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COMMENTARY

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Red blood cell exchange: 2015 American Society for Apheresis consensus conference on the management of patients with sickle cell disease

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Abstract

The American Society for Apheresis (ASFA) conducted a one-day consensus conference on red blood cell exchange (RBCx) in sickle cell disease (SCD) during its annual meeting in San Antonio, TX, on May 5, 2015. The authors of this article, a subcommittee of ASFA's Clinical Applications Committee, developed several questions with regard to pathophysiology of SCD and use of RBCx in the management of various complications. These questions were provided to the seven invited speakers who are the experts in the field of SCD. Two experts in the field moderated the proceedings of the conference, which was attended by more than 150 participants. After each presentation, there was a summary of the main points by the moderators and an open discussion with questions from the audience. A video recording of the proceedings, as well as each presentation, was made available to the authors. Each author's summary was reviewed and approved by the respective speaker before submission of this manuscript. The subcommittee also developed several key questions to generate a consensus amongst the speakers on key issues for using RBCx for patients with SCD.

KEYWORDS
sickle cell disease, red blood cell exchange, acute chest syndrome, pulmonary hypertension, stroke

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1 | INTRODUCTION

Sickle cell disease (SCD) is a hemoglobinopathy that leads to both hemolytic anemia and vaso-occlusion. Though typically

found in African Americans, the disease also affects those of Caribbean, Hispanic, Mediterranean, Middle Eastern, and Indian descent.[1] It occurs in 1 of every 365 births in the African American population and affects approximately 100,000 Americans. The sequelae of the disease lead to approximately 75,000 hospitalizations per year at a cost of approximately $475,000,000.[2]

Clinically, SCD is characterized by chronic hemolytic anemia, acute vaso-occlusive crisis and end organ failure, related to its pathophysiology (described below). Due to the intense morbidity of the disease, patients must be monitored closely and often treated aggressively to prevent disability and in some cases, death. The management for SCD varies greatly with the severity of the symptoms. Some patients may do well with minimal therapy and infrequent transfusions, while others are transfusion dependent. Transfusion therapy could be simple transfusions, which can be offered in any hospital or clinic. However, simple transfusion often leads to iron overload, unless strict iron chelation therapy is followed. Simple transfusion cannot reduce HbS levels rapidly, which may be required to control pathophysiology in certain critical conditions like acute chest syndrome (ACS) or stroke. RBCx on the other hand can prevent iron overload and achieve rapid HbS reduction; however, it is technically challenging and hence not readily available in most places.

Although multiple guidelines exist regarding the treatment of SCD, from the American Society for Apheresis (ASFA) Guidelines for RBCx[3] to the NIH's 2014 expert panel report on evidence-based management of SCD,[4] practice variability still exists for the treatment of SCD, especially with RBCx due to absence of randomized clinical trials. Therefore, on May 5, 2015, ASFA conducted a one-day consensus conference on RBCx in SCD to address areas of controversy in the management of this life-changing disease.

Experts in the field of SCD (Table 1) were invited to deliberate questions generated by the authors of this manuscript, a subcommittee of ASFA's Clinical Applications Committee. Two renowned experts in the field, Drs. George Buchanan and Mark Brecher, were invited to moderate the proceedings of the conference. >150 conference attendees also participated in the discussion by asking questions at the end of each presentation. Following the conference, the authors of this manuscript created a summary of the presentation, which was then approved by the individual speakers. Additionally, email polls were sent to each speaker after the conference to determine a consensus amongst them on key issues in treating SCD.

2 | SUMMARIES OF PRESENTATIONS

2.1 | The first presentation: pathophysiology of sickle cell disease

Dr. Steinberg presented an overview of his topic, then answered questions at the end.

Pathophysiology of Vaso-occlusion:

The formation of hemoglobin S (HbS) secondary to a mutation in the globin gene is the fundamental defect of SCD. The sixth codon of exon 1 of the β-globin gene (on chromosome 11) is normally responsible for the synthesis of the β-globin polypeptide of the Hb molecule (α2β2). However, a mutation in this codon, results in replacement of the normal glutamic acid with valine at position 6 of the β-globin chain and the formation of HbS. The primary process that leads to vascular occlusion is the polymerization of HbS upon deoxygenation, which, in turn results in distortion of the shape of red blood cells (RBCs). This process also causes cellular dehydration, decreased deformability, and "stickiness" of RBCs that promote adhesion to vascular endothelium leading to vascular occlusion. Cellular dehydration is secondary to loss of K+ and water which in turn enhances further polymerization of deoxyhemoglobin.[5–9]

HbS polymers initiate red cell membrane changes leading to hemolysis and vaso-occlusion, the two major pathophysiologic mechanisms that are associated with the complications of SCD. Intravascular hemolysis reduces endothelial nitric oxide (NO) bioavailability and is associated with the following complications: silent and overt strokes, pulmonary hypertension, leg ulcers, cholelithiasis, priapism and impaired renal function with albuminuria.[10] Moreover, hyperhemolysis syndrome may be associated with increased mortality.[11]

Cellular interactions of SCD are more closely associated with the sickle vaso-occlusive complications. These cellular interactions can be erythrocentric or leukocentric. In the erythrocentric perspective, the sickle RBCs display certain ligands that promote their adherence to endothelial cells, thus causing obstruction of the microcirculation. In the leukocentric perspective sickle RBCs interact with neutrophils which then adhere to the endothelium and initiate the vaso-occlusive process.[12] Vaso-occlusion, in turn, leads to reperfusion injury and inflammation that are characteristic of this disease.[13] The common sickle vaso-occlusion-associated complications include acute painful episodes, ACS, osteonecrosis, multiorgan failure with thrombotic microangiopathy, and in HbSC disease retinopathy and splenomegaly.

2.2 | Anemia and its management

Unlike β-thalassemia, where the anemia is mainly due to ineffective erythropoiesis, in SCD the anemia is mainly the result of peripheral RBC destruction.[14] The anemia of SCD is hemolytic in nature with about 5–30% of hemolysis intravascular and the remainder is extravascular. A small component of the anemia of SCD is due to ineffective erythropoiesis.[15–17]

Conceptual approaches for the treatment of the anemia (or complications) of SCD include increasing the level of

TABLE 1 Panel participants and moderators for the 2015 ASFA consensus conference

Name	Position	Institution/location
Speakers		
Araba Afenyi-Annan, MD, MPH	Adjunct Assistant Professor	University of North Carolina, Chapel Hill, Chapel Hill, NC
Michael DeBaun, MD, MPH	Professor of Pediatrics and Medicine; Vice Chair for Clinical and Translational Research; J.C. Peterson Chair in Pediatric Pulmonology; Director; Vanderbilt-Meharry Center for Excellence in Sickle Cell Disease	Vanderbilt University, Nashville, TN
Mark Gladwin, MD	Professor and Chair of Internal Medicine, Division of Pulmonary, Allergy, and Critical Care Medicine; Director, Vascular Medicine Institute	University of Pittsburg, Pittsburg, PA
Cathy Hulitt, BSN, RN, HP(ASCP)	Clinical Nurse Level IV-Apheresis Program	Children's Hospital of Philadelphia, Philadelphia, PA
Haewon C. Kim, MD	Associate Professor of Pediatrics; Medical Director of Apheresis; Attending physician in the Division of Hematology, Blood Bank, and Transfusion Medicine	Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA
Keith Quirolo, MD	Clinical Director of Apheresis, Division of Hematology/Oncology	UCSF Benoiff Children's Hospital, San Francisco, CA
Martin H. Steinberg, MD	Professor of Medicine, Center of Excellence in Sickle Cell Disease Boston Medical Center, Pediatrics, Pathology and Laboratory Medicine	Boston University, Boston MA
Moderators		
George Buchanan, MD	Professor of Pediatrics, Children's Cancer Fund Distinguished Chair in Pediatric Oncology and Hematology	UT Southwestern Medical Center, Dallas, TX
Mark Brecher, MD	Chief Medical Officer, Senior Vice President, Lab Corp; Director Immunohematology, Lab Corp; Adjunct Professor of Pathology and Laboratory Medicine	Laboratory Corporation of America and University of North Carolina, Chapel Hill, Chapel Hill, NC

fetal Hb (HbF), reducing the RBC density by rehydrating sickle erythrocytes, preventing adhesion of sickle RBCs to the endothelium, and minimizing inflammation. To date, the only successful method has been the induction of HbF production using hydroxyurea. Other methods either did not work or are currently under investigation.

On the other hand, blood transfusion has been the practical clinical approach to manage the anemia of SCD. The usual indications for blood transfusion include severe symptomatic anemia, prevention of primary and secondary strokes, severe ACS and preoperatively for major surgeries. Occasionally, blood transfusion may be indicated in pregnancy and renal failure. Blood transfusion, however, is not recommended for the management of painful crises and chronic anemia. Technically, blood transfusion could be simple or blood exchange transfusion.

Severe ACS, multi-organ failure, fat embolization syndrome, and the prevention of primary and secondary strokes are the usual indications for red cell exchange transfusion.[18,19] Moreover, a recent observational study reported the safety and efficacy of blood exchange transfusion in patients with priapism in whom 5 (50%) achieved complete resolution of priapism and 2 (20%) achieve resolution after each recurrence of priapism.[20] None of the patients had any neurological complications such as headache, seizures, neurological deficits, or obtundation post-exchange. This is unlike a previous report indicating that RBC exchange is contraindicated in patients with SCD and priapism due to severe neurological

complications referred to as ASPEN syndrome.[21] A randomized pre-operative transfusion trial showed that simple and RBCx transfusions are equally effective with increased rate of alloimmunization in the exchange transfusion arm.[22] For almost all the indications for blood transfusion, high-grade evidence supporting the superiority of one or the other of these approaches is lacking. In fact, multiple Cochrane analyses have found no evidence for superiority of exchange transfusion (or even benefits of any transfusion).[23] Methodically, RBCx can be automated or manual. The automated method is faster and often meets pre-exchange targets, but uses twice the number of blood units as the manual method. Both methods of blood exchange have similar adverse events.[24]

Major complications of blood transfusion include increasing blood viscosity, loss of venous access, delayed hemolytic transfusion reaction, hyper-hemolysis, iron overload, and alloimmunization. Sickle cell blood has intrinsically increased viscosity compared to normal individuals, especially if HbS is deoxygenated and oxygen transport is optimal at lower Hb level (Figure 1).25 Viscosity complications can often be avoided if the Hb level is kept about 10 g/dL post-transfusion, especially post-simple transfusion.[25,26] Otherwise the increased viscosity and decreased oxygen transport can precipitate serious complications of SCD. Whole blood viscosity is more problematic in HbSC disease whose prevalence is 1/800 African Americans. The pathophysiology of HbSC disease is different from HbSS homozygotes. Moreover the anemia in HbSC disease is milder with a usual Hb level $>$ 10 g/dL. Accordingly, because of higher blood viscosity, patients with HbSC disease are more prone to retinopathy, late splenomegaly and multi-organ failure syndromes which often requires RBCx.

The rate of alloimmunization has been reported to be decreased in exchange transfusion compared to simple transfusion and exchange transfusion reduces iron overload in prevention of secondary stroke.[27] The alloimmunization rate was 18.6% in 1,814 patients enrolled in the Co-operative Study of SCD (CSSCD) transfused between 1979–1984[28] and was 27.3% in 319 Duke/University of North Carolina patients transfused between 2001–2011.[29] Factors that are associated with the development of alloimmunization are not well known–racial disparity is one. The number of transfusions received in one's lifetime is also thought to be a factor. While this still appears to be the case when considering simple transfusion, a article from 2012 reports lower alloantibody formation in patients undergoing chronic RBCx when compared to a cohort receiving simple transfusion.[27] In an effort to determine the genetic basis of alloimmunization the Genome-Wide Association Study (GWAS) of 390 adults with SCD from the CSSCD and Duke University found that the most significant associations with alloimmunization occurred for 46 Single Nucleotide Polymorphisms (SNPs) in the HLA locus and in

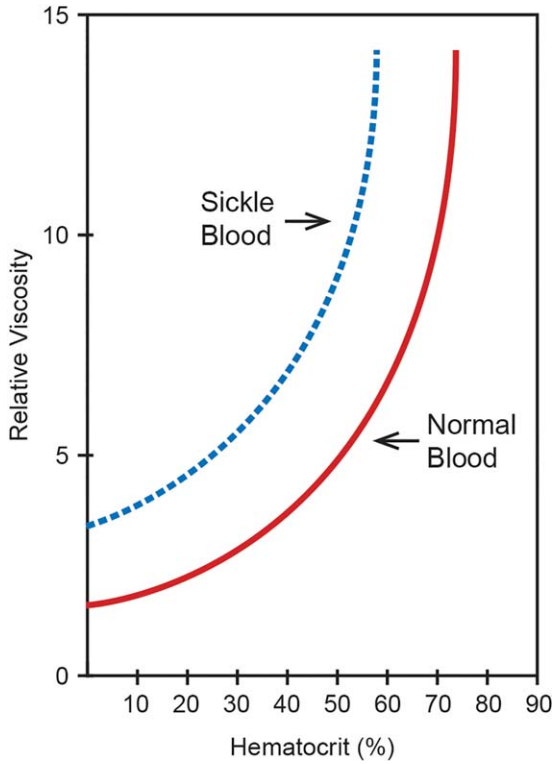

FIGURE 1 Relative viscosity of the blood of patients with SCD versus normal controls

10 SNPS in four other loci: *GZMB* (3 SNPs), *TGFBR2* (4 SNPS), *TLR3* (1 SNP) and *TGFR3* (3 SNPs).[30]

Dr. Steinberg's answers to the questions for his presentation are summarized as follows:

1. Given the pathophysiology of patients with SCD that present with serious complications of vaso-occlusion or endothelial damage, is there high quality evidence, clinical or experimental, to suggest benefits of reducing HbS concentration from $>$ 90% to $<$ 30% in the acute and/or chronic management of certain complications of sickle cell anemia (SCA)?

   Yes. However, this depends on the details of the special circumstances of each situation. Given the lack of randomized controlled trials of transfusion or exchange versus simple transfusion, most decisions are guided by the circumstances that the clinician faces with the individual patient.

2. In patients presenting with ACS, is there evidence of acceptable quality to support benefits of transfusion therapy?

   This is an extremely broadly defined complication we often see in adults and occasionally in pediatrics. Many patients who qualify for the diagnosis of ACS have new infiltrate and chest pain, but everything else is perfectly stable with no hypoxia. We usually do not transfuse such an individual with one lobe involvement and very few hematological changes. Such patients usually get better in 5 or 6 days. Thus, I think it is bad practice to transfuse everybody with ACS.

TABLE 2 Presenting symptoms of patients with ACS according to age

	Age (yr)						
	Total	**<2**	**2–4**	**5–9**	**10–19**	**20+**	***P* Value***
Symptoms	% of Patients						
Fever	80	97	88	87	76	64	<.001
Cough	74	77	86	81	69	63	<.001
Chest pain	57	6	16	48	78	84	<.001
Shortness of breath	28	14	19	19	26	47	<.001
Productive cough	24	7	13	15	28	44	<.001
Severe chest pain	22	0	3	8	29	44	<.001
Chills	18	4	4	8	22	39	<.001
Wheezing	11	13	16	7	8	13	.769
Hemoptysis	2	<1	<1	<1	<1	6	.011
No. of patients	939	124	168	191	204	252	–

**P* values for the difference between age groups 2 to 4 years and 20+ years adjusting for genotype (Hb SS or Hb SC). Results reflect symptoms from only first episode of ACS for each patient.

This is one end of the spectrum but on the other end of the spectrum everybody would transfuse the critically ill patients with ACS. Additionally, there is the broad middle group where the decision to administer simple or exchange transfusion has to be made individually depending on the circumstances of each patient.

3. If the answer is yes to question 2, please answer the following questions:
   a. With the understanding that most transfused red cell units do not carry sufficient 2, 3 DPG to carry oxygen as soon as they are transfused, is the expected benefit of transfusion in ACS related to simply correcting anemia to improve oxygen carrying capacity?

   In stored blood the 2,3 DPG levels are low but they are rapidly regenerated as the cells start to circulate. This regeneration starts immediately and is complete within 24 hours.

   b. Is the expected benefit of transfusion in ACS related to reduction in HbS percent to alter pathophysiology?

   Yes. The transfused blood dilutes sickle erythrocytes and decreases the % of HbS, thus improving the circulation and oxygen delivery to tissues.

4. Should RBC transfusion be the first line of therapy for patients presenting with ACS?

Sick patients who are admitted to the hospital via the emergency department (ED) with hypoxia, WBC $\geq 20 \times 10^9$/L, decrease platelet count and high LDH compared to base-line values are transferred to the intensive care unit (ICU) in preparation for RBCx. Simple transfusions are given until the RBCx is available.

5. STOP1 and STOP2 studies have shown long term benefits of chronic transfusion in primary stroke prevention in patients with increased TCD velocity and transfusion therapy has been shown to be effective in secondary stroke prevention provided HbS values are maintained below 30%. Therefore, in a patient presenting with acute stroke, should RBC exchange should be the first line of therapy rather than simple transfusion to achieve rapid HbS reduction to <30%?

   Yes. This is discussed in detail by Dr. DeBaun in the third lecture.

6. Red cell exchange (RBCx) can reduce or prevent iron overload often seen with chronic simple transfusions for both primary and secondary stroke prevention, as well as for patients on chronic transfusion for other complications of SCD. Therefore, should RBCx be considered the standard or preferred care for patients requiring long term chronic transfusion therapy?

   No. First of all, the complications of iron overload in patients with SCD are far less than in patients with thalassemia. Second, there are currently relatively simple, non-invasive and inexpensive methods to measure cardiac and liver iron frequently. Third, there are effective oral iron chelators to treat iron overload. Therefore, using RBCx as a means to avoid iron accumulation is not currently standard of care in the United States.

7. Is there a role for RBC transfusion or RBCx in priapism?

   There is no high-quality evidence that either simple or blood exchange transfusions are effective in resolving priapism rapidly. The NIH guidelines referred to evidence as of

high, moderate or low quality and recommendations are of high, moderate or low strength. For examples the guidelines indicate that the evidence of blood transfusion (simple or exchange) for priapism is of low quality but with moderately strong recommendation.[4] There are issues with blood exchange being associated with neurological complications but this seems to be due to high Hb levels post-exchange, causing hyperviscosity syndrome with neurological complications.

2.3 | The second presentation: rationale for RBCx and/or simple transfusion in acute chest syndrome

Dr. Quirolo presented an overview of his topic, answered specific questions, then summarized his recommendations at the end of his presentation.

Acute Chest Syndrome is the second most common diagnosis for hospitalized patients with SCD and is the leading cause of death accounting for 25% of deaths. It is also a risk factor for stroke and neurologic complications, especially in adults. Most patients who develop ACS have HbSS (78%), though patients with HbSC are also affected (13%). Risk factors for death from ACS are respiratory failure in the first 48 hours, bacterial sepsis, extremity pain, and pulmonary fat embolism. In the ACS in SCD Study 76% of the subjects were 19 years of age or younger.[31]

3 | ANSWERS TO QUESTIONS

3.1 | What are the etiologies of ACS, the cause-effect relationships and risk factors for both initial and recurrent episodes, with special consideration given to pulmonary hypertension and interstitial lung disease?

The etiology of ACS in adults and children differs. In pediatric SCD a bacterial infectious cause is more common, with very few adults having a bacterial infection with ACS. It is more common to have no etiology for ACS in children compared to adults (Table 2).[31,32] Complications also differ between adults and children. Adults are more likely to have respiratory failure, cardiovascular complications, gastrointestinal bleeding, and neurologic sequela. ACS in children is more frequently seasonal, less often requires transfusion, and children more commonly have a history of asthma. DeBaun et al. found that in children, the following were predictors of future ACS episodes: female gender, age less than four years, history of asthma with shortness of breath/wheezing, and atopy.[33] These findings suggest that adequate treatment of asthma would reduce the frequency of ACS in this group. It is recommended that patients having an episode of ACS be treated with hydroxyurea. Some centers also place patients on 3 to 6 months of prophylactic transfusions to decrease rehospitalization. Adolescents and adults frequently present with only extremity pain, however, then develop ACS following admission for vaso-occlusion. These groups more frequently require transfusion and have an increased risk of mortality, four times that of children. Therefore, expectant and aggressive treatment is important when adolescents and adults present with ACS.

Lastly, the literature supports the finding that pre-existing pulmonary hypertension (PHT) does not predispose patients to ACS. However, during episodes of ACS there is an increased incidence of PHT increasing the morbidity for these patients.[34]

3.2 | Discuss the differential diagnosis of ACS, including relevant tests and clinical findings for early and definitive diagnosis to reduce morbidity and mortality, with a focus on ACS versus pulmonary embolus, pulmonary infarction, and fat embolus

Overall, ACS is a clinical diagnosis. Clinical respiratory score and secretory Phospholipase A_2 ($sPLA_2$) were discussed as aids to the diagnosis of ACS.[35,36] Increased $sPLA_2$ predicts impending ACS, if patients have a fever, and in children an increased respiratory score can predict more severe ACS. However, the respiratory score may not be helpful in rapidly evolving ACS. The respiratory score is not uniformly used in pediatric ACS.

Venous thromboembolism (VTE) is often found during an episode of ACS, predominantly in adults. A study by Naik et al. found that the overall rate of VTE was 25%, with 18.9% unrelated to an indwelling venous catheter.[37] VTE was increased in patients with non-HbSS variant as compared to HbSS and also in patients with PHT defined as a Tricuspid Regurgitant Jet Velocity (TRV) of ≥ 2.5 m/sec. Mortality was increased in patients with VTE (15.8% versus 4.6%). Novelli et al. published a five year discharge database review of pulmonary embolism (PE) in SCD.[38] They found that mortality was increased in patients with PE (6.2% versus 1.4%), there was no difference in mortality by any clinical features or for genotype. Mekontso et al. studied pulmonary arterial thrombosis (PAT) in 125 patients screened by CT.[39] Twenty of the 144 episodes, 17%, of ACS were associated with PAT. The only predictors of PAT were thrombocytosis and a lower bilirubin level compared to the entire cohort. The majority of PAT were in situ, fat emboli was not diagnosed in these patients, but could not be ruled out as a causative factor in the development of PAT.

Fat emboli syndrome (FES) is due to bone marrow necrosis related to a vaso-occlusive episode (VOE) in large bones. The fat embolization causes ACS and can lead to multiorgan failure. The release of free fatty acids contributes to lung injury and hypoxia, resulting in ventilation perfusion

defect creating a cycle of hypoxia and increased VOE, which can lead to multi-organ failure. FES is more common in patients with an elevated hemoglobin, such as SC disease. A literature review of FES by Tsitsikas et al. revealed that 81% of patients had respiratory failure with a mortality rate of 64%.[19] In this review, there was an association between lack of transfusion and mortality. Mortality was 29% for patients who received RBCx (29% of the patients), 61% of those receiving simple transfusion (31% of the population), and 91% in those who were not transfused (38% of the population).

3.3 | What are the laboratory and/or clinical thresholds for treatment of ACS using simple transfusion and/or RBCx?

The decision to whether use simple transfusion or perform an exchange transfusion depend on many factors. Jan et al. published a study of 15 subjects who received transfusion for surgery.[40] In these patients, a hematocrit $\geq 33\%$ resulted in decreased oxygen transport. It is from this study that the recommendation not to transfuse to a hemoglobin of over 33% was derived. In another study on rheology, the relationship between hematocrit and viscosity was evaluated in 26 patients being transfused for stroke.[41] In this group, the HbS was lower than the previous study, but they also found an inverse relationship between viscosity and hematocrit and oxygen delivery. This was particularly pronounced at low sheer stress relative to high sheer stress.

Emre, et al. studied 36 children treated for ACS.[42] All of these patients had clinical severity scores and blood gas measurements before and after simple transfusion. There were six patients without transfusion that served as controls. These patients actually had a variety of transfusion methods including red cell exchange. Oxygen delivery improved in all patients and there was no difference in length of stay or symptom score. These findings indicate that some pediatric patients do well with simple transfusion alone.

Comparing simple transfusion and RBCx in pediatric patients, Saylors et al. performed a retrospective study of 81 pediatric patients with ACS.[43] Fifty-one patients were studied who received simple transfusions, 15 received RBCx and 15 received both simple and RBCX. The patients all had respiratory scores for six variables on an individual scale of 0 to 2 with a maximum score of 12. Respiratory scores improved in all patients receiving simple transfusion with the exception of the 15 who required subsequent RBCx. These were patients who had higher respiratory scores initially and worse scores following simple transfusion. In the simple transfusion group those with lower hemoglobin and lower respiratory scores did well. Those with higher hemoglobin and worse respiratory scores received RBCx, indicating that children who present with more severe ACS should have RBCx as the initial treatment. Of note, the ASFA guidelines give RBCx for ACS a category II indication (second line therapy) based on Grade 1C evidence.[3] In short, RBCx should be used for those patients not responding to other therapies, such as simple transfusion.

Examining simple transfusion in adults, Maitre et al. studied 77 patients who received 107 transfusions over a period of 6 years.[44] The mean age of this cohort was 29 years old. This was a restrictive study, as transfusions were only given to patients who had severe ACS with rapid initial deterioration or deterioration after 72 hours with hypoxia, chest pain, and new infiltrate on chest film. Of these episodes, 35% were transfused within the first 48 hours for severe disease and 65% by days three to fourteen for deterioration. The death rate was higher in the more severe transfused Group (10% versus 0%) with 50% of the severe group admitted to the ICU compared to the less severe group, 7%. This study reveals the need for rapid and aggressive treatment of adults with ACS.

A retrospective study by Turner et al. examined RBCx and simple transfusion in adults with ACS.[45] The study included 30 patients with a mean age of 30 years. Each group of 20 received either simple transfusion or RBCx. Both groups were equally treated with hydroxyurea (40 and 45%). Most patients were treated with bronchodilators. As in other retrospective studies, those receiving simple transfusions were more anemic at presentation. Nine of the RBCx patients had been previously treated with simple transfusion and the percent HbS was not reported. The length of stay was equal in the two groups. This is the only study comparing RBCx to simple transfusion in SCD, but does not address some of the important issues in transfusion for ACS in adults.

Fluid balance, as highlighted by a case study of five ACS patients requiring ventilator support, is also important.[46] All of the patients in the case study had a net positive fluid balance and hypertension for age. All had neurologic events and posterior leukoencephalopathy. In some of these patients, the leukoencephalopathy resolved revealing stroke. This case series illustrates the need to monitor net fluid balance and blood pressure in patients being treated for ACS.

4 | SUMMARY AND RECOMMENDATIONS

Dr. Quirolo highlighted many difficulties encountered when providing guidelines for ACS diagnosis and management. First, the current literature on ACS in SCD is mostly pediatric. Second, the literature is primarily retrospective. There are no randomized prospective controlled trials for transfusion in ACS, nor are there prospective studies comparing simple versus RBCx in ACS. In addition, the definition of ACS is not consistent among studies. Currently, the accepted

criteria are from the ACS in SCD Study. The recommendation of this study was that a diagnosis of ACS should be considered when a patient has a new pulmonary infiltrate, chest pain, a temperature of ≥ 38.5°C, tachypnea and wheezing/cough.[32]

For pediatric patients with a lower respiratory score and anemia, the initial therapy should be simple transfusion. For adults with anemia, simple transfusion is indicated to avoid treatment delay before RBCx. In all patients, net fluid volume should be monitored and a positive balance avoided except in cases of hypovolemia. The findings of the National Acute Chest Syndrome Study Group revealed that transfusion, bronchodilators, and aggressive therapy was indicated for ACS in SCD. Simple transfusion was predominantly used in that study. Chronic transfusion is used in some centers for three to six months following an episode of ACS to prevent re-hospitalization. Hydroxyurea therapy is recommended for adults and children who have had an episode of ACS.

Dr. Quirolo recommended initial treatment with simple transfusions for anemic patients with subsequent RBCx for those patients who do not have significant improvement. For patients who present with an elevated hemoglobin, RBCx is indicated as the initial therapy. The reduction of percent hemoglobin S cannot be achieved with simple transfusion in these patients. Of note, the recent NHLBI guidelines for SCD recommend simple transfusion for ACS when hemoglobin is below baseline (>1 g/dl below baseline, however, if the baseline Hb is 9 g/dl or higher, simple transfusion may not be required), reserving red blood cell exchange (RBCx) for more severely ill patients who meet the criteria in the recommendations (O_2 Saturation $< 90\%$ on room air, progressive pulmonary infiltrates, and decreasing hemoglobin). Although the quality of the evidence was considered low, the available evidence supports RBCx in this setting and RBCx was given a strong recommendation when these criteria were met (Grade 1C).[4]

The goals for RBCx and simple transfusion in both adults and pediatric patients is the same - end hematocrit of 27–30% (hemoglobin of between 9 and 10 g/dl) with the fraction of cells remaining (FCR) to achieve a percent hemoglobin S of $\leq 30\%$. The expectation is improvement in oxygen saturation (~95%) and clinical condition. If the transfusion goals are met and there is no improvement, other etiologies complicating ACS should be entertained such as PE or PV.

4.1 | The third presentation: pathophysiology and management of cerebrovascular accidents

Dr. DeBaun addressed the following questions during his presentation:

1. What is the impact of primary stroke prevention in children with SCD?
2. What is the impact of blood transfusion therapy on secondary stroke prevention, and should we increase the threshold of HbS from 30% to 50%?
3. Should we perform exchange transfusion therapy at initial presentation for focal abnormalities seen on neurological examination?
4. How common are silent strokes and how should we transfuse for these?

Prior to 1998, overt stroke was observed in up to 11% of children by the age of 19, and hemorrhagic stroke was more prevalent in young adults.[47] Adams et al. demonstrated that children with high transcranial Doppler (TCD) studies treated with regular blood transfusion therapy had a 92% relative risk reduction in strokes when compared to those that were only observed.[48] The approach of screening children with sickle cell anemia (SCA) between 2 and 16 years of age using TCD, coupled with regular blood transfusion therapy for children with elevated TCD studies, has become a standard of care in the United States. Based on this strategy, the incidence of overt stroke in a single tertiary care facility has dropped from 0.67 to 0.06 per 100 patient years.[49]

Dr. DeBaun presented the case of an 18-year-old boy that highlights the bedside dilemma of managing a patient with an acute focal neurological deficit. He emphasized that a decision cannot be made to give either simple transfusion or exchange transfusion, or a combination of the two, without a team involving a hematologist, a transfusion medicine specialist, a neurologist, and a neuroradiologist. At Vanderbilt, there is an imaging algorithm in place for such a scenario (see Figure 2 below). They perform both magnetic resonance imaging (MRI) and Magnetic Resonance Venogram (MRV) and the expectation is that these studies are read as soon as possible for appropriate management. If the studies are positive for stroke or dural venous sinus thrombosis, they proceed with transfusion therapy. If a dural venous sinus thrombosis is present, both transfusion therapy and anti-coagulation are implemented. However, if MRI demonstrates posterior reversible encephalopathy syndrome (PRES),[46] then RBCx may not be as time sensitive as focusing the management on decreasing the patient's blood pressure. If the diffusion weighted imaging study is negative, suggestive of no cerebral infarcts, and the suspicion of stroke is high, based on the prior history and presentation, then RBCx should still be performed.

The recent National Heart, Lung, and Blood Institute (NHLBI) guidelines for acute stroke management recommend consulting an expert and getting an MRI to establish the diagnosis.[50] Unfortunately, the NHLBI guidelines do not acknowledge that up to 1/3 of non-disabling strokes will be

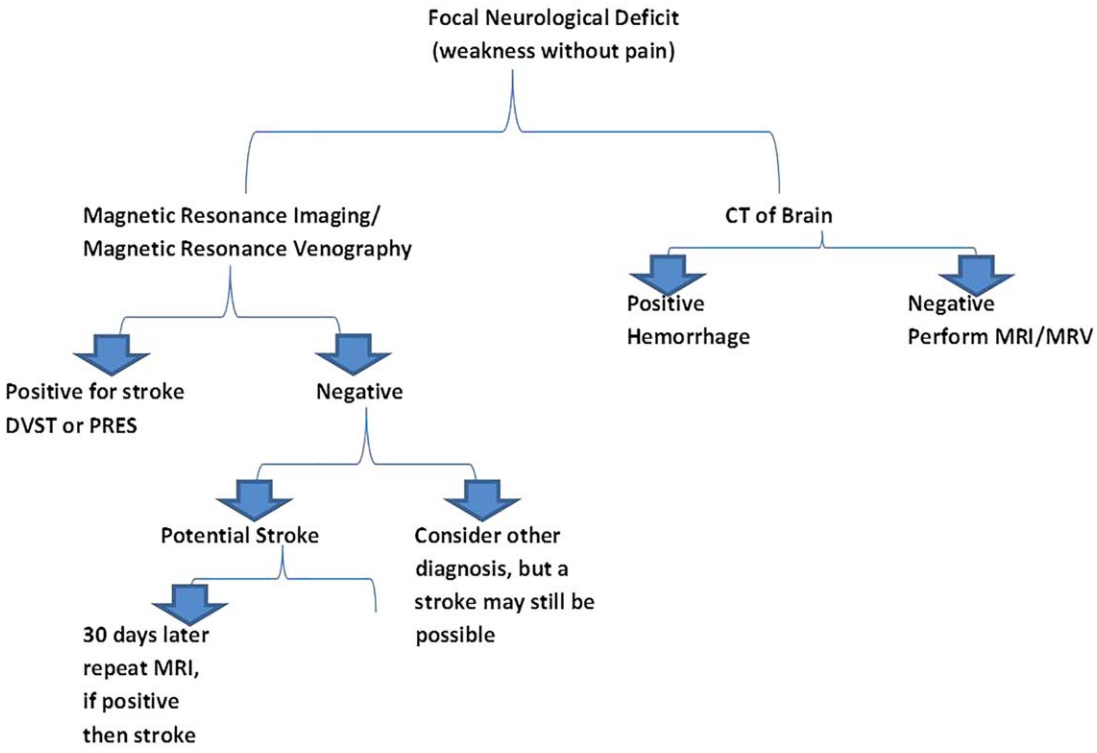

FIGURE 2 Vanderbilt University Algorithm for imaging studies for strokes in patients with SCD. DSVT = Dural venous sinus thrombosis. PRES = Posterior reversible encephelopathy syndrome

MRI negative.[51] Thus, the final decision as to whether RBCx should be performed must take into consideration the presentation and the relative confidence that there is a diagnosis other than a stroke.

Once an acute stroke is confirmed based on MRI of the brain, or believed to be of high likelihood of occurrence based on the clinical presentation, the NHLBI recommendation is to perform RBCx. This recommendation is based on consensus and panel expertise due to lack of high quality data in the literature.[50] Patients who received RBCx had a much better stroke-free interval when compared to simple transfusion.[18] The urgency to diagnose and manage strokes was emphasized-a concept "time is brain" that has been adopted from the adult stroke literature for over a decade.[52] Based on "time is brain" principle, every hour delay in performing RBCx increases the risk of ischemic brain injury. Dr. DeBaun recommends that RBCx be performed within three to four hours of onset of acute neurological symptoms, but may be as efficacious within 24 hours of an acute onset of neurological injury.

However, Dr. DeBaun stated that there is no known reason why RBCx is superior to simple blood transfusion therapy alone for the acute management of strokes. Potential explanations include that blood viscosity increases with increasing levels of total hemoglobin in patients with SCA. Studies from individuals with and without SCA indicate that at the same level of hemoglobin, the blood viscosity level is higher for those with SCA. In individuals with SCA, a simple blood transfusion increases the viscosity and initial oxygen delivery; however, as the hemoglobin level increases with a simple transfusion, there is a decrease in oxygen delivery. This decrease in oxygen delivery can be mitigated if the HbS level is decreased significantly, i.e., $<50\%$.[53]

Since the 1990s, RBCx has been the predominant mode of therapy for initial management of suspected strokes for children and adults.[18] The benefits of RBCx are not well defined, but include an increase in HbA, without increasing viscosity, to improve cerebral blood flow and provide better oxygen delivery to the brain tissue, which may limit the volume of damaged and ischemic brain tissue. The treatment goals for acute stroke include restoring cerebral blood flow, maximizing tissue oxygen delivery to the brain, reversing neurological injury, and preventing further neurological injury.

The long-term treatment for secondary stroke prevention can include simple transfusion or RBCx (mostly automated and rarely manual). Without regular blood transfusion therapy, based on pooled analysis from recent studies, the stroke recurrence rate is very high, with 29 recurrent stroke events per 100 patient years compared to 1.9 recurrent stroke events per 100 patient years in those that receive regular blood transfusion therapy.[54] However, the consequences and side effects of regular blood transfusion therapy include excessive iron stores and the burden of chelation therapy.[55] Apart from

regular blood transfusion therapy, other options for secondary stroke prevention include allogeneic stem cell transplantation, hydroxyurea therapy, and revascularization. Only hydroxyurea therapy has been studied in a randomized clinical trial when compared to blood transfusion therapy (standard therapy) for secondary stroke prevention. The trial was stopped prematurely because the hydroxyurea and phlebotomy arm was shown to be futile for the composite primary end point when compared to the transfusion and chelation arm. In the hydroxyurea and phlebotomy arm there were 10% strokes and in the transfusion and chelation arm there were no strokes.[56] Based on the pooled analysis, hydroxyurea therapy has an impressive benefit when compared to no therapy for strokes– 3.8 events per 100 patient years vs.29 events per 100 patient years, but it is not as efficacious as blood transfusion therapy which had a stroke recurrence rate of 1.9 events per 100 patient years.[54]

Despite the common belief that keeping the HbS level < 30% protects against stroke, significant evidence exists that hemoglobin S levels < 30% are not necessarily protective for future strokes. In the largest study to date involving a retrospective cohort of 137 children with SCA and strokes on continuous transfusion for at least five years with a gap of not more than two months, there was clear evidence of stroke recurrence while being transfused. As indicative of the palliative nature of treatment even with blood transfusion therapy, 23% of the children with SCA had recurrent strokes while receiving regular blood transfusion therapy at an event rate of 2.2/100 patient years. The HbS level at the time of the stroke recurrence was measured in only a few patients. Among those that had a HbS level obtained during the stroke recurrence, the HbS level was 1%, 9%, 22%, 25%, 26%, and 55%. Two of these patients had a third stroke with HbS percentages of 8% and 30% at the time of the second recurrence.[57]

Similar findings from the retrospective cohort study were replicated in a prospective single arm trial performed at seven clinical centers with 40 children with SCA who were receiving regular blood transfusion therapy for secondary stroke prevention. Surveillance MRIs of the brain were performed at regular intervals and read centrally. Over a course of 5.5 years, new cerebral infarcts, both overt and silent strokes, occurred in 45% (18/40) of the children even when the mean pre-transfusion HbS levels were <30%. Seven patients had second overt strokes when their HbS was 10%, 17%, 21%, 28%, 38% and 48% suggesting that the HbS levels are probably unrelated to recurrence of stroke. Eleven patients had new silent cerebral infarcts (SCI).[5]

The natural history of overt strokes in adults with SCA or other sickle cell syndromes has not been well defined. However, based on the current evidence, adults with SCA will likely benefit from blood transfusion therapy for secondary prevention of strokes.

SCI is characterized by no history of a focal neurological deficit and an increased signal on a T2 weighted image on MRI with a neurologist's confirmation of a normal neurological examination or focal exam not corresponding with a prior stroke.[58] The epidemiology of SCI revealed that 39% of children have SCIs by 18 years of age.[59] The causes or risk factors for SCI include low baseline Hb levels, high systolic blood pressures and male gender. In fact, children with SCA developing an acute drop in hemoglobin level < 5.5 g/dL have a significant risk of ischemic injury to the brain.[60] Similarly, cerebral ischemic events have been shown to occur even in children without SCA presenting with a hemoglobin <5.5 g/dL. The incidence of SCI is between 5 and 13.5% in children with HbSC,[61,62] with no evidence on how to best manage this population to prevent further neurological injury. SCI in children with SCA is associated with a decreased Full Scale Intelligence Quotient (IQ). In a pooled analysis of children with SCA, King et al. demonstrated that the presence of an SCI is associated with a 5-point drop in IQ when compared to children with SCA without SCI.[63]

In addition to increased morbidity, SCIs are also associated with an increased risk of overt strokes[64] and new SCIs.[62] Based on these findings, a prospective controlled trial of regular blood transfusion therapy for SCI (Silent Cerebral Infarction Transfusion, SIT) was conducted in 186 patients. The primary hypothesis was that prophylactic transfusion in children with SCI will result in reduction in clinically evident stroke or further progression of SCI.[58] A total of 90 participants completed monthly transfusions for three years. Based on an intention to treat analysis, the incidence rate of progressive cerebral infarcts (overt stroke or new cerebral infarcts) and transient ischemic attacks was 2.0 and 5.6 per 100 person years respectively, with an incidence rate ratio of 0.36 (95% CI: 0.10–0.83; $P = 0.02$). Given that SCIs are common and are associated with a decreased IQ[63] and with progressive neurological injury that can be attenuated with regular blood transfusion therapy,[58] every parent of a child with SCA should at least be aware of the risk of SCIs. For children with SCA, we perform at least one MRI of the brain by six years of age, the age at which the child can undergo an MRI scan of the brain without sedation. Additionally, academic assessment, behavior assessment, and at least one cognitive assessment for patients with SCI during routine clinical visits is beneficial.

In summary, Dr. DeBaun stated that the best evidence for regular transfusion therapy as a standard of care is in the prevention of overt stroke and SCI for patients with SCA.

During the question-and-answer period, Dr. DeBaun clarified and emphasized that apart from the HbS percentage, keeping the Hb above 9 g/dl is an important additional strategy to prevent strokes and SCI. He also clarified that despite regular transfusion therapy for secondary stroke prevention,

the central nervous system vasculopathy does not typically revert back to normal. Rather, children with overt strokes and progressive vasculopathy are at highest risk of having stroke recurrence.[5]

Dr. DeBaun stated that TCDs are still recommended only for children up to 16 years of age because one study reported that individuals above the age of 16 do not have a higher rate of abnormal TCDs values.[65] He did not think that increased white blood cell count is a major determinant for stroke. The high rate of stroke recurrence in children with SCA and HbS levels $< 30\%$[5,57] undergoing regular transfusion therapy may possibly be related to low hemoglobin levels < 9.0 g/dl. Dr. DeBaun is reluctant to add daily aspirin therapy for secondary prophylaxis unless the child has had a third stroke, and even then he is unsure of the risk benefit ratio. As to the time interval from the onset of symptoms to acute management, he believes that a child presenting within 24 hours of the onset of the neurological symptoms, for whom stroke is suspected or confirmed, and suspected stroke or confirmed stroke should receive RBCx.

4.2 | The fourth presentation: chronic hemolytic anemia and pulmonary hypertension in patients with sickle cell disease

Dr. Gladwin provided an overview of PHT in the context of the complications of SCD. He described the overall improved survival seen in adults with SCD over the past 3 decades, attributing progress to improved prevention and treatment of complications with advancements in newborn screening, antibiotic regimens, hydroxyurea, and transfusion management. With these improvements, there has been a decreased occurrence of the acute life threatening complications of SCD, such as ACS. However, there are more consequences of end organ complications including PHT, chronic renal insufficiency, and systemic hypertension, raising the issue of whether management with chronic red cell exchange would be helpful in limiting end organ disease progression.

Dr. Gladwin answered the following questions during his presentation:

4.2.1 | How does chronic hemolytic anemia damage blood vessels?

Patients with SCD have a high rate of ongoing extravascular and intravascular hemolysis, releasing large amounts of cell-free hemoglobin, sufficient to deplete the patient's haptoglobin levels. The circulating free hemoglobin rapidly reacts in an irreversible deoxygenation reaction with nitric oxide, effectively scavenging nitric oxide. Produced by endothelial cells, nitric oxide vasodilates, prevents vascular proliferation, and maintains healthy blood vessels. Hemolysis also releases enzymes, such as arginase. Arginase catabolizes arginine, the substrate which is converted by nitric oxide synthases to nitric oxide; thus, hemolysis limits nitric oxide production. Additionally, cell-free hemoglobin can lead to increased ferric heme which can have proinflammatory and toxic effects.[66]

Nitric oxide depletion leads to impaired cyclic GMP production in smooth muscle, causing vasoconstriction and over time resulting in proliferative remodeling of vasculature. Over decades, chronic free hemoglobin exposure leads to pathologic vascular remodeling via this mechanism, resulting in the development of PHT.[66] Additionally, hemolysis with nitric oxide scavenging and oxidative stress activates platelets and drives thrombosis, suggesting that hemolysis is a procoagulant phenomenon accounting for the increased thrombotic complications seen in patients with SCD.[66]

Dr. Gladwin summarized experimental evidence supportive of the above mechanism as follows:

- Patients with hemoglobin SS disease at baseline have detectable free hemoglobin in their plasma and undetectable haptoglobin.[67]
- When plasma from a patient with SCD is combined in vitro with a solution of nitric oxide, the nitric oxide is consumed in proportion to the amount of heme present in the plasma.[67]
- In an in-vivo study, nitroprusside, a source of nitric oxide, was infused via a brachial artery catheter into patients with SCD. Nitroprusside infusions typically lead to an increase in blood flow. Patients with higher levels of plasma hemoglobin had impaired blood flow responses to nitroprusside, suggesting that high steady state hemolysis leads to nitric oxide resistance.[67] The degree of resistance, or impaired responsiveness, correlated with level of plasma hemoglobin.
- Using a humanized sickle cell mouse model, Kaul et al. confirmed the phenomenon of nitric oxide resistance which was proportional to the presence of free hemoglobin; higher free hemoglobin was associated with increased nitric oxide resistance.[68]

4.2.2 | How little cell-free plasma hemoglobin is necessary to impair nitric oxide signaling and affect vascular function?

In an experimental rat model, the infusion of free hemoglobin is extremely vasoconstrictive, as demonstrated by a significant hypertensive response with increased pulse pressure. Even after the hemoglobin infusion is stopped, the hypertension persists. This hypertensive response occurs at very low concentrations of free hemoglobin (as low as 6 micromolar levels). Methemoglobin and cyanomethemoglobin do not react with nitric oxide and their infusion does not result in a

significant hypertensive effect. These studies demonstrate that very low levels of free hemoglobin are able to react with endothelial nitric oxide promoting vasoconstriction.[69]

This pathway of hemolysis-mediated endothelial dysfunction is seen in a number of hemolytic conditions, including malaria, surgery with cell-saver and thrombotic thrombocytopenic purpura. Following prolonged storage, red blood cells may demonstrate this phenomenon, since supernatant hemoglobin increases in stored red cell units under normal conditions. The degree of cell-free hemoglobin in stored red cell units is affected by genetic variability, such as the G6PD deficiency or other genetic determinants which affect the viability of red cells under storage conditions. When rats were infused 39 day supernatant as compared to 4 day supernatant from human stored blood, an increase in mean arterial pressure was seen which correlated to the amount of free hemoglobin in the supernatant; this increase in blood pressure was related to the property of nitric oxide scavenging by free hemoglobin.[69] Similar findings were demonstrated in a guinea pig model; the transfusion of fresh blood had no effect on blood pressure, but the transfusion of blood after prolonged storage had a significant hypertensive response which could be blocked by co-infusion of haptoglobin. Kidney disease was also seen related to the infusion of blood after prolonged storage; the deleterious renal effects were decreased when haptoglobin was infused.[70]

Measurable hemoglobinuria is found in 20–30% of patients with SCD. If hemoglobinuria was present, there was a decreased time to progression to kidney disease and time to progression to albuminuria.[71] These findings suggest that this hemolysis could be contributing to the progression of end organ disease, such as chronic renal insufficiency.

The role of hemin in the amplification of sterile inflammation is of growing interest. In a mouse model of SCD, the intravenous infusion of heme induced ACS. Using a toll-like receptor 4 (TLR 4) knockout model, the effect is blocked preventing lung injury and death, suggesting that heme is activating the innate immune system through TLR 4.[72]

The evolving model includes red cell hemolysis releasing DAMPs or damage associated molecular pattern molecules; damage associated molecular pattern molecules (DAMPs) drive vascular dysfunction and inflammation. Red cell hemolysis releases oxyhemoglobin which scavenges nitric oxide and generates reactive oxygen species (ROS); heme can activate TLR 4 and neutrophils release DNA neutrophil extracellular traps (NETs), all leading to inflammation and complications, as discussed above.[73]

4.2.3 | What is the clinical relevance of hemolysis?

Hemolysis-associated PHT has been associated with almost every chronic, hereditary or acquired hemolytic disease, including SCD, thalassemia, paroxysmal nocturnal hemoglobinuria, spherocytosis, stomatocytosis, alloimmune hemolytic anemia, pyruvate kinase deficiency, and microangiopathic hemolytic anemia.

Anemia, as an independent factor, does not cause PHT. In severe non-hemolytic anemia, pulmonary artery pressure and vascular resistance are not abnormally high. Pulmonary artery mean pressure only begins to rise at very low levels of hemoglobin. Pulmonary vascular resistance decreases with decreasing hemoglobin levels, due to lower viscosity and higher cardiac output.[74]

Dr. Gladwin's group performed a screening study of the prevalence of PHT in patients with SCD using non-invasive echocardiography and determination of the TRV to estimate pulmonary artery pressure. Normal estimated pulmonary pressures (TRV <2.5 m/s) were found in 67% of 195 adults studied. An intermediate range TRV of 2.5 to 2.9 m/s was seen in 24% of subjects and 9% had a TRV ≥ 3 m/s, a level at which follow-up with right heart catheterization for further evaluation of PHT is indicated. Patients with a TRV >2.5 m/s had a 10-fold increased risk of death.[75] This prevalence of high TRV is greater than seen in any other disease except for scleroderma, which is known to have a high prevalence of PHT. Subsequent clinical studies have confirmed that high TRV is associated with a higher mortality rate.[76–78]

Gladwin et al. showed that high pulmonary pressures correlated with markers of hemolysis, including high total bilirubin, high LDH and low hemoglobin. High pulmonary pressures with high TRV also correlated with markers of organ dysfunction related to systemic vasculopathy, including systemic hypertension, renal dysfunction and leg ulcers. There was no correlation of high TRV to markers of inflammation, such as high white cell count, platelet count, or fetal hemoglobin level. High TRV did not correlate with the number of episodes of vaso-occlusive pain crisis or ACS, suggesting that the causal mechanism of PHT is related to chronic hemolysis and not to ACS.[75]

Echocardiography with determination of TRV is a non-invasive, surrogate screening test for PHT. Right heart catheterization, a more definitive diagnostic test, has been used in three major studies of PHT in patients with SCD. Pulmonary arterial hypertension is defined by: (1) mean pulmonary artery pressure > 25 mm HG, and (2) Pulmonary capillary wedge pressure ≤ 15 mm. Pulmonary vascular resistance > 3 Wood Units is no longer a defining feature, but is used to guide therapy.

Mehari et al. reported the NIH experience of over 530 patients with SCD screened over 9 years; 86 patients underwent right heart catheterization revealing 56 patients (10.5%) with PHT.[79] Although these patients had mild to moderate increases in PHT, their mixed venous oxygen saturation was low and their 6 minute walks were abnormally low. Patients with PHT had statistically higher creatinine, LDH and ferritin. The patients with PHT had a 30% 9 year survival as

opposed to 80% for those who did not have PHT. The individuals who had a normal TRV and did not undergo right heart catheterization had equivalent survival to the patients who did not have PHT by right heart catheterization, confirming that a normal TRV can be used as a screening test to exclude PHT. Patients with SCD complicated by PHT had a 30% chance of living to age 60 as compared to 70% without PHT. When correlating TRV and the diagnosis of PHT by right heart catheterization, a TRV of 2.5 to 2.9 m/s is associated with a 39% chance of having PHT. A TRV $\geq$ 3 m/s is associated with a 77% chance of having PHT. If the high TRV cutoff (>3.0) is integrated with a low 6 minute walk or a high N terminal pro-Brain Naturietic Protein (NT-proBNP), the predictive value of the TRV is increased.

Using right heart catheterization, PHT was found in 10% of patients with SCD in a Brazilian study.[80] The patients with PHT were older, with lower 6 minute walks, more severe anemia, more hemolysis, more renal dysfunction and decreased survival. Parent et al. evaluated 398 adult patients; all patients with a TRV $\geq$ 2.5 m/s underwent right heart catheterization. PHT was found in 6% of patients, including 25% of patients with a TRV > 2.5 m/s. If TRV $\geq$ 2.5 m/s was combined with low 6 minute walk (<333 m) or high NT-proBNP (>164 pg/mL), the positive predictive value increased to 62%. Similarly, they found PHT was associated with indicators of hemolytic anemia, leg ulcers, renal insufficiency, and increased risk of death.[81]

In conclusion, all 3 studies which used right heart catheterization to diagnose PHT found that: 1) the prevalence of PHT in adult patients with SCD is 6-10.5%, 2) PHT is a risk factor for death, and 3) PHT is associated with hemolytic anemia.[81–83]

4.2.4 | What is the role of transfusion therapy in SCD and PHT?

There is very little data on the role of transfusion therapy for PHT.

An unpublished survey of 62 transfusion services associated with sickle cell centers yielded 31 responses and determined that 10% of children and adults receive chronic transfusions (personal communication from Shannon Kelly). For adults, the indications for chronic transfusions were vasculopathic complications associated with aging, including renal insufficiency and PHT.

Although patients with PHT are receiving chronic transfusion therapy, the data to support this practice is minimal. A recent Cochrane report aimed at evaluating chronic red cell transfusion for managing chronic chest complications in SCD, including PHT, found no relevant studies.[82] A recent publication reports 2 patients with SCD complicated by PHT who were managed with chronic automated RBCx.[83] With transfusion, one patient had improvement in pulmonary pressure by right heart catheterization, stable or decreased TRVs, decreased BNP, and increased 6 minute walk. The second patient had stable pulmonary pressure by right heart catheterization, TRV was stable, BNP decreased, and 6 minute walk did not improve; this patient ultimately died.

The American Thoracic Society recently published guidelines for the diagnosis, risk stratification and management of PHT in SCD.[84] Recommended PHT screening for adults included echocardiography, BNP and 6 minute walk. A TRV < 2.5 m/s warrants continued routine screening. Patients with a TRV between 2.5 and 2.9 m/s should undergo increased frequency of screening with consideration of their BNP and 6-minute walk results. With a TRV >3.0 m/s, patients should undergo right heart catheterization. Recommendations for management should follow mortality risk assessment based on TRV, BNP and documentation of PHT based on right heart catheterization. Optimization of SCD-specific therapy is recommended, with a strong recommendation for hydroxyurea therapy. Consideration of transfusion therapy is recommended for severe patients who have failed to respond to hydroxyurea; this recommendation for transfusion is weak due to lack of evidence.

Although transfusion therapy is effective treatment for vaso-oclusive complications, there is no definitive evidence that transfusion will improve PHT. It seems likely that chronic transfusion would benefit patients with PHT based on extrapolation of evidence; consequently, this area warrants specific investigation.

In conclusion, the complications of SCD are driven by two major pathways, intravascular hemolysis and inflammatory vaso-occlusion.[85] Although these pathways can lead to differing complicating symptoms, they are overlapping biologies. Transfusion therapy is effective for vaso-occlusive complications, such as stroke; but it is not known if transfusion therapy is effective in managing PHT. Consequently, this area is an opportunity for further investigations.

4.3 | Part A of the fifth presentation: RBCx procedure—standard and isovolemic hemodilution (IHD) RBCx for chronic transfusion therapy

Dr. Kim presented a brief overview, then answered targeted questions regarding RBCx procedures.

Chronic or indefinite red blood cell transfusion (RBCT) is now standard therapy for prevention of primary and secondary stroke in patients with SCD. The major side effects of chronic RBCT include alloimmunization and transfusion related iron overload. Chelation therapy, initially with parenteral deferrioxamine and recently with oral iron chelators (deferasirox and deferriprone), has increased the options in managing iron overload. However, adherence to iron chelation therapy has remained a major obstacle.

Long-term RBCx prevented or markedly reduced iron overload in patients with SCD.[86–90] The main drawback with

RBCx is increased blood requirements in comparison with simple transfusion. To reduce blood requirements, the standard RBCx (S-RBCx) was modified by incorporating Isovolemic Hemodilution (IHD) followed by S-RBCx.[91] IHD-RBCx is performed in two phases: the first phase is red cell depletion with replacement by an equal volume of 0.9% NaCl until the desired/target hematocrit level is reached, followed by S-RBCx with packed-RBC. Recently the Spectra Optia (Terumo BCT, Lakewood, CO) is FDA approved for IHD-RBCx.

Dr Kim responded to questions posed to her as follows:

4.3.1 | What are the optimal target levels for Hb and HbS after RBCx?

Prior to defining the post-RBCx target levels for Hb and HbS, pre-RBCx target levels must be established to achieve the post-exchange goals. However, the optimal pre-exchange Hb level is not clearly defined. Numerous publications reported that steady-state low Hb level is one of the known risk factors for SCI.[60,92,93] A multivariable logistic regression analysis by DeBaun et al. showed that the Hb level in the lowest quartile, <7.6 g/dL, compared with the highest quartile, ≥8.6 g/dL, was associated with a significantly increased risk of a SCI.[60] In a recent controlled trial of transfusions for SCI in SCA, the Hb level >9 g/dL was used as the target Hb level for the transfusion group.[58] All these findings suggest that maintaining the pre-exchange or baseline Hb level >9 g/dL may be beneficial to patients with SCD to reduce neurologic injury.

Similarly, the optimal post-exchange Hb level is not clearly established. However, before making a decision as to the post-Hb level, its effects, primarily on baseline Hb levels while on exchange program, oxygen delivery to tissues, blood viscosity, and iron overload should be considered. A previous study reported that children with SCD who underwent partial RBCx for priapism developed serious neurological complications known as ASPEN Syndrome (Association of SCD, Priapism, Exchange transfusion, and Neurological events).[21] Most of these cases had post-exchange Hb levels >12 g/dL. The authors postulated that some of the responsible mechanisms were increased blood viscosity due to the acute rise in Hb value and subsequent release of vasoactive substances during penile detumescence. The 2014 NIH guidelines state that post-transfusion Hb level should be raised to 10 g/dL in adults and children with SCA prior to undergoing a surgical procedure involving general anesthesia in order to reduce perioperative mortality and complications.[50] Dr. DeBaun stated in his presentation that the post-RBCx Hb level may be maintained at 10–12 g/dL. From these findings, post-exchange Hb levels may be maintained within the target range of 9 to 12 g/dL, but should not be raised >12 g/dL. However, to prevent iron overload, an effort should be made not to raise the post-exchange Hb level higher than the pre-Hb level, if possible.

Even though the optimal pre-transfusion/exchange target HbS level is not exactly known, maintaining the HbS level <30% is generally considered a goal of acute and chronic RBCT therapy in SCD. Numerous studies including STOP I and II showed that primary strokes in patients with SCD were markedly reduced with chronic RBCT therapy when the target HbS level was maintained <30%.[48,94] However, despite adherence to this transfusion regimen, SCI and progressive cerebral infarcts still occur.[5]

To further reduce blood requirements, some centers raise the target HbS level from <30% to <50%, when stroke patients remain neurologically stable for ≥3 years following the initial event. Post-exchange target HbS level is also affected by the exchange intervals. In general, when the exchange interval is longer, post-exchange target HbS level should be further lowered so that HbS level will not rise higher than the pre-exchange target level over time. For example, for those patients maintaining HbS <30% at the pre-exchange target, post-HbS may be reduced to approximately 15% with an exchange interval of 3 weeks, but with exchange intervals longer than 3 weeks, the HbS level should be further reduced to sustain the target HbS level until the next RBCx procedure.

4.3.2 | Should these targets be adjusted based on the patient's pre-procedure Hb and serum ferritin levels?

As long as the pre-target Hb level is >9 g/dl and HbS is <30% with no evidence of iron overload, there is no need to adjust the post-exchange target Hb and HbS levels. If not, the post-target levels should be adjusted based on the patient's pre-exchange levels and serum ferritin levels as stated in the response to the first question. If the baseline Hb levels have remained at <9 g/dL, the post-Hb level may be raised to 9–12 g/dL to improve oxygen delivery to the brain. One should realize that iron accumulation will occur when the post-Hb level is raised higher than the pre-Hb level. If the patient's serum ferritin level is elevated or begins to rise higher than the normal range, efforts should be made not to raise the post-Hb level higher than the pre-Hb level but to keep it at ≥9 g/dL.

If the pre-HbS level is higher than the target pre-level, RBCx should be performed by processing a larger blood volume with more units of donor blood than usual, in order to achieve the desired post-target HbS level. In this case, the FCR should be calculated to determine the volume of donor blood needed.

4.3.3 | What are the challenges of performing RBCx in small children?

To ensure safe and effective RBCx in pediatric patients, considerations should be given primarily to technical/procedural and vascular access.[95] RBCx procedures designed for adults must be modified for children.[96] Apheresis instruments require a fixed volume of blood to fill the disposable set, known as extracorporeal volume (ECV) which will represent a larger fraction of total blood volume (TBV) for smaller

children than for adults. Therefore, to prevent large intravascular volume shifts and fall in patient's Hb level, priming the extracorporeal circuit with donor red cells may be required. Indications for RBC prime include: 1) The ECV is >15% of TBV in children, 2) Young children weighing <20 kg regardless of the Hb level, and 3) when any degree of reduction in the circulating red cell volume is deemed undesirable regardless of the patient's weight and Hb level, such as patients with severe anemia, hemodynamic instability, tissue/organ ischemia, or underlying cardiopulmonary disease, such as cardiomyopathy or PHT with hypoxia.

The Optia system automatically makes the recommendation for red cell prime based on the TBV and RBC volume, whereas the COBE Spectra requires manual calculation. Generally, the rinseback is not recommended for both S-RBCx and IHD-RBCx regardless the type of equipment as the calculation for the post-hematocrit does not include rinseback volume.

4.3.4 | What are the advantages and disadvantages S-RBCx and IHD-RBCx?

Advantages

Both exchange methods offer the same short-term advantages.

Immediate advantages include:

- Rapidly increase Hb level without volume overload, thus improving tissue oxygen delivery
- Rapidly reduce HbS to the target level, thus reducing viscosity
- Maintain isovolemia, thus avoiding the risk of circulatory volume alterations and hemodynamic instability, which offer a safer procedure than simple RBCT
- Shorter duration of procedure compared to simple RBCT

Long-term advantages include:

- Both standard and IHD-RBCx markedly reduce or prevent iron overload.

4.3.4.1 | Disadvantages

- RBCx not universally available, as it requires equipment and experienced personnel to perform.
- Often require a central venous catheter/port, especially in pediatric patients.
- Significantly increases donor-RBC requirements compare to simple RBCT.

4.3.4.2 | Comparison of S-RBCx to IHD-RBCx

- IHD-RBCx offers reduction in donor-RBC requirements compared to S-RBCx, which may reduce the cost due to less blood usage and number of blood donor exposure.
- When the same volume of donor RBC is used for both methods, IHD-RBCx offers higher efficiency of exchange than S-RBCx, which will further reduce HbS level and may prolong the exchange intervals.
- The short-term and long-term effects of acute anemia at the end of the depletion phase with IHD-RBCx on brain and other organs are not known.

4.3.5 | What are the long-term benefits of each procedure?

Both methods of RBCx markedly reduce the rate of transfusional iron accumulation and/or prevent iron overload in most of patients. IHD-RBCx requires less donor blood than S-RBCx, thereby reducing donor exposure and overall cost, while increasing inter-procedure intervals.

4.3.6 | Should IHD-RBCx become the "standard of care" for patients requiring long-term transfusion therapy?

To implement IHD-RBCx as the standard of care for patients with SCD, the critical question as to the effects of acute anemia in each patient with SCD must be addressed. Specifically, is there any increased risk for SCI or worsening of cerebral vasculopathy, due to decrease in oxygen delivery to the brain by creating an iatrogenic acute severe isovolemic anemia (ASIA)? Dowling et al. demonstrated that children with SCD and normal brain MRA had evidence of SCI, which is temporarily associated with acute severe anemia.[97] Acute anemic events (AAE) are defined as an Hb concentration of 5.5 g/dL or less, regardless of etiology, with at least a 30% decrease from the patient's clinically established baseline.

However, since risks vs. benefits of ASIA in patients with SCD is not clearly known, it must be stressed that whether to modify S-RBCx by applying IHD must be determined after discussion between sickle cell specialists/hematologists and apheresis physicians by careful evaluation of the patient's clinical, neurologic, and cardiovascular status, radiological studies of brain, and history of adherence to iron chelation therapy.

In short, to determine whether IHD-RBCx should become the "standard of care" for patients requiring long-term transfusion therapy, a prospective randomized controlled trial comparing these two RBCx methods is warranted.

4.3.7 | What are the contraindications for IHD-RBCx?

Because of unknown effects of short duration of acute anemia, the following conditions must be taken into consideration on whether to perform the IHD-RBCx:

1. Body weight <20 kg because of low total red cell volume
2. Pre-Hct <27% in the target HbS <30% group and Hct <24% in target HbS <50% group: Red cell depletion to ≥24% for the target HbS <30% group and ≥21% for the target HbS <50% group, respectively.

3. Acute stroke within the past 6 months
4. Cardiopulmonary disease (e.g., dilated cardiomyopathy, PHT), especially with hypoxemia
5. Hemodynamic instability
6. Recent changes in or unstable neurologic condition including recurrent strokes, transient ischemic attacks (TIAs), frequent headaches of unknown etiology, weakness, or speech problems, worsening neurocognitive functions,
7. Recent changes in brain imaging studies including TCD, MRI & MRA
8. When any degree of reduction in the circulating red cell volume is deemed undesirable

4.3.8 | Summary

Compared to chronic simple transfusion, long-term RBCx markedly reduces or prevents transfusional iron overload, but requires significantly more donor blood. The IHD-RBCx procedure requires less donor blood than S-RBCx and is now easy to perform with the Spectra Optia. However, since the risk of ASIA in patients with SCD is not clearly known, a decision to switch from S-RBCx to IHD-RBCx requires careful evaluation for each patient. The primary goal of maintaining the target HbS level to prevent primary and secondary stroke or other serious SCD complications, and the secondary goal of preventing iron overload, can be achieved effectively with RBCx.

4.4 | Part B of the fifth presentation: selection of red cells for patients with SCD

Dr. Afenyi-Annan addressed targeted questions during her presentation.

4.4.1 | What evidence exists for using phenotype matched units during RBCx to prevent alloimmunization and which antigens should be matched?

Phenotyping identifies expression of various antigens on RBCs. Partial phenotype matching consists of matching donor RBCs for D, C, c, E, e, and Kell (K) antigens. Extended phenotype matching includes additional antigens for Duffy (Fya and Fyb), Kidd (Jka and Jkb), and sometimes S antigens. Patients with SCD are typically exposed to many RBC units during their lifetime and are reported to have high rates of alloimmunization, ranging from 3% to 29% in randomized control trials (RCTs) and from 6% to 85% in longitudinal and cross-sectional studies.[4,28]

In racially unmatched blood transfusions, 30% of patients with SCD became alloimmunized versus only 5% of anemic patients in the comparison group.[98] The STOP Trial in SCA reported that prospective partial phenotype (D, C, c, E, e, and Kell) matching reduced the per unit alloimmunization rate from 3% to 0.5%.[99] However, a recent study reported that 14% of patients with SCD still formed alloantibodies despite partial phenotype matching.[100] Since most of the antibodies discovered were anti-C and anti-E, this could indicate an Rh variant issue, or the patients could have received units outside of the study facility.

A retrospective study reported that partial phenotype matching would have prevented alloantibody formation in 53.3%, whereas extended phenotype matching would have prevented alloimmunization in 70.8% patients.[101] However, the latter strategy was viewed as impractical due to the difficulty in finding such units in the random donor population. Sosler et al. reported that the likelihood of finding phenotype matched units in the typical donor pool (90% Caucasian) versus an African American donor pool was 3% versus 25%.[102]

The recent Evidence-based Guidelines for the Treatment of SCD from the NIH evaluated studies (four RCTs, 63 longitudinal and cross-sectional, and 46 case reports) that reviewed the results from a combined 7,000 patients. The review was unable to find sufficient evidence to support any particular matching strategy to reduce or prevent the alloimmunization side effects of RBC transfusion. However, given the relative ease of partial phenotype matching and the mixed evidence, the NIH committee recommended partial matching for (D, C, c, E, e, and K) for all patients with SCD receiving RBC transfusions. Due to a lack of evidence, the NIH committee made no comment on extended phenotype matching.[4]

In addition, all units should be pre-storage leukoreduced, and should be negative for the presence of HbS.[103] A recent study by Chou, et al. demonstrated that phenotype matching patients with donors from the same ethnic group still led to alloimmunization in 45% of chronically transfused patients and 12% of episodically transfusions patients, partially due to the presence of Rh variants.[104] Therefore, in the future, genotype matching may provide better chance for decreasing alloimmunization rates in patients with SCD.

4.4.2 | What is the cost-benefit ratio of phenotype matching?

The 2014 NIH expert panel for the SCD guidelines determined that even though the compiled studies evaluated over 7,000 patients, the number of patients combined with the quality of the data available was insufficient to perform a meta-analysis regarding the cost-benefit ratio of phenotype matching and extended phenotype matching.[4] In 2014, Kacker et al. reported the findings of a computer simulation of 8,500 patients over a period of 10 years, using reported alloimmunization rates and testing them against protocols using history-based matching, partial phenotype matching, and extended phenotype matching. They found that partial phenotype matching and extended matching would result in 2,072 and 2,424 fewer alloimmunization events at an additional cost of $765 million and $1.86 billion, respectively.

They estimate that it costs approximately $369,000 to $769,000 to prevent a single alloimmunization.[105]

The ASFA consensus committee commented that if standard or extended phenotype matching is definitively proven to be of benefit to patients with SCD, then cost should not be a consideration in the selection of RBCs. However, to accomplish this, direct, indirect, patient, and societal costs must be included in the cost analysis.

4.4.3 | For RBCx in acute chest syndrome, should "fresh" blood (<7 days old) be used to provide better O2 carrying capacity?

It is thought that RBC storage lesions may impair the O_2 delivering capacity of transfused RBCs and that these lesions progress as the storage time of the blood increases.[106–110] Given the limited supply of fresh blood, the amount of blood necessary for a typical RBCx procedure, and mixed results from studies of old versus fresh blood,[111–113] use of fresh blood is not a practical requirement for RBCx procedures in all institutions. However, if fresh blood is available, it could provide the benefit of increased O_2 carrying capacity for patients with SCD especially ACS in addition to longer RBC survival.

4.4.4 | Should RBCs be screened for glucose-6-phosphate dehydrogenase (G6PD) deficiency and other hemoglobinopathies to ensure normal function?

Currently there is not much evidence to support screening donors for G6PD deficiency and other hemoglobinopathies and this may be a potential future direction.

4.5 | The sixth presentation: technical and nursing aspects of red blood cell exchange

Ms. Hulitt addressed targeted questions during her presentation.

4.5.1 | What are the access options for acute and chronic red cell exchange?

4.5.1.1 | Peripheral access

When possible, peripheral access is ideal for red cell exchange (RBCx) because peripheral IVs are placed only for the duration procedure. Patients whose procedures can be done peripherally have none of the activity restrictions, home care needs, infection risks, or body image concerns that come with permanent access options. Peripheral access can be obtained using 16–18 Gauge steel needles with an elongated bevel and a back-eye that are traditionally used for dialysis. Many centers also use the more flexible angiocaths for both draw and return access to offer more mobility during the procedure.

Although it is possible to perform long-term, chronic RBCx therapy using peripheral veins in some patients, factors such as dehydration, weight gain, venous sclerosis, and needle phobia are obstacles that prohibit peripheral access in many patients with SCD. When RBCx is required for an acute indication, possible access sites are further limited by the patient's clinical condition.

4.5.1.2 | Flexible catheters

Temporary catheters are non-tunneled, polyurethane or silicone catheters placed for acute indications. Permanent catheters can be placed for chronic therapy, and are similar to temporary catheters, except that they have a cuff, which facilitates adhesion through scar formation. Flexible catheters vary in size from 7fr to 13 fr dual lumen catheters.[114]

Flexible catheters are easy to access and usually provide good flow rates through the apheresis instrument. However, external catheters pose a risk of infection and thrombosis. They are packed with a high concentration of heparin, and if accidentally flushed through the catheter into the patient it could result in excessive anticoagulation. Additional disadvantages are that they require regular flushing and dressing changes at home, impair body image, and inhibit the patient's ability to shower, swim, and participate in other activities with their peers.

Insertion sites for catheters are femoral, Internal Jugular (IJ), or Subclavian veins.[115] The femoral vein has a high risk of infection and should only be used for very short term access. The IJ vein is generally considered to pose less risk of infection and thrombus formation than the subclavian vein for central lines.[116] Additional risks of the subclavian approach include "pinch off syndrome," in which the catheter becomes impinged between the clavicle and the first rib, and pneumothorax on insertion. The SVC/RA junction is the optimal location for the catheter tip for both external catheters and implantable ports. Tip location should be confirmed radiologically prior to use.[117–120]

4.5.2 | What are the options for various implantable ports (Vortex and Sport) with a focus on advantages/disadvantages, accessing issues, durability, effects on patient's lifestyle, etc.?

Implantable ports are metal disks that are placed under the skin in a pocket in the upper chest wall and accessed with a needle via a silicon port.[121] The Vortex Port (Angiodynamics, Latham, NY) is the most commonly used port and this silicon port is generally durable for up to two thousand sticks using a standard needle. Access for apheresis, however, requires a 16 gauge non-coring needle, which likely diminishes the port' life span. Vortex ports come in 7.5 and 9.6 fr single lumen, and 11.4 fr double lumen sizes. Access for RBCx can be achieved using a single lumen Vortex port for the draw line, and a peripheral IV or a standard port for return, or using 2 single lumen or 1 dual lumen Vortex ports in patients weighing >40 kg. Implantable ports are used for chronic, long-term, intermittent therapy.[26] Advantages of ports over external catheters include the

TABLE 3 Results of electronic polling of speakers and moderators

	Question	Result
1.	Considering the pathophysiology of vaso-occlusive complications, is there high quality evidence to support the reduction of HbS to <30% as acute and/or chronic management of certain complications of SCD?	Yes 6/7 = Strong agreement
2.	What is the quality of evidence in support of transfusion therapy (simple or apheresis-based) for the treatment of patients who present with acute chest syndrome?	High/Moderate 3/5
	A. High/Moderate	Low/Very Low 2/5
	B. Low/Very Low	(2 abstained) = No consensus agreement
3.	If the evidence for transfusion therapy is high or moderate, is the potential benefit of raising the patient's hemoglobin compromised by the decline in 2,3-DPG that occurs during blood bank storage of red cells?	No 7/7 = Unanimous agreement
4.	Does the benefit of transfusion therapy in ACS derive primarily from countering pathophysiology through the reduction in the content of HbS in the patient's blood?	Yes 2/4
		No 2/4 (3 abstained) = No consensus agreement
5.	Does high or moderate quality evidence support the use of red cell exchange as the first line of therapy for patients presenting with ACS?	No 4/5 (2 abstained) =Simple majority agreement
6.	For patients with SCD who present with acute stroke, should red cell exchange, if available, be used as first line therapy, rather than simple transfusion, to achieve rapid reduction of HbS to <30%?	Yes 5/5 (2 abstained) =Simple majority agreement
7.	Chronic red cell exchange can mitigate iron overload that occurs with chronic simple transfusion therapy for complications of SCD such as for primary or secondary stroke prevention and others. Does this justify consideration of red cell exchange as the standard of care for patients requiring chronic transfusion therapy?	Yes 7/7 = Unanimous agreement
8.	Red cell exchange with IHD can increase the interval between procedures, reduce blood utilization and mitigate iron overload in chronically treated patients. Should IHD red cell exchange be considered the preferred therapy for primary or secondary stroke prevention?	No 5/7 = Simple majority agreement
9.	In the treatment of acute chest syndrome, does moderate or high quality evidence support the use of fresh red cells (<7 days of storage)?	No 7/7 = Unanimous agreement
10.	Should red cells for transfusion in SCD be phenotypically matched for Rh and K antigens?	Yes 7/7 = Unanimous agreement
11.	Should red cell units used for patients with SCD be screened for G6PD or for hemoglobinopathies other than sickle cell?	No 7/7 = Unanimous agreement
12.	Is there a role for red cell transfusion or red cell exchange in priapism?	No 6/7 = Majority agreement

following: patients require no care at home, can bathe, swim, participate in most other activities with their peers, and experience less alteration in body image.[122] Ports also present less risk of infection than an external catheter.

Ports can become infected if strict aseptic technique is not observed during their access and use. They are also at risk for thrombosis.[123,124] Disadvantages of ports include slow flow rates, and they require skill and technique to obtain access and maintain adequate flow throughout the procedure. A new spherical shaped port by Norfolk Medical has demonstrated improved flow rates according to limited in vitro study reported by University of Texas Southwestern Medical

Center.[125] Port access should be deferred for 2 weeks after placement in order to promote healing of the pocket.[122]

4.5.3 | What are the optimal anticoagulants and techniques for flushing and locking access lines?

Both catheters and ports require a normal saline flush after blood draws, transfusion, or infusion of medications. Delivering the flush in a pulsatile fashion facilitates patency by producing a turbulent flow that helps to remove precipitants and fibrin. When flushing catheters and ports, the use of a syringe size smaller than 10 mL may exceed the pressure parameters of the device, and could result in rupture or damage.[118] Practice related to heparin lock administration varies widely from 300–5000 units. If a high-concentration of heparin is used, the volume should be equal to the fill volume of the port or catheter. The fill volume is listed on the outside of most catheters, but must be calculated based on the length of the catheter inserted for ports. An alternative to heparin for locking catheters and ports is 4% sodium citrate. It is less costly and eliminates the risk of heparin induced thrombocytopenia (HIT) and could reduce the risk of bleeding. Regardless of the agent used, it is important to pressure lock the catheter by clamping the device, while simultaneously delivering the last portion of the locking solution. Doing so decreases the risk of thrombus formation because it creates positive pressure in the catheter and prevents back up of blood into the tip. Instilling tissue plasminogen activator (tPA) anywhere from 30 minutes to 3 days prior to RBCx procedures reduces clot formation and facilitates adequate blood flow.

4.5.4 | What are the considerations for sedation versus no sedation in children

Child life, play therapy, and preparative education are used to facilitate cooperation in children. In cases of extreme needle phobia, a small dose of lorazepam may be administered to decrease anxiety.[126]

4.5.5 | Summary

The RBCx in SCD Consensus Conference concluded with a round table discussion amongst the speakers regarding key questions in the field of SCD treatment. The deliberations were very open and fruitful with active participation of the audience. These questions were later sent out for electronic polling to gather consensus among the speakers and moderators. The results of these electronic polling is given in the Table 3. The speakers and moderators who participated in electronic polling also had an option to provide comments on these questions and anything related to these topics. These comments are compiled in no particular order in Appendix A. Overall the conference was deemed very successful because for the first time SCD experts in the field of Hematology interacted very closely with Apheresis Medicine and Transfusion Medicine physicians who are actively involved in providing red cell transfusion and exchange therapies. The key recommendations were to continue to collaborate at local, regional and national level to develop registries, and report large case series of experience since randomized clinical trials are difficult to conduct due to lack of funding from government or public agencies.

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APPENDIX A

Note: The responses below are the opinions of the respondents and may or may not be supported by the literature. See Table 3 for a summary of their "yes/no" answers to these questions.

Question 1: (Evidence for reducing HbS to <30%)

1. This is largely limited to stroke and pre-operative management and offhand, only the latter is supported by a randomized trial.
2. I would say ±30% HbS, not necessarily < 30% S, there are no studies that I am aware of that had as a criterion of hemoglobin S of < 30%. The STOP study for stroke prevention showed keeping S at ±30% decreased stroke risk, STOP II showed that those patients who were protected by decreased hemoglobin S did have stroke and abnormal TCD when transfusions were discontinued. Does not hold for completed stroke.
3. Primary and secondary prevention of strokes in patients with overt stroke and SCIs.
4. STOP I and II strongly support transfusion therapy for primary and secondary stroke prevention.
5. Evidence exists in the following scenarios: Primary and secondary prevention of strokes in patients with overt stroke and SCIs; and the preoperative setting.
6. Management of chronic complications: Yes (prevention of primary and secondary stroke, reduction of other vaso-occlusive and chest syndrome event). Management of acute complications: Yes but limited to acute stroke and to peri-operative complications; little evidence supporting other use in other acute complications.

Question 2: (Evidence for transfusion therapy in ACS)

1. No randomized trials so the evidence is low. But it is the customary clinical practice to use transfusion in sick hypoxic people with ACS.
2. There are no randomized studies. There is evidence that simple transfusion increases oxygenation, in patients with high hemoglobin and ACS with multi-organ failure do better with apheresis compared to simple or no transfusion.
3. When the patient with ACS develops increasing respiratory distress, progressive pulmonary infiltrates, and increasing oxygen requirements, I strongly recommend urgent RBCx, even if the evidence is weak.
4. The answer is yes, but only when the severity of the ACS results in respiratory compromise.
5. Both simple and apheresis based therapy highly effective and potentially life-saving following hemoglobin decline and/or evolving respiratory failure.

Question 3: (Effect of decreased 2.3 DPG on transfusion effect)

1. Increasing hemoglobin in patients with decreasing saturation, improves outcomes.

Question 4: (Effect of decreasing HbS on pathophysiology of ACS)

1. It seems to work.
2. Most likely explanation, also improves anemia and oxygen delivery in anemic patients. Caveat: fluid overload can exacerbate ACS increase risk of stroke.
3. No way to know for sure, but evidence is that simple transfusion is adequate in most cases, and a subgroup

will progress with respiratory failure and subsequently improve with apheresis.

4. This remains unresolved. However, extensive anecdotal evidence speaks to the efficacy of transfusion therapy.
5. Not sure reduction of HbS is "primary" benefit in all cases; simple correction of anemia, when Hb has declined appreciably below steady state (which it often does in ACS) is probably just as important.

Question 5: (RBCx as first line for ACS)

1. No trials in ACS. The dogma should be, if sick transfuse, if really sick exchange transfusion, don't delay transfusion if exchange not available.
2. Only in patients with high hemoglobin at onset (SC, SS with alpha thalassemia) who are at risk for multiorgan failure. Patients with low hemoglobin should have simple transfusion initially. Followed by exchange when stabilized or if simple transfusion not effective.
3. Depends on severity of ACS.
4. Yes, but only when the ACS has resulted in respiratory compromise.
5. In many cases of mild/moderate ACS, simple transfusion to reduce anemia suffices, plus it is less costly and potentially limits donor exposure.

Question 6: (RBCx as first line for acute stroke)

1. Again, don't delay and wait for exchange availability.
2. Supported by clinical evidence.
3. Depends on timing of apheresis, if can't be done quickly then simple is preferred over no transfusion, ultimately followed by apheresis in a timely fashion.
4. A retrospective cohort study of 137 children with SCD and first strokes showed that children receiving simple transfusion at the time of stroke presentation had a 5-fold greater relative risk of having a second stroke than those receiving RBCx.[18]
5. Yes, but therapy should not be delayed with an acute stroke. If apheresis is not rapidly available, simple transfusion should be initiated in the interim.

Question 7: (RBCx to mitigate iron overload)

1. Iron reduction has been shown in retrospective studies and clinical practice.
2. Only when the patient is non-compliant with iron chelation therapy.
3. But chronic simple transfusions are better than "nothing" in patients whose venous access, for one reason or another, renders RBC exchange difficult or impossible.

Question 8: (IHD-RBCx preferred over S-RBCx)

1. There has never been a study to show that this is safe in patients with SCD and cerebral vascular disease, or other patients for that matter. This procedure is driven by economics. In my opinion, this IHD is an experimental procedure that has not been validated as safe in SCD. Particularly in children and adults who have cerebral vascular disease and are at risk for brain ischemia during periods of anemia.
2. Most hematologists are not aware that IHD is associated with an acute drop in hemoglobin levels during the procedure and most blood bank physicians are not aware that the acute drop in hemoglobin can be associated with CNS complications. Until a randomized clinical trial is done and it should be done, we do not know the optimal way to perform a transfusion in patients with SCD.
3. Extensive experience at many large university medical centers over many years has shown that when performed properly results in a decreased blood exposure, more rapid procedures with no compromise for safety. Many hematologists remain unaware of the advantages and safety experience that exists related to to the use of IHD.
4. However, additional published experience with IHD is required to make the most convincing possible argument in favor of this approach.

Question 9: (Fresh (<7 days old) RBCs better for ACS treatment)

There were no additional comments for this question

Question 10: (Phenotype matching)

1. As extensive phenotyping as feasible should be done. What about Rh genotyping?
2. Acute Chest Syndrome study and others have shown that there is a decrease in alloimmunization using phenotypically matched cells for D, Cc, Ee, and Kell. There are retrospective studies that show the alloimmunization rate can be further decreased with an increase in the level of phenotyping. Though this is only practical in some centers.
3. In a survey of 38 academic medical centers in the US and Canada, they found that 73% routinely provided antigen matching for SCD patients. The most common approach was to phenotypically match for C, E, and K (24 of the 27 matching institutions) however, they concluded that there was no single standard of care in academic medical centers in the US and Canada.

Thus, at least for large medical centers (which generally have extensive experience with sickle cell patients) in the United States and Canada, the use of phenotypically matched

red cells has been, for some time, largely the standard of care.[127]

1. Better yet would be genotypic matching not only for Rh and K but other antigens as well.

Question 11: (Screening for G6PD or other hemoglobinopathies)

1. Occasional it is reported (and I have seen) post transfusion SS patients with hemoglobin C on hemoglobin electrophoresis which does not seem to present a problem. Screening would be huge burden on a blood bank.
2. Most transfusion centers feel the advantage of minimizing allo-immunization in this multiply transfused population far exceed the cost of such a program. However, there may be some unintended consequences of such a program. For example, it has been recently reported that when one selects for C and E antigen negative units (which are frequently utilized phenotypically matched transfusion programs for patients with SCD) there is an observed enhanced risk of transfusion of G6PD deficient RBCs (from 0.3% in the general inventory to 12.3% in the selected units). Fortunately, transfusion of G6PD deficient erythrocytes is frequently accompanied by only a mild transient (<48–72 hours) hemolysis characterized by mild jaundice with a 2–3 fold increase in bilirubin and LDH. In select patients screening for G6PD may be appropriate. Similarly, the choice of phenotypic matched red cells can be associated with the use of donor units with other hemoglobinopathies (typically of little clinical significance). Thus, one needs to be aware that additionally unexpected hemoglobins may transiently appear during therapy.[128–131]
3. Unnecessary and would cause delays in emergent situations.

Question 12: (Evidence for RBCx or transfusion in priapism)

1. Not for acute episodes.
2. There are no studies that show red cell exchange improves acute episodes or decreases recurrence of priapism.
3. Yes, prophylaxis is quite effective, but acute RCT or exchange is not necessarily effective and should be considered a second line therapy after aspiration of the dorsal vein of penis.
4. No evidence available other than some reports from case series that reported adverse neurologic effects.
5. There is a role for red cell exchange when prophylaxis is clinically indicated. In an acute episode, it is a secondary therapy to be used only after urologic attempts for detumescence have failed.
6. Current data don't support transfusions, but this is a rich area for conduct of high quality studies (both in acute and recurrent priapism).