Transfusion Camp 2022-2023

Day 2: Seminar 2B, November 18, 2022

"Sickle Cell Disease and Transfusion", developed by Dr. Jacob Pendergrast

Case 1

A 30 year-old female with HgbSß^0 presents to the emergency department with acute onset pain in her lower back and shins, consistent with her usual vaso-occlusive pain crises. She is under shared care at your institution and a local peripheral hospital closer to her home. On examination she is alert and oriented, with all vital signs within normal limits with the exception of sinus tachycardia. Physical examination reveals conjunctival pallor, scleral icterus, and digital clubbing. She is initially managed with intravenous (IV) fluids, supplemental oxygen and frequent doses of morphine sulfate, but after eight hours there is little improvement in her pain symptoms. Her current laboratory investigations reveal a hemoglobin (Hgb) of 63 g/L, white blood cell count (WBC) 8.1 x 10^9/L, and platelets 225 x 10^9/L. Her reticulocyte count is elevated at 200 x 10^9/L..

1. Which of the following pieces of information would be most useful in her initial management?
   a) Coagulation times
   b) MRI scan of lumbar spine
   c) Presence of anti-Parvovirus B19 antibodies
   d) Transfusion history from other hospitals where she has been treated

a) Patients with sickle cell disease are susceptible to a number of life-threatening complications, such as fat embolism from massive bone marrow necrosis, acute liver injury in the setting of multiorgan failure syndrome, and disseminated intravascular coagulation secondary to sepsis with encapsulated organisms such as meningococcus, and in all such cases it would be useful to assess the patient's coagulation times. However, as this patient has presented with what clinically appears to be an uncomplicated pain crisis, the likelihood that her coagulation tests are abnormal is low.

b) Sickle cell disease can cause chronic low back pain via a variety of mechanisms, such as osteomyelitis and vertebral compression fractures, and imaging for these diagnoses should be considered in patients with chronic, localized spinal pain. But the acute onset of low back pain, especially when combined with bony pain in other areas such as the extremities, is more consistent with a vaso-occlusive pain crisis. While MRI imaging of the affected areas may reveal osteonecrosis, these lesions will eventually heal and do not require specific management beyond analgesia. Note that osteonecrosis in certain high-risk areas such as the femoral or humeral head, by contrast, may not heal properly and can therefore progress to bony collapse and degenerative joint disease that will eventually require arthroplastic surgery.

c) Parvovirus B19) infections are rare after age 18 as most individuals have already been infected by that age and have developed lifelong immunity. In the acute setting, infections are marked by near complete reticulocytopenia with relative preservation of WBC and platelet counts in the setting of a falling hemoglobin, and most patients with chronic hemolytic anemia who develop pure red cell aplasia from a

B19 infection will present to hospital after having already developed severe anemia (Hgb < 50 g/L). This patient does not show signs of pure red cell aplasia and very well may already be immune to this virus; confirming by checking serology is unlikely to change her current management.

d) While this patient does not appear to be in imminent need for transfusion support, they may progress to that point during their hospitalization, and it will be very important for the blood bank to know at that point which anti-RBC antibodies she may have already developed. Since patients with sickle cell disease have often received care at multiple hospitals, including intermittent transfusions, and since any antibodies detected at those hospitals may no longer be reactive in the current group and screen, alerting the blood bank to contact those other hospitals can sometimes reveal the presence of antibodies that will require matching for and which might otherwise be missed. Several strategies to facilitate this sharing of information may be available depending on your geographic area of practice (eg., linkage of blood bank databases between hospitals, provision of antibody cards to patients, and creation of central registries by the local blood supplier). However, direct communication between hospital blood banks is still the preferred means of ensuring that critically important information is shared. Communicating a patient's transfusion history to your local blood bank whenever they present for acute care (ie., as an order comment accompanying a group and screen), even before a transfusion is ordered, is prudent, since it also allows the blood bank time to source phenotypically-matched units which might not otherwise be available in their local inventory.

2. Given the patient's current status, what should the goal of transfusion therapy be?
   a) Decrease HgbS to < 30%
   b) Keep serum lactate within normal range
   c) <u>Maintain Hgb > 50 g/L</u>
   d) Target Hgb at approximately 100 g/L

a) Decreasing the HgbS% to less than 30% will require an exchange transfusion, as it is generally impossible to dilute the HgbS% down this low through a top-up transfusion without simultaneously driving the total hemoglobin to dangerously high levels (eg., > 100 g/L). As exchange transfusions are more labour and resource-intensive than top-up transfusions, and carry additional harms, they are generally reserved for patients with severe organ injury; top-up transfusions to a Hgb of 100 g/L will usually reduce the HgbS% down to 60%, which may be adequate for less severely ill patients. Of note, however, in the absence of severe anemia (eg., a Hgb < 50 g/L) the patient in this scenario may not require any transfusion support at all: much of the pain that accompanies an uncomplicated acute pain crisis is secondary to the inflammation that follows an episode of tissue necrosis. In this setting, increasing oxygen delivery may not decrease pain and may even worsen it due to reperfusion injury. Thus, transfusions (particularly exchange transfusions) are generally regarded as more effective for the *prevention* rather than the *treatment* of uncomplicated vaso-occlusive pain crises.

b) In most instances, an increase in serum lactate levels indicates a transition to anaerobic glycolysis secondary to inadequate oxygen delivery, and is occasionally advocated as a "physiologic transfusion trigger". However, standard of care in sickle cell patients is to monitor response to transfusion through changes in either Hgb or HgbS%, particularly since serum lactate levels may be elevated at baseline in this patient population. In situations in which it is impossible to acutely manipulate either the Hgb or HgbS% (ie., due to an inability to transfuse a patient) the augmentation of oxygen delivery may have to be pursued by increasing the quantity of oxygen dissolved in patient plasma, or by using non-traditional oxygen delivery vehicles (e.g, bovine hemoglobin extracts). Only in this context would titrating the intervention to achieve a reduction of serum lactate rather than a change in Hgb of HgbS% be necessary.

c) Guidelines for when to transfuse a sickle cell patient with acute anemia vary. American guidelines define acute anemia as a fall in Hgb of > 20 g/L from baseline but state that transfusions should only be administered if the anemia is symptomatic. British Guidelines allow for prophylactic transfusions in the setting of acute anemia, but propose a threshold Hgb of 50 g/L in addition to a fall > 20 g/L from baseline. A reasonable practice therefore is to only transfuse patients with a hemoglobin greater than 50 g/L if they are actively bleeding, experiencing significant symptoms of anemia, or are experiencing acute organ dysfunction. Transfusing for compensated anemia or an uncomplicated vaso-occlusive crisis, such as this patient is experiencing, is not advised and in some cases may worsen the patient's symptoms due to the resulting increase in blood viscosity. This is of particular concern in low-shear vascular beds such as the bone marrow, which is where this patient's vaso-occlusive symptoms are presumably originating.

d) Topping up the hemoglobin to 100 g/L may improve oxygen delivery in sickle cell patients within their high-shear vascular beds, but as the patient in this scenario does not appear to be suffering either a stroke or an acute chest syndrome (as two examples of such areas) there is little benefit from transfusing and even some potential harm. This is due to baseline elevation in blood viscosity in sickle cell patients, particularly in de-oxygenated and low-shear vascular beds such as is found in post-capillary venules within the bone marrow (thought to be the source of pain in uncomplicated sickle pain crises). Increasing the hemoglobin through transfusion may actually worsen oxygen delivery in these areas as further increases in viscosity will decrease blood flow.

3. When selecting blood products for patients with sickle cell disease, it is most important that they be:
   a) As fresh as possible
   b) **Matched for RhCE and K**
   c) Sickledex®-negative
   d) Washed

a) Fresh blood may have slightly longer *in vivo* survival than older blood and may therefore be preferable in order to decrease the number of necessary donor exposures and, long-term, mitigate transfusional iron

overload. However, the size of benefit is very small (less than one week additional circulating lifespan when only "neocytes" are transfused) and, given the recently confirmed absence of any other clinical benefit from giving fresh blood to critically ill patients, the age of RBCs selected is a relatively minor concern

b) Matching for phenotype (eg., C, c, E, e, K and, for patients who are demonstrably prone to antibody sensitization, Fy^a, S and s) is by far the most important consideration when selecting blood products for patients with sickle cell disease, for the following three reasons:

i. Certain minor blood group antigens are less common in individuals of African descent (the majority of sickle cell patients) than European descent (the majority of blood donors), as shown by the accompanying table (Yazdanbakhsh, Blood 2012;120:528). This discrepancy partly explains the very high rate of alloimmunization (~25%) observed in sickle cell patients who are transfused without prophylactic matching

Table 1. Blood group differences between donors and recipients

Category	% in white donors	% in black recipients
Common antigens		
ABO group		
A	43	27
B	9	20
O	44	49
AB	4	4
RH		
D	85	92
C	68	27
E	29	20
c	80	96
e	98	98
KEL		
K	9	2
FY		
Fy^a	66	10
Fy^b	83	23
JK		
Jk^a	77	92
Jk^b	74	49
MNS		
S	51	31
s	89	93

ii. It often takes a month after initial sensitization for a red blood cell antibody to become detectable in a group and screen; once formed, approximately 30-50% of such antibodies will subsequently have their titres fall below detectable limits within a year. Thus, unless a patient returns to hospital for

follow-up shortly after a transfusion, such antibodies may never be detected until they are re-challenged by another transfusion, triggering a more rapid anamnestic response. Even when such antibodies are known to a hospital's blood bank, this information is often not available to blood banks at other hospitals. As many sickle cell patients receive care only during periods of acute illness, and may present or be taken to different hospital emergency departments within their community, there is a high risk of missed primary sensitizations

iii. As with all patients, the secondary exposure to an antigen to which a sickle cell patient has already been sensitized may trigger a delayed hemolytic transfusion reaction (DHTR). As is not the case with other patients, however, these DHTRs carry additional morbidity in patients with sickle cell disease as they may trigger a vaso-occlusive crisis or be complicated by hyperhemolysis (discussion of this last point to follow in a subsequent case).

c) Since patients with sickle cell disease are not permitted to donate blood, Sickledex®-positive units generally means blood from patients who have sickle-cell trait. While avoiding such donors is desirable when attempting to track the effect of transfusion on patient HgbS%, blood from donors with sickle cell trait is not itself intrinsically inferior to any clinically-relevant degree and therefore need not be avoided if it means unduly shrinking the pool of available donors. Indeed, many blood donors who are sickle cell trait are from ethnic origins that are usually in great demand for the transfusion support of sickle cell patients, due to their similarity in red blood cell surface antigen alleles. A growing number of hospitals are not mandating that patients with sickle cell disease only receive blood from Sickledex®-negative donors (Aneke et al, Transfus Med. 2019 Dec;29:466)

d) Washing blood products was at one point used as a method for removing the contaminating leukocytes which so often triggered adverse transfusion reactions (eg., febrile non-hemolytic transfusion reactions) in patients with sickle cell disease, many of whom had often developed anti-leukocyte antibodies from prior transfusion exposures. However, once blood products have been pre-storage leukoreduced, as has been the case in Canada since 1999, there is little additional benefit from washing unless the patient has a history of adverse reactions to other substances in donor plasma (eg., patients with a history of anaphylactic transfusion reactions).

Case 2

An otherwise previously-well 14 month-old baby girl with HgbSS is brought to the emergency room by her mother after the baby was noted to be increasingly irritable, with pallor, jaundice, and thready pulses. On examination, the baby is confirmed to be pale and icteric, with a tender mass palpable at the umbilicus. Heart rate is 170 bpm, with blood pressure of 70/40 mmHg. The baby is afebrile with pulse oximetry of 100% SpO2 on room air. Laboratory investigations reveal a Hgb of 52 g/L, a WBC of 3.4 x 10^9/L, a platelet count of 100 x 10^9/L, with normal coagulation times but serum chemistry revealing a newly elevated creatinine at 130 µmol/L.

4. Which one of the following statements is true regarding splenic sequestration crises?

a) They are the most common cause of death amongst children with sickle cell disease

b) Sickle cell patients undergo autosplenectomy as a complication of sequestration crises

c) <u>Once a child has had one sequestration crisis, they are likely to have more</u>

d) Most cases of sequestration crises occur abruptly, without any apparent preceding illness

a) Sequestration crises are common in sickle cell disease (affecting up to 30% of patients) and historically, the second most common cause of death after infection in the first decade of life. However, more recent cohort studies indicate that sequestration is now a rare cause of sickle cell mortality in high-resource environments. This is likely due to the effects of increased recognition of this condition by physicians, who are now taught to suspect sequestration in any patient with sickle cell disease who presents with a rapid fall in hemoglobin from baseline of over 20 g/L in the absence of hemorrhage, accompanied by a rapidly enlarging spleen (as determined by imaging or physical examination). The increased prevalence of newborn screening has also provided an opportunity to educate parents on the signs and symptoms of sequestration (abdominal pain and distension, pallor, weakness, breathlessness, and rapid heart rate) which may present as early as 5 weeks of age, and, due to the risk of hemodynamic instability (which may occur over a period of hours) must be treated as a medical emergency. The rapid initiation of transfusion support in this setting can be life-saving and is likely one reason that most sickle cell patients in Canada now survive their sequestration crises.

b) Autosplenectomy is common in sickle cell patients, with splenic atrophy usually complete by age 5. However, the mechanism is recurrent injury from vaso-occlusion, resulting in infarction and fibrosis. Sequestration crises, by contrast, often leave sickle cell patients with splenomegaly, which may persist for life and result in hypersplenism (defined as splenomegaly accompanied by cytopenias with compensatory increase in bone marrow hematopoiesis). Note, however, that sickle cell patients with splenomegaly and hypersplenism should still be considered functionally hyposplenic (ie., susceptible to infections, particularly by encapsulated organisms such as pneumococcus, meningococcus and hemophilus influenza B, as well as thrombotic complications). The loss of splenic filtering function in sickle cell patients with intact spleens may result from either shunting of blood flow away from filtration beds, or shunting of macrophage activity towards ingestion of sickled erythrocytes

c) Unless a patient undergoes a splenectomy or is initiated on chronic transfusion support following their first sequestration crisis, the risk of recurrence is high – cohort studies have shown that 50-75% of patients will have experienced more than one episode. Risk of relapse is particularly high when the first episode occurred before 1 year of age. As both chronic transfusions and splenectomy carry their own risks, many parents opt for careful observation only, in the hope that the spleen will eventually atrophy through repeated infarction, and some experts have advised splenectomy only after two episodes of sequestration have occurred. Splenic sequestration is overall rare after age 6, but occasional patients with persistent splenomegaly may continue to be at risk of relapse even as adults.

d) While the causal linkage is not proven, over half of sequestration crises appear to have been preceded by an acute illness (ie, isolated fever, upper respiratory or gastrointestinal infection, or a vaso-occlusive crisis). Some studies have also observed a particularly strong association with a preceding infection with Erythrovirus (aka Parvovirus) B19, and have recommended close observation of children for both sequestration and aplastic crises. The mechanism by which a preceding illness would trigger sequestration is not entirely known but likely involves the accumulation of sickled RBCs in the red pulp, which in turn causes mechanical obstruction of the draining veins. The lack of flow then induces a state of hypoxia, further sickling, and with progressive distension of the spleen, rapid accumulation of the circulating RBC mass.

5. Which transfusion reaction is this patient most at risk for?
   a) Delayed hemolytic transfusion reaction
   b) Hyperkalemia
   c) <u>Hyperviscosity</u>
   d) Transfusion-associated circulatory overload

a) Delayed hemolytic transfusion reactions are a significant hazard in patients with sickle cell disease, which is why extended antigen matching is advised. However, these reactions are essentially anamnestic immune responses against red blood cell antigens, meaning that they virtually never occur without the patient first being sensitized by a previous pregnancy or transfusion, neither of which is the case in the current scenario.

b) Neonates are considered to be at higher risk of transfusion-induced hyperkalemia than adults due to the relatively high proportion of RBC supernatant to plasma volume that accompanies a typical transfusion order of 10-15 cc/kg. However, this risk only becomes significant in patients undergoing massive or exchange transfusion, neither of which is indicated in this patient. In any case, blood banks generally know to remove the supernatant of stored red blood cells prior to issuing RBCs to pediatric patients for these indications.

c) Although RBCs may become trapped within splenic sinusoids during sequestration crises, they are still viable and, once dislodged by a blood transfusion, can be released back into circulation over the next few days as the spleen returns to normal size, providing an unexpectedly high post-transfusion hematocrit. There is therefore an increased risk of overshooting the target and provoking hyperviscosity. In children, cautiously administering 3-5 mL/kg every few hours has been advised in the management of sequestration crises. As with all transfusion decisions in patients with sickle cell disease, the total hemoglobin should not exceed 100-120 g/L. In sequestration, a target level of ~80-90g/L is prudent given the risk of autotransfusion.

d) Although poorly-defined and likely under-reported, there is evidence that transfusion-associated circulatory overload is common amongst critically ill children. However, as the shock that accompanies

sequestration crises is hypovolemic, the risk of circulatory overload from transfusion can be considered relatively low.

Case 3

A 17 year-old man with HgbSC is recovering on the ward after undergoing a right total hip replacement for avascular necrosis. On post-op day #2 he begins experiencing chest pain, fever and dyspnea. Physical examination reveals a patient in moderate respiratory distress but is alert and oriented, with HR 80 bpm, BP 110/70, RR 24, Temp 38.2ºC and SpO2 of 95% on 2L O2 by nasal prongs. He has mild conjunctival pallor and scleral icterus, with bilateral inspiratory crepitations. Jugular venous pressure (JVP) is 2 cm above sternal angle and there is no peripheral edema. Laboratory investigations reveal a Hgb of 80 g/L (100 g/L pre-op), WBC of 16 x 10^9/L (6), and a platelet count of 400 x 10^9/L (250), with normal coagulation times and serum chemistry, and BNP, troponin and serum lactate levels all within normal limits.

6. Which one of the following features on CXR would suggest the patient is experiencing an acute chest syndrome?
   a) Decreased lung volumes
   b) Enlarged pulmonary arteries
   c) Interstitial edema
   d) **Lobar consolidation**

a) Decreased lung volumes are also commonly encountered in patients with sickle cell disease and many may be diagnosed with restrictive lung disease following spirometry testing. This type of lung disease likely represents progressive fibrosis due to repeated episodes of infection, acute chest syndrome (ACS), pulmonary infarction and extra-pulmonary restriction, but does not itself indicate the patient is experiencing an acute chest syndrome currently.

b) Enlarged pulmonary arteries are commonly noted on plain chest radiographs of patients with sickle cell disease and reflect high cardiac output and/or pulmonary hypertension, but do not reflect an ACS, which is defined as new airspace disease. Notably, high cardiac output and pulmonary hypertension are complications typically seen in sickle cell disease patients with lower baseline hemoglobin levels and higher hemolytic rates, whereas acute chest syndrome is more often seen in patients with higher baseline hemoglobin levels.

c) Increased interstitial markings may be seen in certain types of atypical pneumonia but are also likely to indicate pulmonary edema, either due to intravascular volume overload (a common complication of over-zealous hydration) or cor pulmonale secondary to pulmonary hypertension. As with atelectasis (which can mimic lobar consolidation) these conditions may predispose toward but should not be confused with ACS, a condition which requires its own specific treatment intervention.

d) The presence of new alveolar consolidation in a patient with sickle cell disease who has fever and/or respiratory symptoms can be considered sufficient to make a diagnosis of ACS. ACS may therefore may be impossible to distinguish from pneumonia. Children usually have fever and upper or middle lobe involvement, whereas adults are often afebrile and present with multilobe disease. Chest or back pain is a common presenting symptom but is neither sensitive nor specific for ACS. Note that ACS is a syndrome rather than a specific disease entity, and underlying causes such as atelectasis from hypoventilation, fat emboli from bone marrow necrosis, pulmonary emboli, and fluid overload should be considered as possible etiologies. While some guidelines state that a diagnosis of ACS may be made on the basis of any new pulmonary infiltrate in chest x-ray, the definitional criteria used in a landmark observational study is more specific and may avoid over-transfusion: "new pulmonary infiltrate involving at least one complete lung segment… consistent with the presence of alveolar consolidation, but excluding atelectasis. " (Vichsinky et al, NEJM 2000;342:1855)

7. What sort of transfusion support should you provide this patient?
   a) None
   b) <u>Top-up RBC transfusion</u>
   c) Exchange RBC transfusion
   d) Therapeutic phlebotomy

a) Observational studies suggest that RBC transfusions in patients with sickle cell disease experiencing an ACS result in improved indices of oxygenation, particularly if administered early in the course of disease. Once the diagnosis is confirmed, therefore, most guidelines recommend some degree of transfusion support, unless the patient's condition is exceptionally mild (eg., no hypoxia or worsening anemia). Importantly, these same guidelines also recommend a multimodal treatment approach that includes antibiotics with coverage of atypical organisms, respiratory therapy, bronchodilators if evidence of wheeze or history of asthma, and adequate pain medication to prevent respiratory splinting. If pulmonary thrombi are detected then full anticoagulation is also recommended; prophylactic doses of anticoagulants are otherwise recommended until patients are ambulatory. The benefit of incentive spirometry in ACS has been called into question by a recent RCT (van Tuij, Am J Hematol. 2020 Jul; 95(7): E160–E163)

b) Deciding whether a patient with ACS requires a top-up or an exchange transfusion can be challenging and in the absence of randomized controlled trials is a matter of clinical judgment. Recently published guidelines from the UK (Davies et al, Br J Haem 2017:176;192) state that "exchange transfusion is recommended in patients with features of severe ACS, those who fail to respond to initial simple transfusion, or patients with a higher Hb (>90 g/l) where there is little leeway for simple transfusion." The following signs and symptoms may in turn be considered signs of acute chest syndrome (Johnson, Hematol Oncol Clin N Am 2005:19;857).

Physical Examination Findings

1. Altered mental status
2. Persistent HR > 125/min
3. Persistent RR > 30 or other evidence of incr work of breathing
4. Temp > 40C
5. Hypotension vs baseline

Laboratory and Radiology Investigations

1. Arterial pH < 7.35
2. SpO2 persistently < 88% despite aggressive ventilatory support
3. Serial decline in SpO2% or A-a gradient
4. Hgb decr by ≥ 20 g/L
5. Plts < 200/fL
6. Elevated BNP or troponin
7. Evidence of multiorgan failure
8. Pleural effusion
9. Progressive pulm infiltrates

Given the absence of any of these features in the current presentation, and the fact that the patient has a less severe phenotype of sickle cell disease (HgbSC), a top-up transfusion is a reasonable first intervention; typically, RBCs are administered to achieve a Hgb of approximately 100 g/L. A top-up transfusion of 2 units will decrease the HgbS% in most adult patients to approximately 60%. Note that the prognostic significance of COVID19 pneumonia in sickle cell patients is still being determined but is not itself yet considered an indication for an exchange transfusion.

c) As noted, the patient does not appear unwell enough to require an exchange transfusion, which, when ordered, typically has as its goal the reduction of HgbS to < 30%. Manual exchange transfusions, while a procedure that should be available in any hospital that treats sickle cell patients, are very time consuming and imprecise in achieving their targets. An apheresis exchange, by contrast, can be completed more quickly and still achieve more aggressive HgbS% targets than a manual exchange using phlebotomies. However, there is often a delay in initiating an apheresis exchange due to the need to transport the patient to a healthcare facility that offers the service, and the fact that apheresis exchanges require a large number of units. This latter consideration in turn necessitates the removal of the anticoagulant and additive solution. When performing apheresis exchanges it is also advisable to use fresh blood (<7 days old) if possible to avoid infusing a large potassium burden. Patients with poor venous access may require a centralized venous access device to be inserted to facilitate the phlebotomy phase of an exchange transfusion; when the exchange is performed by apheresis, the central line should be something relatively stiff and large caliber (eg., a dialysis line). For all these reasons, it is not advised to perform an exchange transfusion in a patient with an ACS of only moderate severity.

d) Phlebotomy is often prescribed to decrease blood viscosity in patients with sickle cell disease with a hematocrit > 32% (or Hgb > 100 g/L), which is often encountered in those with HgbSC and likely the reason patient with this specific genotype are more prone to certain complications such as retinopathy. However, in this situation the patient's hemoglobin is already below this threshold and in fact is probably too low to accommodate phlebotomy anyway.

8. Which one of the following interventions could have prevented this complication?

   a) Aggressive hydration at 1.5x maintenance for first 48 hours post-op

b) Full anticoagulation as soon as surgical hemostasis attained

c) Hydroxyurea

d) <u>Pre-operative exchange transfusion</u>

a) Hydration at 1.5x normal has traditionally been advised as an important component of supportive care for patients with sickle cell disease due to the increased prevalence of hyposthenuria in this population. However, for many patients this degree of intravenous fluid support, particularly if continued for too long, may result in volume overload which, due to its effect on ventilation and gas exchange, can actually induce an ACS. For this reason, oral fluid should be pushed as soon as the patient is able to drink, with intravenous fluid supplementation based on a daily patient volume assessment

b) Full anticoagulation has not been consistently shown to modify the clinical manifestations of sickle cell disease and if introduced too early in the post-operative period is more likely to provoke bleeding than mitigate complications such as ACS

c) Hydroxyurea can in a best-case scenario achieve a HgbF of 30% (corresponding to a HgbS of 70% in a patient with HgbSS or Sß⁰), a level which has not been shown to be adequate for the prevention of post-operative acute chest syndrome in patients with sickle cell disease, even with exemplary supportive care (including adequate pre-operative hydration and careful attention to the prevention of perioperative hypothermia and acidosis). Combined with the fact that it may take many months to titrate hydroxyurea to maximal tolerated dose, this medication should not be relied upon to prevent post-operative complications in patients with sickle cell disease for any but the most minor procedures.

d) The recent publication of the TAPS randomized controlled trial confirmed that pre-operative transfusion is standard of care for patients with sickle cell disease scheduled for moderate-risk (and, presumably, high-risk) procedures (Howard, Lancet 2013; 381: 930). Note that this includes common same-day procedures such as tonsillectomy and adenoidectomy procedures. In most patients, a top-up transfusion to > 90 g/L results in an adequate decrease in HgbS% to approximately 60%, but in patients with significant comorbidities, those undergoing very high-risk surgical procedures, and those with baseline hemoglobin > 90 g/L (as was the case here), an exchange transfusion should be considered instead. Whether an exchange transfusion in this scenario needs to be performed manually or by apheresis is largely dependent upon what resources are available locally; the advantages of apheresis are shorter time and greater precision in achieving target hemoglobin and hemoglobin S% Pre-operative transfusion is not necessary in patients undergoing minor surgical procedures (eg., those lasting less than one hour and not requiring a general anesthetic), particularly in low-risk patients (eg., those with HgbSC, HgbSß+, or those on chronic hydroxyurea). Note however, that tonsillectomy and adenoidectomy should be considered moderate risk surgeries and therefore offered pre-operative transfusion support.

Case 4

A 28 year-old woman with HgbSß$^+$ is admitted to hospital with a hemorrhagic ovarian cyst and a Hgb of 60 g/L (baseline 95 g/L). She is transfused 2 units of RBCs and undergoes an otherwise uncomplicated oophorectomy. One week after discharge she presents with a vaso-occlusive pain crisis. Her initial Hgb is 78 g/L but over the course of 48 hours it falls to 59 g/L, accompanied by a stable WBC of 12 x 10^9/L and platelet count of 180 x 10^9/L. She is hemodynamically stable and abdominal imaging confirms no ongoing bleeding or hepatosplenomegaly, but her LDH increases to 850 U/L, with indirect bilirubin of 50 µmol/L. Reticulocyte count decreases from a baseline of 400 to 100 x 10^9/L. She is transfused 1 unit of RBCs; the blood bank notifies you that the pre-transfusion sample reveals an anti-E antibody that was not detectable on her earlier sample from 1 week ago. Direct antiglobulin test is negative. The next morning after her transfusion her Hgb is 50 g/L. She is transfused another unit of RBCs and her Hgb the next morning has fallen again to 42 g/L. The patient remains hemodynamically stable but is complaining of increasing fatigue.

9. What is the most likely explanation for the lack of response to transfusion?
   a) Autoimmune hemolysis
   b) Hyperhemolysis
   c) Intra-abdominal bleeding
   d) Units are serologically incompatible (ie., delayed hemolytic transfusion reaction)

a) The diagnosis of autoimmune hemolysis is made much less likely by the presence of a negative direct antiglobulin test and in any case would be more likely to manifest as transfusion refractoriness (inability to increase the hemoglobin by transfusion) rather than progressive declines in hemoglobin despite transfusion support, which is what was seen in this case

b) Hyperhemolysis is defined as a post-transfusion hemoglobin that is lower than the pre-transfusion level accompanied by a rapid decline of posttransfusion HbA% by hemoglobin electrophoresis; while awaiting the results of electrophoresis, accelerated hemolysis of transfused blood can be assumed if there are increases from baseline in hemolytic markers without any signs of hemorrhage. The mechanism by which hyperhemolysis occurs is poorly understood (macrophage activation? Bystander lysis from complement-fragment deposition? T-cell mediated cytolysis? Eryptosis in response to labile plasma iron?) but it is often triggered by a delayed hemolytic transfusion reaction, and patients with sickle cell disease appear to be particularly at risk.

c) Intra-abdominal hemorrhage should always be considered in a patient who fails to respond to RBC transfusions, particularly if they have a recent history of bleeding, but the increasing hemolytic markers and hemodynamic stability suggest another etiology.

d) Because the blood bank was not notified that the patient had sickle cell disease and therefore did not select units that were prophylactically matched for Rh and Kell antigens, it is likely that at least one of the two units she was initially transfused for her ovarian hemorrhage was E-positive and therefore triggered an

anamnestic response, ie., an anti-E that became detectable less than one month after transfusion. The hemolysis that accompanied the detection of this antibody can therefore be reasonably ascribed to serologic incompatibility; the fact that the direct antiglobulin test was negative at the time this anti-E was picked up likely reflects the complete destruction of any E-positive RBCs that had been previously transfused (this could be confirmed by phenotyping the patient's blood for the E-antigen, or by checking for HgbA on electrophoresis: both tests will likely be negative). That being said, any RBC units administered *after* this anti-E was detected would have been E-negative, and the fact that these units were also immediately hemolyzed despite being crossmatch compatible suggests that another phenomenon beyond serologic incompatibility is to blame. It is also important to note that the patient's hemoglobin is lower after transfusion than before, which suggests that the patient's own RBCs are being destroyed at an increased rate as well. This is again another argument that the accelerating hemolysis the patient is developing is not being mediated by serologic incompatibility.

10. What is the first-line treatment for this patient?
    a) Eculizumab and rituximab
    b) Intravenous iron
    c) <u>IVIG and steroids</u>
    d) Top-up transfusion to Hgb > 80 g/L, followed immediately by exchange transfusion

a) One proposed mechanism for hyperhemolysis is the deposition of complement fragments on RBCs which, although serologically compatible with the patient, are nonetheless at increased susceptibility to complement-mediated lysis. Rituximab has also been proposed as a means of halting the production of pathogenic alloantibodies, which may have triggered hyperhemolysis even in cases where they were not detectable during routine compatibility testing, but is generally used to prevent rather than treat hyperhemolysis in high-risk patients While there are a growing number of case reports describing good outcomes in patients treated with eculizumab and/or rituximab, their actual efficacy remains uncertain and given their high cost and potential toxicity, current guidelines from the American Society of Hematology recommend them as second line therapies only.

b) Although the reticulocyte often falls slightly below baseline in patients with hyperhemolysis, there is no evidence that this is driven by inadequate iron delivery to the bone marrow. Indeed, there is some evidence that hyperhemolysis is propagated by *increases* in labile plasma iron. Given the current state of knowledge, there is no place for IV iron in the management of hyperhemolysis. It has been noted, incidentally, that patients experiencing hyperhemolysis often have extreme elevations in serum ferritin, possibly indicating the release of intracellular contents by activated macrophages. Erythropoietin is often required to accelerate recovery from the severe anemia of hyperhemolysis, but in the absence of a response it is usually adequate to continue increasing the dose rather than to add IV iron as an adjunct.

c) Although there are no controlled clinical trials proving the efficacy of this approach, multiple case reports and practice guidelines suggest that high dose IVIG (2 g/kg over 2-5 days) combined with high-dose steroids (e., prednisone 1 g/kg daily x 2 weeks, or methylprednisolone 500 mg x 1-2 doses) may dampen the severity of hyperhemolysis, possibly by blunting macrophage activity. Caution should be exercised before giving IVIG to patients with non-O blood groups, however, as the IVIG itself can induce an unpredictable degree of hemolysis. In general, patients with hyperhemolysis should be managed with the assistance of a hematology consult. The most important role for the referring physician is to recognize the phenomenon of hyperhemolysis when it occurs and cease further transfusions.

d) Further transfusions may exacerbate hyperhemolysis once it is underway and should only be administered to treat life-threatening complications of anemia, preferably after some degree of immunosuppressive medication has been administered pre-transfusion. It should be remembered that although in normal conditions only 1-2% of the blood's oxygen carrying capacity is in the plasma, this proportion can increase to up to 15-20% in patients with severe anemia (Hgb 50 g/L) whose arterial oxygen tension has been increased from a normal baseline of 100 mmHg up to 450 mmHg via an FiO2 of 1.0. In other words, oxygen delivery can be meaningfully augmented, even if the SpO2 is already 100%, by putting the patient on 100% oxygen via non-rebreather. Studies in healthy volunteers have found this approach to be physiologically equivalent to increasing the hemoglobin by 30 g/L, or transfusing 3 units of RBCs (Feiner, Anesthesiology, 2011:115:492-8)

Case 5

A 31 year-old woman with HgbSS is admitted to obstetric triage with a generalized pain episode. Of note, she had been taking hydroxyurea with excellent disease control prior to becoming pregnant, but has held it due to concerns with potential teratogenicity. Her Hgb at her current presentation is 65 g/L (baseline 80-90 g/L pre-pregnancy). She is 17 weeks gestation and this is her third acute pain episode in the pregnancy.

11. Which of the following is true about transfusion support during pregnancy in patients with sickle cell disease?

a) Regular transfusion support during pregnancy can decrease maternal pain crises

b) Intrauterine transfusion support may be required to protect the fetus from experiencing vaso-occlusive episodes

c) Pregnant women with sickle cell disease should be routinely transfused to maintain their HgbS < 30% in order to optimize fetal development

d) Sickling complications tend to be less frequent due to the increase in maternal HgbF% that accompanies pregnancy

a) Maintaining a HgbS < 30% appears to be an effective means of decreasing the incidence of painful vaso-occlusive crises in patients with sickle cell disease, regardless of what the primary goal of therapy is (eg.,

this effect was seen in randomized controlled trials of stroke prevention as well as trials aiming to improve fetal outcomes). Because transfusions are a relatively dangerous and expensive form of medical therapy, hydroxyurea is usually relied upon as first-line therapy for patients with frequent pain crises. Since hydroxyurea is contra-indicated in pregnancy, however, it is now advised that any patient with a history of severe complications from their sickle cell disease be considered for prophylactic transfusions during pregnancy. It should be emphasized that current evidence suggests that transfusing sickle cell disease during pregnancy benefits the mother only. However, while pain crises are not themselves clearly associated with worse fetal outcomes, they can necessitate sufficiently high doses of narcotic medication to result in neonatal withdrawal. While no single HgbS% target can be recommended for all patients, maintaining levels of < 50-60% is usually adequate.

b) The majority of fetal hemoglobin is HgbF, which does not contain ß-globin and as such will not manifest the sickle mutation that affects that gene. Fetal complications of sickle cell disease are therefore due not to problems with fetal circulation but presumably with the growth and perfusion of the maternal placenta.

c) While patients with sickle cell disease tend to have worse pregnancy outcomes than other patients (intrauterine growth retardation, premature labour, miscarriage and stillbirth are all more likely), available evidence from randomized controlled trials suggests that initiation of chronic transfusion support during pregnancy will not improve these outcomes, although close obstetrical follow-up through a high-risk pregnancy program is advised regardless. Note that observational studies with historical controls have suggested that transfusion may in fact improve fetal outcomes in selected patients, and current guidelines do support the provision of transfusion support to women with either prior or current fetal difficulties attributable to sickle cell disease. A local practice is to screen pregnant women at approximately 22 weeks gestation for impaired fetal or placental development which, if seen, would prompt initiation of transfusion support; earlier transfusions would be initiated in women with a prior such history.

d) Fetal erythrocytes do not enter the maternal circulation in sufficient numbers to affect the maternal HgbF% and will therefore not mitigate the mother's risk of experiencing sickle cell complications. In fact, maternal HgbF% (and total hemoglobin) are more likely to decrease in pregnancy due to discontinuation of hydroxyurea, which carries theoretical risks of teratogenicity.