RB, Gavrilis PK, Rothenberg SP. In vitro and in vivo effect of hypotonic saline on the sickling phenomenon. The American Journal of the Medical Sciences 1973; 266(4): 267-277. https://doi.org/10.1097/00000441-197310000-00005 PMid:4757805
38. Carden MA, Fay M, Sakurai Y, McFarland B, Blanche S, DiPrete C, Joiner CH, Sulchek T, Lam WA. Normal saline is associated with increased sickle red cell stiffness and prolonged transit times in a microfluidic model of the capillary system. Microcirculation. 2017 Jul 1;24(5). https://doi.org/10.1111/micc.12353 PMid:28106307
39. Carden MA, Fay ME, Lu X, Mannino RG, Sakurai Y, Ciciliano JC, Hansen CE, Chonat S, Joiner CH, Wood DK, Lam WA. Extracellular fluid tonicity impacts sickle red blood cell deformability and adhesion. Blood. 2017 Dec 14;130(24):2654-63. https://doi.org/10.1182/blood-2017-04-780635 PMid:28978568
40. Vichinsky EP, Styles LA, Colangelo LH et al. Acute chest syndrome in sickle cell disease: clinical presentation and course. Blood 1997; 89(5), 1787-1792. PMid:9057664
41. Haynes J, Allison RC. Pulmonary edema: complication in the management of sickle cell pain crisis. The American Journal of Medicine 1986; 80(5): 833-840. https://doi.org/10.1016/0002-9343(86)90624-8
42. Jones J, Quinn R. Fluid Replacement Strategies in Sickle Cell Disease. Proceedings of UCLA Healthcare. 2017;21.
43. Kaul DK, Fabry ME, Costantini F, Rubin EM, Nagel RL. In vivo demonstration of red cell-endothelial interaction, sickling and altered microvascular response to oxygen in the sickle transgenic mouse.

Journal of Clinical Investigation 1995; 96(6): 2845. https://doi.org/10.1172/JCI118355 PMid:8675655 PMCid:PMC185995
44. Embury SH, Garcia JF, Mohandas N, Pennathur-Das R, Clark MR. Effects of oxygen inhalation on endogenous erythropoietin kinetics, erythropoiesis, and properties of blood cells in sickle-cell anemia. New England Journal of Medicine 1984; 311(5): 291-295. https://doi.org/10.1056/NEJM198408023110504 PMid:6738642
45. Zipursky A, Robieux IC, Brown EJ, et al. Oxygen therapy in sickle cell disease. Journal of Pediatric Hematology/Oncology 1992; 14(3): 222-228. https://doi.org/10.1097/00043426-199208000-00007
46. Reinhard EH, Moore CV, Dubach R, Wade LJ. Depressant effects of high concentrations of inspired oxygen on erythrocytogenesis. Observations on patients with sickle cell anemia with a description of the observed toxic manifestations of oxygen. Journal of Clinical Investigation 1944; 23(5): 682. https://doi.org/10.1172/JCI101539 PMid:16695150 PMCid:PMC435388
47. Blaisdell CJ, Goodman S, Clark K, Casella JF, Loughlin GM. Pulse oximetry is a poor predictor of hypoxemia in stable children with sickle cell disease. Archives of Pediatrics & Adolescent Medicine 2000; 154(9): 900-903. https://doi.org/10.1001/archpedi.154.9.900
48. Bellet PS, Kalinyak KA, Shukla R, Gelfand MJ, Rucknagel DL. Incentive spirometry to prevent acute pulmonary complications in sickle cell diseases. New England Journal of Medicine 1995; 333(11): 699-703. https://doi.org/10.1056/NEJM199509143331104 PMid:7637747
49. Niss O, Cole-Jenkins C, Davis B, Brooks T, Woolery K, Fetters T, Rollins J, McGann PT, Kalinyak K. Prevention of Acute Chest Syndrome By Implementing a Standardized Process to Improve Incentive Spirometry Use in Hospitalized Patients with Sickle Cell Disease. Blood 2017; 130 (Suppl 1):132.
50. Jacob B, Amoateng-Adjepong Y, Rasakulasuriar S, Manthous CA, Haddad R. Preoperative pulmonary function tests do not predict outcome after coronary artery bypass. Connecticut Medicine 1997; 61(6): 327-332. PMid:9238826
51. Smetana G W. Preoperative pulmonary evaluation. New England Journal of Medicine 1999; 340(12): 937-944. https://doi.org/10.1056/NEJM199903253401207 PMid:10089188
52. Alotaibi GS, Alsaleh K, Bolster L, Sean McMurtry M, Wu C. Preoperative transfusion in patients with sickle cell disease to prevent perioperative complications: A systematic review and meta-analysis. Hematology 2014; 19(8): 463-471. https://doi.org/10.1179/1607845414Y.0000000158 PMid:24611757
53. Howard J, Malfroy M, Llewelyn C, et al. The Transfusion Alternatives Preoperatively in Sickle Cell Disease (TAPS) study: a randomised, controlled, multicentre clinical trial.The Lancet 2013; 381(9870): 930-938. https://doi.org/10.1016/S0140-6736(12)61726-7
54. Edwin F, Aniteye E, Tettey M, et al. Hypothermic cardiopulmonary bypass without exchange transfusion in sickle-cell patients: a matched-pair analysis. Interactive cardiovascular and thoracic surgery 2014; 19(5): 771-776. https://doi.org/10.1093/icvts/ivu249 PMid:25080509
55. Davies SC, Roberts-Harewood M. Blood transfusion in sickle cell disease. Blood Reviews 1997; 11(2): 57-71. https://doi.org/10.1016/S0268-960X(97)90012-6
56. Yawn B P, Buchanan GR, Afenyi-Annan AN, et al. (2014). Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA 2014; 312(10):1033-1048. https://doi.org/10.1001/jama.2014.10517 PMid:25203083
57. Griffin TC, Buchanan GR. Elective surgery in children with sickle cell disease without preoperative blood transfusion. Journal of Pediatric Surgery 1993; 28(5): 681-685. https://doi.org/10.1016/0022-3468(93)90031-F
58. Vichinsky EP, Haberkern CM, Neumayr L, et al. A comparison of conservative and aggressive transfusion regimens in the perioperative management of sickle cell disease. The Preoperative Transfusion in Sickle Cell Disease Study Group. N Engl J Med. 1995; 333(4):206-13. https://doi.org/10.1056/NEJM199507273330402 PMid:7791837
59. Al-Samak ZM, Al-Falaki MM, Pasha AA. Assessment of perioperative transfusion therapy and complications in sickle cell disease patients undergoing surgery. Middle East J Anesthesiol. 2008;19(5):983-95. PMid:18637600
60. Wali YA, al Okbi H, al Abri R. A comparison of two transfusion regimens in the perioperative management of children with sickle cell disease undergoing adenotonsillectomy. Pediatr Hematol Oncol. 2003; 20(1):7-13. https://doi.org/10.1080/0880010390158487 PMid:12687748
61. Aziz AM, Meshikhes AW. Blood transfusion in patients with sickle cell disease requiring laparoscopic cholecystectomy. JSLS: Journal of the Society of Laparoendoscopic Surgeons. 2011 Oct;15(4):480. https://doi.org/10.4293/108680811X13176785203996 PMid:22643502 PMCid:PMC3340956
62. Al-Jaouni S, Al-Muhayawi S, Qari M, Nawas MA, Abdel-Razeq H. The safety of avoiding transfusion preoperatively in patients with sickle cell hemoglobinopathies.Blood 2002 Nov 16 (Vol. 100, No. 11, pp. 21B-21B). 1900 M STREET. NW SUITE 200, WASHINGTON, DC 20036 USA: AMER SOC HEMATOLOGY.
63. Amar KO, Rouvillain JL, Loko G. Perioperative transfusion management in patients with sickle cell anaemia undergoing a total hip arthroplasty. Is there a role of red-cell exchange transfusion? A retrospective study in the CHU of Fort-de-France Martinique. Transfusion Clinique et Biologique. 2013 Mar 1;20(1):30-4. https://doi.org/10.1016/j.tracli.2012.11.001 PMid:23522689
64. Marulanda GA, Minniti CP, Ulrich SD, Seyler TM, Mont MA. Perioperative management for orthopaedic patients with sickle cell anaemia. Journal of Orthopaedic Surgery. 2009 Dec;17(3):346-50. https://doi.org/10.1177/230949900901700321 PMid:20065378
65. Augier R, Tennant I, Reid M, Harding H, Crawford-Sykes A, Bortolusso-Ali S, Isaacs M, Duncan N. Perioperative transfusion of patients with sickle cell disease undergoing surgery at the University Hospital of the West Indies (UHWI). The Internet Journal of Anesthesiology. 2008 Volume 21 Number 2
66. Bhattacharyya N, Wayne AS, Kevy SV, Shamberger RC. Perioperative management for cholecystectomy in sickle cell disease. Journal of Pediatric Surgery. 1993 Jan 1;28(1):72-5. https://doi.org/10.1016/S0022-3468(05)80359-8
67. Fu T, Corrigan NJ, Quinn CT, Rogers ZR, Buchanan GR. Minor elective surgical procedures using general anesthesia in children with sickle cell anemia without pre-operative blood transfusion. Pediatric Blood & Cancer. 2005 Jul 1;45(1):43-7. https://doi.org/10.1002/pbc.20283 PMid:15880471
68. Neumayr L, Koshy M, Haberkern C, Earles AN, Bellevue R, Hassell K, Miller S, Black D, Vichinsky E. Surgery in patients with hemoglobin SC disease. American Journal of Hematology. 1998 Feb 1;57(2):101-8. https://doi.org/10.1002/(SICI)1096-8652(199802)57:2<101::AID-AJH2>3.0.CO;2-#
69. Firth PG. Anaesthesia for peculiar cells—a century of sickle cell disease. British Journal of Anaesthesia 2005; 95(3): 287-299. https://doi.org/10.1093/bja/aei129 PMid:15863440
70. Rubenstein E. Studies on the relationship of temperature to sickle cell anemia. The American Journal of Medicine 1961; 30(1): 95-98. https://doi.org/10.1016/0002-9343(61)90066-3
71. Edwin F, Aniteye E, Tamatey M, Frimpong-Boateng K. eComment: Cardiopulmonary bypass without exchange transfusion in sickle cell disease–An update. Interactive Cardiovascular and Thoracic Surgery 2010; 10(1): 68-69. https://doi.org/10.1510/icvts.2009.214395A PMid:20019041
72. Gross ML, Schwedler M, Bischoff RJ, Kerstein MD. Impact of anesthetic agents on patients with sickle cell disease. The American Surgeon 1993; 59(4): 261-264. PMid:8489089
73. Yaster M, Tobin JR, Billett C, Casella JF, Dover G. Epidural analgesia in the management of severe vaso-occlusive sickle cell crisis. Pediatrics 1994; 93(2): 310-315. PMid:8121746
74. Haberkern CM, Neumayr LD, Orringer EP, et al. Cholecystectomy in sickle cell anemia patients: perioperative outcome of 364 cases from the National Preoperative Transfusion Study. Blood 1997, 89(5), 1533-1542. PMid:9057634
75. Tagge EP, Othersen HB, Jackson SM, et al. Impact of laparoscopic cholecystectomy on the management of cholelithiasis in children with sickle cell disease. Journal of Pediatric Surgery 1994; 29(2): 209-213. https://doi.org/10.1016/0022-3468(94)90320-4
76. Al-Mulhim AS, Al-Mulhim A A. Laparoscopic cholecystectomy in 427 adults with sickle cell disease: a single-center experience. Surgical Endoscopy 2009; 23(7): 1599-1602. https://doi.org/10.1007/s00464-009-0501-8 PMid:19444510
77. Al-Mulhim AS, Alshehri MH. Laparoscopic cholecystectomy in adult patients with sickle cell disease. Surgical Laparoscopy Endoscopy & Percutaneous Techniques 2012; 22(5): 454-458. https://doi.org/10.1097/SLE.0b013e31826194O8 PMid:23047392

78. Delatte SJ, Hebra A, Tagge EP, et al. Acute chest syndrome in the postoperative sickle cell patient. Journal of pediatric surgery 1999; 34(1): 188-192. https://doi.org/10.1016/S0022-3468(99)90254-3
79. Roizen MF. Anesthesia implications of concurrent diseases. In: Miller RD,ed. Anesthesia. 5th ed. Philadelphia: Chuchill Livingstone, 2000; 986.
80. Adu-Gyamfi Y, Sankarankutty M, Marwa S. Use of a tourniquet in patients with sickle-cell disease. Canadian Journal of Anaesthesia 1993; 40(1), 24-27. https://doi.org/10.1007/BF03009313 PMid:8425239
81. Stein RE, Urbaniak J. Use of the tourniquet during surgery in patients with sickle cell hemoglobinopathies. Clinical Orthopaedics and Related Research 1980; 151: 231-233. https://doi.org/10.1097/00003086-198009000-00033
82. Al-Ghamdi AA. Bilateral total knee replacement with tourniquets in a homozygous sickle cell patient. Anesthesia & Analgesia 2004; 98(2): 543-544. https://doi.org/10.1213/01.ANE.0000099363.42829.0A
83. Tobin JR, Butterworth J. Sickle cell disease: dogma, science, and clinical care. Anesthesia & Analgesia 2004; 98(2): 283-284. https://doi.org/10.1213/01.ANE.0000099364.07751.3F PMid:14742355
84. Fisher B, Roberts CS. Tourniquet use and sickle cell hemoglobinopathy: how should we proceed?. Southern medical Journal 2010; 103(11):1156-1160. https://doi.org/10.1097/SMJ.0b013e3181efaf3b PMid:20890260
85. Rao VM, Rao AK, Steiner RM, et al. The effect of ionic and nonionic contrast media on the sickling phenomenon. Radiology 1982; 144(2): 291-293. https://doi.org/10.1148/radiology.144.2.7089282 PMid:7089282
86. Campbell KL, Hud LM, Adams S, et al. Safety of iodinated intravenous contrast medium administration in sickle cell disease. The American Journal of Medicine 2012; 125(1): 100-e11. https://doi.org/10.1016/j.amjmed.2011.06.010 PMid:22195536
87. Ballas SK, Gupta K, Adams-Graves P. Sickle cell pain: a critical reappraisal. Blood 2012; 120(18): 3647-3656. https://doi.org/10.1182/blood-2012-04-383430 PMid:22923496
88. Stein PD, Beemath A, Meyers FA, Skaf E, Olson RE. Deep venous thrombosis and pulmonary embolism in hospitalized patients with sickle cell disease. The American Journal of Medicine 2006; 119(10), 897-e7. https://doi.org/10.1016/j.amjmed.2006.08.015 PMid:17000225
89. Ataga KI, Orringer EP. Hypercoagulability in sickle cell disease: a curious paradox. The American Journal of Medicine 2003; 115(9): 721-728. https://doi.org/10.1016/j.amjmed.2003.07.011
90. Whelihan MF, Lim MY, Walton BL, et al. Hypercoagulability in Sickle Cell Disease: The Importance of the Cellular Component of Blood. Blood 2014; 124(21): 4060.
91. Galicier C, Richet H. A prospective study of postoperative fever in a general surgery department. Infection Control 1985; 6(12): 487-490. https://doi.org/10.1017/S0195941700063608 PMid:3852797
92. Pile JC. (2006). Evaluating postoperative fever. Cleveland Clinic Journal of Medicine 2006; 73(1): S62-6. https://doi.org/10.3949/ccjm.73.Suppl_1.S62 PMid:16570551
93. Halvorson DJ, McKie V, McKie K, Ashmore PE, Porubsky ES. Sickle cell disease and tonsillectomy: preoperative management and postoperative complications. Archives of Otolaryngology–Head & Neck Surgery 1997; 123(7): 689-692. https://doi.org/10.1001/archotol.1997.01900070033005
94. Homi J, Reynolds J, Skinner A, Hanna W, Serjeant G. General anaesthesia in sickle-cell disease. BMJ 1979; 1(6178): 1599-1601. https://doi.org/10.1136/bmj.1.6178.1599 PMid:466140 PMCid:PMC1599173

Supplements:

Supplementary Appendix 1.

SAMPLE PRE-OPEARTIVE DATA ABSTRACT FORM

NAME: _____ AGE: _____

SICKLE CELL GENOTYPE: _____
(*Hb SS, Hb SC, Hb S b thal*, Other ----------)

PREVIOUS SURGERIES: _____

PREVIOUS GENERAL ANESTHESIA: Yes or No

PREVIOUS ANESTHESIA COMPLICATIONNS: _____

PREVIOUS POST-OPERATIVE COMPLICATIONS: _____

EXISTING MEDICAL CONDITIONS:

Hypertension	Heart Failure	Diabetes Mellitus
TIA/STROKE	MI	Angina
Asthma/COPD	Home oxygen	Others:_____

PREVIOUS SICKLE CELL PAINFUL CRISIS:

How often? _____ episodes in last year Date of last crisis: _____

Known triggers: _____

Usual length of hospital stay: _____days

Pain medicatios used in the last crisis:

CURRENT HOME MEDICATIONS:

BASELINE (or CURRENT) LAB PARAMETERS:

WBC:	Hb/HCT:
Retic Count:	Total bilirubin:
LDH:	

CURRENT ACTIVITY LEVEL:

Independent:

Can walk a flight of stairs? Yes or NO

How far can patient walk without dyspnea? _____

Needs assistance with daily activities? Bathing, feeding, toileting, dressing

VITALS:

Supplementary Appendix 2

COMMON SICKLE CELL GENOTYPES

Full Names	Abbreviations	Genotype
Sickle cell disease –SS, Sickle cell anemia	SCD-SS; SS	β^s/β^s Hb SS
Sickle Cell disease –SC	SCD-SC; SC	β^s/β^c Hb SC
Sickle Cell disease –S β^0thalassemia	SCD-S β^o thal; S β^o thal	β^s/β^0thalassemia Hb Sβ^o thal
Sickle Cell disease –S β^+thalassemia	SCD-S β^+thal S β^+thal	β^s/β^othalassemia Hb Sβ^+thal
Sickle Cell disease – S O-Arab	SCD – S OArab S OArab	$\beta^s/\beta^{o\text{-Arab}}$ Hb SOArab