ALTHOUGH IT IS likely that sickle cells have been responsible for morbidity and mortality in humans for thousands of years, it was not until 1910 that the first description of sickle cell anemia appeared. Subsequently, sickle cell anemia has become the prototype of modern molecular disease, its history tracing the evolution of science and medicine in the 20th century. Sickle cell disease (SCD), including homozygous hemoglobin (Hb) S and doubly heterozygous HbS/C and HbS/β-thalassemia, is among the most common of inherited hemoglobinopathies. The incidence of SCD is greatest in equatorial Africa, where the frequency of heterozygous carriage is as high as 35%. The incidence of sickle trait in African-Americans is approximately 8% with 1 in 200 to 500 newborns affected with SCD.

Although full discussion of the pathophysiology of SCD is beyond the scope of this report (the reader is directed to recent reviews), certain features of HbS merit emphasis. Via direct and indirect mechanisms such as polymerization, instability, and membrane binding, HbS induces a cascade of alterations in red blood cell (RBC) structure and function. Consequently, RBCs from patients with SCD are both rigid and adherent, resulting in marked abnormalities in microcirculation. It should be emphasized that although such properties both promote and are exacerbated by cellular sickling, the adverse effects of HbS come into play even in the absence of this characteristic shape change. Hyperviscosity, cellular adherence, sickling, and possibly hypercoagulability may all contribute to the vascular effects associated with SCD. Vaso-occlusion, intimal hyperplasia, impaired vasomotor activity, marrow fat embolism, thrombosis, and thromboembolism have in turn all been postulated to contribute to the tissue ischemia responsible for the clinical symptoms of SCD. Finally, infarction-induced hypoplasplenia leads to a high incidence of severe infection in young children, particularly sepsis with encapsulated organisms.

The major manifestations of SCD include hemolytic anemia and complications of vascular occlusion. Although there is significant variability in clinical severity, recent data suggest that most African-Americans with SCD have crises and require hospitalization at some point. Furthermore, chronic vasculopathy leads to irreversible organ damage in at least a third of patients, and as such, is the most frequent cause of death beyond early childhood. Survival in SCD has improved dramatically around the globe due in large part to changing living conditions, early diagnosis, and improvements in supportive care, especially the judicious use of antibiotics. Nonetheless, SCD remains a debilitating and life-threatening disorder.

RATIONALE FOR TRANSFUSION

In light of the often severe anemia associated with SCD, it is not surprising that RBC transfusion was used early in the history of the disorder. By 1930, transfusion was considered by some to be an integral part of treatment. In the simple case of severe anemia, increasing the hematocrit (Hct) improves oxygen (O2) carrying capacity and, thus, is useful in a variety of clinical situations (see below). As understanding of the pathophysiologic role of HbS in SCD has evolved, additional potential benefits of transfusion have become apparent. Transfusion of normal blood into patients with SCD lowers the fraction of cells that contain HbS by dilution. By increasing the Hct, such a maneuver may also reduce the erythropoietic drive and decrease the production of sickle Hb. Finally, HbS can be "replaced" with HbA by exchange transfusion. Thus, the end result of transfusion by any method is some combination of an increased Hct and a decreased proportion of RBCs that contain HbS. The goal of such therapy is to improve O2 carrying capacity and/or prevent sickle-related vascular effects.

PREVALENCE OF TRANSFUSION

The likelihood that a person with SCD will receive a transfusion depends in large part on age and genotype. Although estimates are confounded by the fact that hospital-based studies may not adequately account for those who do not seek or require medical attention, it seems clear that the majority of persons affected with SCD receive at least one transfusion during their lifetime. The recent Cooperative Study of SCD survey suggests that approximately 60% have received blood, rates varying from 0% to 95% with age, sex, and genotype.

Those with HbSS or HbS/β-thalassemia are...
transfused more often than those with HbS/C or HbS/β+-thalassemia (Fig 1).

PARAMETERS FOR TRANSFUSION

As noted above, transfusions are used in SCD to reverse or prevent the effects of anemia, vaso-occlusion, or both. Although the parameters vary with the specific indication, in many cases the goal is to maximize O₂ delivery to tissues by adjusting the Hct and percent HbS. O₂ delivery is a complex function of Hct, blood volume, viscosity, vascular perfusion, and other factors such as Hb O₂ affinity. Functionally, the primary determinants of whole blood viscosity are Hct and RBC deformability. Consequently, improvements in O₂ delivery associated with increases in Hct are eventually counterbalanced by the opposing action of Hct on viscosity (Fig 2). Due to the marked RBC abnormalities encountered in SCD, this balance is particularly delicate.

Ham and Castle were the first to demonstrate that deoxygenated cells from patients with sickle cell anemia display increased viscosity. The adverse effects of HbS on blood viscosity are magnified by, but not restricted to, the deoxy state and are caused in large part by dramatic alterations in cellular flexibility. Such abnormal viscoelastic properties likely play a major role in the vaso-occlusive complications of SCD. In examining the in vitro relationships between Hct and viscosity with mixtures of sickle and normal RBCs, Schmalzer et al made a number of important observations. First, the major determinant of viscosity seemed to be the quantity of RBCs that contained HbS, ie, the sickle Hct (roughly equal to percent HbS × total Hct). Adverse effects of Hct on viscosity were seen at a sickle Hct level in the low 20s. Oxygen delivery, as gauged by the maximal point on the Hct versus viscosity curve, was markedly improved by "exchanging" normal for sickle RBCs. Notably, this effect was observed even when the total Hct was held constant. Furthermore, Hct elevation by simple transfusion resulted in decreased delivery even at Hcts significantly lower than those frequently used in clinical practice (Fig 3). These data are in keeping with the in vivo observation of improved O₂ delivery and exercise capacity associated with isovolemic exchange transfusion at a fixed Hct. Additional clinical corroborative data might also be found in reports of exacerbation of sickle-related complications following simple transfusion, as well as in our experience with exchange transfusion after "failed" simple transfusion for acute chest syndrome (see below).

Given in vivo variability, it is difficult to define "optimal" target values for the Hct and percent HbS that are applicable to all clinical situations. Consequently, a variety of transfusion strategies have evolved. In light of inter-species observations in normal animals, some follow a teleologic approach and assume that for an individual, the customary Hct is the value at which O₂ delivery is maximized. In the setting of acute illness, anemia below baseline is often corrected by simple transfusion. Others guide transfusion according to particular levels of Hct and percent HbS considered "safe." Unfortunately, in vivo data are frequently lacking and studies are desperately needed. The following discussion of the methods and approach to transfusion attempts to integrate available clinical data with the concerns for Hct, percent HbS, viscosity, and the clinical scenario (Tables 1 through 3).
ACUTE SIMPLE TRANSFUSION

In general, acute simple transfusion is indicated when increased \( \text{O}_2 \) carrying capacity is desired, but no significant decrease in HbS is required (Table 1). Such transfusion should be considered in patients with symptomatic anemia (eg, dyspnea, postural hypotension, impending high output congestive heart failure).\(^{36} \) The most frequent examples are crises manifested by an exacerbation of anemia. An absolute indication for simple transfusion is severe anemia associated with hypovolemia where restoration of both Hct and blood volume is necessary. This is best exemplified by acute splenic (or hepatic) sequestration, for which immediate simple transfusion can be life-saving.\(^{37} \) In most other situations, one must take into account the volume and viscosity changes associated with simple transfusion. Patients with aplastic crisis or accelerated hemolysis (eg, coexistent G6PD crisis)\(^{38} \) may not tolerate the volume required to reverse the often severe degree of anemia. If clinical status allows gradual correction, we recommend slow transfusion with small aliquots (eg, 5 mL/kg over 6 hours) of packed RBCs (PRBCs) with or without diuretics as necessary. Multiple such transfusions may be required, consequently, for children; units should be steriley divided into small transfer packs to reduce donor exposure.\(^{39} \) If rapid correction is demanded, partial or automated exchange transfusion can be performed, usually in less than an hour (see below). Calculations for determining transfusion volumes are found in Table 4.

The most controversial use of simple transfusion is in the setting of mild to moderate anemia and acute illness. Because patients with sickle cell anemia often have Hcts in the low

<table>
<thead>
<tr>
<th>Table 1. Indications for Acute Simple Transfusion</th>
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<tr>
<td>Symptomatic anemia</td>
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<tr>
<td>Sequestration crisis</td>
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<tr>
<td>Aplastic crisis</td>
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<tr>
<td>Accelerated hemolysis</td>
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<tr>
<td>Blood loss</td>
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<tr>
<td>Preoperative preparation*</td>
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* Under investigation.
20s, transfusions are commonly given during hospitalization for a variety of complications. However, in light of the potential for hyperviscosity, such practice may be counterproductive because it may further compromise tissue perfusion. This and the possibility of other side effects (see below) should serve to temper the indiscriminate use of blood transfusion. Although no absolute recommendations can be made for the employment of simple transfusion in such scenarios, patients should be closely scrutinized for clinical and laboratory evidence of deterioration. In such an event, consideration should be given to exchange transfusion. It should be emphasized that there is no role for transfusion in the management of routine, uncomplicated painful crises. Finally, the use of preoperative transfusion is currently under investigation (see below).

CHRONIC SIMPLE TRANSFUSION

Currently, suppression of HbS and maintenance of levels of HbA by chronic transfusion is probably the most physiologic method of treating SCD short of marrow transplantation. Nonetheless, the complications of lifelong transfusions limit such therapy to a few clinical situations, most notably cerebrovascular disease (Table 2).

Cerebrovascular disease. The estimated lifetime incidence of stroke in SCD ranges from 5% to 17%, 19,40-42 Children usually manifest ischemic infarction caused by endothelial proliferation and occlusion of large, often multiple, cerebral blood vessels. Without transfusion, the recurrence risk is extremely high, reported rates ranging from 66% to 90%. 30,43 Surgically correctable lesions are rare and encountered most often in adults with central nervous system (CNS) hemorrhage. 44-46 Chronic transfusion therapy to maintain the percent HbS below 30 dramatically decreases the risk of recurrent stroke, probably to less than 10%. 43 However, recurrence rates of 70% have been reported when transfusions are discontinued after 1 to 2 years of transfusion. 47 There are growing data to support the need for prolonged, possibly lifelong transfusion therapy in some of these patients. 32

The maximum allowable level of HbS that is still effective in preventing recurrent stroke is not known. The standard approach is to maintain HbS below 30%, 48 although recent reports suggest that less intensive therapy may have a role in particular patients after the initial years of transfusion. 49,50 However, even with chronic maintenance below 30%, there is some risk of recurrence. It is possible that such individuals might benefit from further reduction of HbS.

Table 2. Indications for Chronic Simple Transfusion

<table>
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<th>Indication</th>
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<tr>
<td>Cerebrovascular disease</td>
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<tr>
<td>Debilitating vaso-occlusive symptoms*</td>
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<tr>
<td>Pulmonary disease*</td>
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<tr>
<td>Cardiac disease*</td>
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<tr>
<td>Complicated pregnancy*</td>
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<tr>
<td>Preoperative preparation†</td>
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* Selected patients, see text. † Under investigation.

Table 3. Indications for Exchange Transfusion

<table>
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<th>Indication</th>
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<tbody>
<tr>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>Arterial hypoxemia syndrome</td>
</tr>
<tr>
<td>Acute chest syndrome*</td>
</tr>
<tr>
<td>Priapism*</td>
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<tr>
<td>Chronic transfusion regimen*</td>
</tr>
<tr>
<td>Eye surgery</td>
</tr>
<tr>
<td>Preoperative preparation†</td>
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<tr>
<td>Retinal arterial vaso-occlusion†</td>
</tr>
<tr>
<td>Hepatic failure</td>
</tr>
<tr>
<td>Septic shock†</td>
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<tr>
<td>Cerebral angiography†</td>
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* Selected patients, see text. † Under investigation. ‡ Possible benefit, see text.

Other indications for chronic transfusion are not absolute. Selected patients with severe, recurrent, debilitating symptoms such as painful crises, leg ulcers, and priapism may benefit from chronic transfusion. 51,54 Chronic transfusion has been used in young children with sequestration crisis in an attempt to delay or avoid splenectomy. 55 Although such therapy may result in improved splenic function, 56-59 outcome from sequestration is probably minimally affected. 59 Although longer-term studies of chronic transfusion in the setting of recurrent acute chest syndrome and/or chronic pulmonary disease are not available, due to the risk of evolution to end-stage lung disease we recommend such therapy for severely affected individuals. 60-62 We also recommend transfusion for the rare patient with symptomatic congestive heart failure or coronary artery disease. 63,64 Finally, although some recommend prophylactic transfusion during pregnancy, 65 results of the recent

Table 4. Formulas for Transfusions

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<th>Formula</th>
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<tr>
<td>1. Simple transfusion</td>
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<tr>
<td>PRBC volume (PRBCV) (mL) = ( \frac{(Hct_{fa} - Hct_{fe}) \times TBV}{Hct_{fa}} )</td>
</tr>
<tr>
<td>2. Dilutional effects of transfusion on HbS</td>
</tr>
<tr>
<td>HbSf(%) = \left[ 1 - \frac{PRBCV \times Hct_{fa}}{TBV \times Hct_{fa} + PRBCV \times Hct_{fe}} \right] \times HbS</td>
</tr>
<tr>
<td>3. Manual partial exchange transfusion for anemia*</td>
</tr>
<tr>
<td>Exchange volume (mL) = ( \frac{(Hct_{fa} - Hct_{fe}) \times TBV}{Hct_{fa} - \frac{(Hct + Hct_{fa})}{2}} )</td>
</tr>
<tr>
<td>4. Automated exchange transfusion</td>
</tr>
<tr>
<td>RBC volume (mL) = Hct_{fa} \times TBV</td>
</tr>
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</table>

Abbreviations: TBV, estimated total blood volume in mL (children 80 mL/kg, adults 65 mL/kg, nomograms are also available); Hct_{fa}, desired hematocrit; Hct, initial hematocrit; Hct_{fe}, hematocrit of replacement cells (usually 0.7-0.8); HbS, initial hemoglobin S; HbSf, final hemoglobin S; Hct and HbS should be in the form of fractions (eg, 40% = 0.40).

* From Nieburg and Stockman. † Linderkamp et al. ‡ Under investigation.
National Institutes of Health (NIH) sponsored national cooperative trial suggest that such therapy is not routinely indicated.64,65 Certainly, transfusion therapy has a role in selected high-risk situations.66,67 We consider transfusions for pregnant women with severe sickle-related complications, multiple gestation, or a history of recurrent fetal loss. Particularly close monitoring is essential during the course of therapy, especially considering the potential adverse effects of hyperviscosity on placental perfusion.

Transfusion requirements vary from patient to patient and we recommend following the percent HbS with each transfusion as a guide. In practice, about 10 mL/kg of PRBCs every 3 to 4 weeks is usually sufficient to maintain the percent HbS near 30 and the pretransfusion Hct between 25% and 30%. The posttransfusion Hct should be carefully considered and monitored, particularly early in therapy when the HbS level is still high. In our experience, the posttransfusion Hct can usually be safely increased to the mid 30s once the HbS level decreases below 50%. Alternatively, partial or total RBC exchange can be used to initiate chronic transfusion. Patients should be observed closely for exacerbation of sickle symptomatology during initiation and cessation of chronic transfusions and the regimen adjusted if necessary.70 To decrease the risk of iron overload, alternative approaches to chronic simple transfusion have been attempted in recent years (see below).

EXCHANGE TRANSFUSION

RBC exchange (RCE) offers numerous potential advantages over simple transfusion for the management of certain complications of SCD. Most important, the Hct and HbS can be adjusted rapidly and simultaneously allowing emergent intervention and eliminating the risks associated with alterations in viscosity and blood volume. In theory, acute sickling episodes might be interrupted before tissue damage becomes irreversible. Decreasing the percent HbS can result in dramatic improvements in the rheologic state,38,70 oxygen delivery,30 and clinical condition.71,72 The major role for exchange transfusion is in the management and/or prevention of life- or organ-threatening events. Because randomized trials in such settings have rarely been possible or appropriate, the indications for RCE have evolved largely based on anecdotal reports.

Acute chest syndrome (ACS). The clinical scenario characterized by some combination of respiratory symptoms, pain in the thorax or abdomen, fever, an abnormal chest exam, and eventual development of an infiltrate on chest x-ray is known as ACS.61,77,78 This common and often recurrent symptom complex affects 20% to 50% of persons with SCD and accounts for 14% to 33% of acute hospitalizations.19,62,79 Although there is great variability in outcome, acute mortality rates as high as 2% to 14% have been reported.77,80,81 Furthermore, ACS is the major risk factor for chronic lung disease and contributes to the leading cause of death in adolescents and adults with SCD.19,62,82

The most severe cases of ACS are marked by arterial hypoxemia, multi-lobe lung involvement, and anemia.80 Although there are numerous etiologies of ACS, the underlying pathophysiology in this subset may well involve pulmonary vaso-occlusion.62,83-85 Presumably, diffuse arteriolar occlusion ensues when sickle erythrocytes are unable to traverse the pulmonary microcirculation. Progressive respiratory failure may culminate in multiple-organ vaso-occlusion and death. Consequently, many advocate exchange transfusion for severe, progressive ACS associated with arterial hypoxemia.86 Our experience supports this recommendation.

The clinical features of patients we have treated with RCE for ACS are summarized in Table 5. All had been managed with intravenous (IV) hydration, supplemental O2 to maintain a saturation above 97%, antibiotics, and antipyretics and analgesics as necessary, for an average of 2 days before RCE (range, 0 to 13 days). In addition, 14 had received acute simple transfusions. Despite this therapy, all patients manifested progressive respiratory deterioration.

Outcome. Thirty-two of 35 patients responded dramatically to RCE, stabilizing immediately, improving rapidly, weaning steadily off supplemental O2 in 3.1 ± 1.9 days (x ± 1 SD), and leaving the hospital in 5.4 ± 2.3 days. Of the seven who required ventilatory support before RCE, five recovered quickly and were extubated within 3 days. One treated late in the course of illness died of respiratory failure. Another deteriorated despite early intervention and required intubation 1 day after RCE. His course was complicated by gastric aspiration, progressive adult respiratory distress syndrome (ARDS), and eventual death despite extracorporeal membrane oxygenation.87 Finally, one patient manifested a prolonged, but moderate respiratory illness characterized by large, recurrent pleural effusions.

It should be emphasized that RCE was performed at a point of progressive and often rapid respiratory decline. Furthermore, many patients had received prior simple transfusion to no avail or associated with clinical deterioration. Consequently, the dramatic response, including the rapid decrease in the O2 requirement, suggests that exchange trans-
fusion may have resulted in rheologic and clinical improvement in this subset of patients. Others have reported similar experience.\textsuperscript{71,72,74,75,80,88} On the other hand, some investigators have suggested that simple transfusion alone may have a role in the treatment of ACS.\textsuperscript{89} The wide variability in clinical definition, severity, and outcome of ACS makes generalization difficult. Nonetheless, we suggest that exchange be considered for those with evidence for diffuse pulmonary involvement. If simple transfusion is used, close monitoring is critical in light of the potential adverse effects of hyperviscosity on pulmonary vascular perfusion.

\textbf{Cerebrovascular disease.} Acute or impending cerebrovascular episodes, whether caused by infarction, hemorrhage, hypoxemia, or transient ischemia, are absolute indications for exchange transfusion.\textsuperscript{48} Furthermore, most patients will go on to require chronic transfusion. Exchange is the safest way to initiate such therapy because it avoids hyperviscosity and volume perturbation that might exacerbate the situation.\textsuperscript{91} In addition, many recommend RCE before angiography to avoid intravascular sickling induced by IV hyperosmolar contrast agents.\textsuperscript{48,90,91} Although the newer non-ionic contrast agents are associated with fewer overall side effects, they seem to carry a higher risk of thrombosis.\textsuperscript{92} Until their use is proven safe in SCD, we continue to perform pre-angiographic RCE even when these newer agents are employed.

\textbf{Priapism.} Refractory priapism is associated with significant morbidity, most notably impotence.\textsuperscript{94} In light of the fact that corporeal hypoxemia and acidosis predispose to ongoing sickling and vaso-occlusion, there is a theoretical role for exchange transfusion. Anecdotal success with RCE has been reported.\textsuperscript{72,74,95,96} We routinely offer this modality to patients who demonstrate minimal response to 12 to 24 hours of conservative management with IV hydration, narcotics, and supplemental oxygen. In our experience, the response to therapy varies at least in part with the duration of symptoms at the time of exchange. Although improvement has rarely been noted sooner than 24 to 48 hours post-RCE, all patients treated within the first few days of onset have gradually improved over 2 to 7 days (some in association with urologic intervention as well).

\textbf{Preoperative preparation.} There is controversy over the optimal preoperative hematologic management of SCD. Historically, general anesthesia and surgery have been associated with significant perioperative morbidity and mortality in patients with SCD. With modern techniques and monitoring, outcome is seemingly improved.\textsuperscript{97} Nonetheless, there is still potential for severe sickle related complications and many recommend preoperative lowering of HbS.\textsuperscript{97-100} A prospective study is currently underway to evaluate the role and various methods of preoperative transfusion in SCD.\textsuperscript{81} In this cooperative trial, patients receive no transfusion or are randomized to “aggressive” (HbS ≤ 30%, Hb 10 g/dL) or “simple” (HbS 60%, Hb 10 g/dL) transfusion therapy. Until further data are available, our approach is to offer chronic or exchange transfusion to lower the HbS to about 30% in preparation for ophthalmologic\textsuperscript{96} and major surgical procedures. Of the 28 patients we have treated with RCE, 26 underwent the planned procedure. There were no intraoperative complications and postoperative recovery was uneventful in all but three.\textsuperscript{101} Two sustained wound infections and one developed pyelonephritis in the setting of nephrostomy drainage. Surgery was cancelled in two cases because of severe alloimmunization (see below). Notably, we have not encountered ACS as a postoperative complication, in contrast to the 13% incidence reported in preliminary review of the cooperative trial.\textsuperscript{81}

Exchange transfusion has also been used in the management of other acute, severe sickle-related complications such as hepatic failure, sepsis, retinal arteriolar vaso-occlusion, and multisystem failure.\textsuperscript{71,74,76,102,103} Our recommendation is that RCE be used when immediate restoration of circulation is vital to the preservation of life or organ function (Table 3). In addition, exchange can be used to initiate chronic transfusions as well as to decrease iron loading associated with such therapy (see below). Finally, when rapid correction of severe anemia is required, but limited by volume intolerance, automated or manual exchange should be considered.\textsuperscript{104-106}

\textbf{Methods.} There are multiple approaches to “exchanging” RBCs in patients with SCD for those from normal donors. Most efficient are automated cell separators that selectively remove RBCs from whole blood.\textsuperscript{107} Manual methods are also available and are summarized elsewhere.\textsuperscript{36} For acute emergencies, rapid exchange is preferred over gradual or subacute techniques. Although automated RCE requires the use of an anticoagulant (see below) and, frequently in children, central venous access, manual methods are more time-consuming, less accurate, require larger quantities of blood, and result in volume perturbation. With proper modification, automated RCE can be performed even in critically ill patients where precise control of Hct, HbS, and blood volume is essential.\textsuperscript{104} Priming of the extracorporeal circuit with blood and the use of continuous flow separators are required in small children, particularly those with cardiovascular instability.\textsuperscript{108} Using these techniques, we have found automated RCE to be safe and reproducible (Fig 4).\textsuperscript{73}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{hematologic_parameters.png}
\caption{Hematologic parameters before (pre) and after (post) automated RCE. Values from 80 procedures are expressed as the mean ± 1 SD. (Hct S, sickle Hct.)}
\end{figure}
COMPLICATIONS

Comprehensive review of the side effects of RBC transfusion is beyond the scope of this report and can be found elsewhere. The discussion herein will focus on issues of particular relevance to SCD.

Hyperviscosity. As discussed in detail above, transfusion-induced elevations in Hct are associated with increases in viscosity unless combined with significant lowering of HbS. This may account for the occurrence of sickle crisis and other adverse effects following simple transfusion or marked Hct elevations. Consequently, most recommend maintaining an Hct below 35%, although with extremely low levels of HbS it may be safe to transfuse up to 40%. Finally, one must consider the effects of volume expansion or contraction before proceeding with transfusion or phlebotomy, as such fluctuations can result in severe complications.

Hypersplenism. As mentioned above, when begun early in life, chronic transfusion sometimes results in restoration of splenic function and presumably prevents ongoing autoinflammation. Consequently, hypersplenism and increased blood requirements may develop. When suspected, a RBC survival scan can be used for confirmation. Splenectomy may be beneficial in this circumstance.

Iron overload. At the usual rate of chronic transfusion, iron-induced organ toxicity is rarely seen until more than 500 mL/kg of total PRBCs are administered. In SCD, the group of patients most at risk are those with a history of stroke. To decrease the transfusional iron burden in such patients, a variety of maneuvers may be attempted. As discussed, splenectomy should be considered for the occasional patient with accelerated RBC requirements caused by hypersplenism. RBC exchange markedly improves iron balance over conventional transfusion. This approach may be limited by several practical considerations such as availability and vascular access. In our experience, more blood is needed to maintain the HbS near 30% with RCE when compared with chronic simple transfusion. Although pre-exchange phlebotomy may decrease the amount of blood required, associated alterations in Hct and/or volume may be dangerous, especially in those with severe cerebrovascular disease. As mentioned above, less aggressive transfusion programs may be safe for a subset of patients, although this remains to be proven. Finally, transfusion with young RBCs (ie, neocytes) that have enhanced in vivo survival may eventually prove to be useful in SCD. Although initial apheresis collection procedures were costly, difficult, and somewhat inefficient, newer methods of in vitro density separation have proven more practical. In our experience with β-thalassemia major, neocyte transfusion has proven to be both manageable and effective, leading to a 20% decrease in transfusion requirements. Notably, both RBC exchange and neocyte transfusion results in increased unit exposure, conferring additional risks and cost.

In patients who receive regular transfusions, it is likely that iron overload will eventually ensue despite all such attempts. Desferal chelation is currently the only therapy proven effective in combating transfusional hemochromatosis. Although expensive, somewhat difficult to administer, and often limited by noncompliance, treatment with desferal is essential in patients with SCD and iron overload. We recommend instituting such therapy when transferrin becomes fully saturated and a chelatable pool is demonstrated or if there is evidence for iron-induced tissue damage.

Viral infection. The recent identification of the hepatitis C virus (HCV) and the development of diagnostic screening tests for anti-HCV antibody (Ab) offer great hope that the incidence of transfusion associated non-A, non-B hepatitis (NANB) will be reduced. Coupled with surrogate testing, it is likely that 75% to 90% of such infection will be prevented. Given the high rate of NANB transmission in the past and the associated risk of chronic active hepatitis, follow-up HCV and liver function testing should be performed in those with a history of transfusion. Novel therapies such as α-interferon may offer hope for this common and previously untreatable infection.

The risk of transmitting hepatitis B virus (HBV) from blood screened by modern methods is relatively low, with estimates of 1/200,000 per unit. Notably, HBV infection is common in persons with SCD, with reported rates as high as 15% to 20%. In populations where HBV is endemic, even higher rates have been documented. Evidence for active as well as past HBV infection has also been reported in the setting of SCD and chronic liver disease. For these reasons, and given the frequency of transfusion in SCD, we recommend hepatitis B vaccination for all persons with major sickle hemoglobinopathies. Importantly, universal HBV immunization has recently been proposed in the United States. Such vaccination has been shown to be effective in children and adults with SCD.

Finally, improved donor selection and diagnostic screening will likely decrease the risk of transfusion-related HIV and HTLV infection. Nonetheless, the chances for such transmission, though very small, still exist and are a source of anxiety for patients and caregivers alike.

Nonhemolytic transfusion reactions. Febrile, nonhemolytic reactions are among the most common complications of RBC transfusion with a reported incidence of 0.25% to 1% per unit. The likelihood of an individual having a subsequent reaction depends in large part on the number of future transfusions, with observed rates of 10% to 40%. These can be prevented in virtually all instances by the use of leukodepleted RBCs. Given the frequency of transfusion, we recommend using deglycerolized or leukofiltered RBCs for all patients with SCD. Deglycerolized cells have the added benefit of decreasing the risk of allergic reactions to plasma proteins. Although rare, urticarial reactions have been reported to account for 17% of symptoms of nonhemolytic reactions in patients with β-thalassemia transfused with leukodepleted RBCs. Finally, in addition to direct benefits, preventing transfusion reactions is worthwhile because associated symptoms such as fever and pain may complicate the subsequent management of persons with SCD.

Complications of exchange transfusion. There are a number of side effects somewhat uniquely associated with RCE. For those with limited peripheral access, central venous
catheterization may be required. The major associated complication is pain at the insertion site that is easily managed with analgesics. Additional risks such as thrombosis, infection, and vascular perforation are rare, especially with short-term catheterization. We have experienced two significant access related problems. One patient could not undergo exchange because of inability to place a catheter, and another developed a local venous thrombosis that responded to anticoagulation therapy.

To prevent clotting in the extracorporeal circuit during automated RCE an anticoagulant is required. Acid-citrate-dextrose (ACD) solution is most routinely used. Although this is usually well tolerated by adolescents and adults, reactions to citrate are among the most frequent side effects ofapheresis. The symptoms and management of citrate toxicity are identical to those described in massive blood transfusion. Because citrate toxicity is common in pediatric apheresis, we rely almost entirely on heparin for anticoagulation during automated RCE in children. Nonetheless, with a single exception we have not encountered hemorrhagic complications. One patient treated for priapism after corporal irrigation developed a severe penile hematoma that necessitated a prolonged hospitalization. This low rate of bleeding despite the use of heparin is in keeping with the experience of others.

Recently, nine patients who manifested severe neurologic events in close proximity to RCE have been reported. Notably, seven of nine had been treated for priapism. We have encountered a similar case of a 10-year-old with priapism who suffered a subarachnoid hemorrhage 6 days after RCE and 3 days postoperatively from a corporal shunt procedure. Diffuse cerebrovascular disease was demonstrated on angiography, and he currently remains well on chronic transfusions. Although the etiology and/or causality of this association have not been established, patients should be closely monitored of heparin as is in keeping with the experience of others.

The administration of large volumes of blood during RCE carries a number of particular risks. To avoid potentially dangerous alterations in the RBC and/or total blood volumes, exchange transfusion should be performed by those experienced in such procedures and with close monitoring of hemodynamics, clinical status, and serial Hcts. To avoid potential impairments in O2 delivery, fresh or 2,3-DPG-enriched PRBCs can be used, although such concerns are likely of minimal physiologic significance. Given the large exposure to foreign RBC antigens (Ags), and in light of the fact that a very high proportion of circulating cells are at risk of hemolysis, RBC alloimmunization can be particularly hazardous after exchange transfusion. Despite the use of extended Ag-matched blood (see below), we have encountered three cases of severe alloimmunization in the setting of RCE. Two patients were known to have been sensitized by transfusions earlier in life. After exchange transfusion, both manifested anamnestic responses as well as developed new alloanabodies and autoantibodies. One subsequently died of complications of profound anemia. In the other, a prolonged delay in the planned cholecystectomy was necessitated because of difficulty accumulating adequate quantities of Ag-negative blood. A third patient developed massive intravascular hemolysis 7 days after RCE. Considering these risks, exchange should be undertaken cautiously in those with a possible history of alloimmunization.

Alloimmunization. Sensitization to RBC Ags other than A, B, or Rhesus(D) is a well-known complication of transfusion not confined to persons with SCD. The likelihood of antibody formation depends on foreign Ag exposure, the relative immunogenicity of the Ag, the individual's immunologic responsiveness, and other factors. Historically, the Ags most frequently involved have included Rhesus (Rh), Kell (K), Duffy (Fy), and Kidd (Jk).

In recent years, growing numbers of reports have emerged suggesting that patients with SCD have high rates of alloimmunization to RBC Ags, with an incidence ranging from 8% in pediatric series to 50% in multiply transfused adults. Most report rates of about 20%, which is corroborated by the recent Cooperative Study of SCD. The risk of sensitization is greatest with the first exposure, but continues to increase with the number of transfusions even with over 100 units. Although the majority of antibodies are directed against Rh and K, more than 50% of those affected develop multiple antibodies, making it difficult and sometimes impossible to find compatible blood. In addition, alloimmunization may be associated with autoantibody production, a phenomenon not restricted to SCD. Finally, at least a third of the antibodies become nondetectable over time, potentially confounding future transfusions and placing the patient at risk of anamnestic antibody production and severe delayed hemolytic reactions. For all of these reasons, such sensitization can be life-threatening. Importantly, delayed transfusion reactions can mimic various complications of SCD and should be suspected when patients present with appropriate symptoms (eg, pain, fever, accelerated hemolysis) after recent transfusion.

It is clear that numerous differences in RBC phenotype exist between African-Americans and the largely European-American donor pool in the United States. For example, although both groups are predominantly Rh(D)-positive, there are significant disparities in regard to other Ags of the Rh system. Importantly, although about 40% of Rh(D)-positive African-Americans lack the Rh(C) and Rh(E) Ags, the vast majority of Rh(D)-positive European-American donors possess one or both of these additional Rh Ags. Such differences are seen in other blood groups as well, with African-Americans frequently missing many of the "minor" RBC Ags (Table 6). Therefore, it is not surprising that in the setting of a racially discordant donor-recipient pool, transfusing with regard only to ABO and Rh(D) type results in a high frequency of exposure to foreign Ags. In all likelihood, this accounts for much of the risk of sensitization in SCD. Furthermore, our experience in thalassemia suggests that antibody formation may be more likely when transfusion is intermittent and begun beyond early childhood. For these and possibly other reasons, persons with SCD may be at increased risk of alloimmunization.
Table 6. Interracial Frequencies of RBC Phenotypes

<table>
<thead>
<tr>
<th>RBC Phenotype</th>
<th>European-American (%)</th>
<th>African-American (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhesus group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>83</td>
<td>92</td>
</tr>
<tr>
<td>C</td>
<td>68</td>
<td>33</td>
</tr>
<tr>
<td>E</td>
<td>29</td>
<td>20</td>
</tr>
<tr>
<td>cDe</td>
<td>1.6</td>
<td>42</td>
</tr>
<tr>
<td>Kell group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Duffy group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fy (a+b+)</td>
<td>49</td>
<td>2.6</td>
</tr>
<tr>
<td>Fy (a−b−)</td>
<td>Rare</td>
<td>68</td>
</tr>
</tbody>
</table>

Data derived from Giblett\textsuperscript{193} and Rosse.\textsuperscript{194}

MANAGEMENT AND PREVENTION OF ALLOIMMUNIZATION

In an attempt to prevent alloimmunization, a program of extended Ag-matched RBC transfusion for patients with SCD was begun at our institution in the late 1970s. The following outlines the components and outcome of this approach.

Blood collection and RBC phenotyping. To increase the pool of Ag-compatible blood, units that are to be used for patients with SCD are largely collected from African-American donors.\textsuperscript{174} After routine blood bank testing, all units are checked for sickle trait\textsuperscript{*} and typed for Ags in the Rh, K, MNS, and Fy blood groups. Selected donors are also tested for Lewis (Le) and Jk Ags. To further expand the pool for this program, O Rh(C,D,E)-negative banked blood is routinely screened for K, S, and Fy Ags regardless of donor ethnic background. To maintain adequate supplies of extended Ag-negative blood, such units are cryopreserved and stored.\textsuperscript{176}

In addition, to salvage older units, blood is frequently rejuvenated before freezing.\textsuperscript{195} Finally, the Rare Donor Registry of the American Red Cross is used as a resource when necessary.

All patients with SCD are routinely typed for the above-noted RBC Ags. When transfusing in pregnancy, efforts are also made to phenotype the father so that Ags which might induce maternal sensitization against fetal RBCs can be avoided.

Extended antigen-matched transfusion. In all cases, blood is matched for Rh(C,D,E,c,e) and K, and in most cases for S, Ags. In addition, the best possible match for Fy and Jk is provided. For patients with a known or potential history of antibody formation, an attempt is made to match particularly closely. When emergent transfusion is required, O, Rh(C,D,E)-negative, K-negative RBCs are used.

Antibody screening. It is essential that persons with SCD have antibody screening performed before each transfusion. Furthermore, to avoid missing “silent” antibodies (i.e., titers that are no longer detectable; see above), screening should be performed 4 to 8 weeks after all transfusions. For increased sensitivity, enhanced antibody detection techniques are used when there is a history of alloimmunization or if 6 months have elapsed since transfusion without interval screening.\textsuperscript{177}

Outcome. Over the past 2 decades, 116 of the 230 children and adolescents with SCD cared for at least intermittently at Children’s Hospital are known to have been transfused. The average number of units administered per patient approaches 30 (range 1 to 400). Twenty of these 116 have formed anti-RBC antibodies for a 17% overall incidence of alloimmunization (Table 7). Notably, 13 of 20 were exposed to nonextended Ag-matched blood at other institutions or before the mid-1970s when our current program began. Three of these are known to have been sensitized elsewhere, and based on the antibodies formed, it can be concluded that nine others were first sensitized through prior exposure. Thus, seven patients have developed primary alloimmunization on our Ag-matched transfusion program. Importantly, two of these received Rh(C) mismatched blood.

If one excludes those persons known to have been exposed to blood outside of the Ag-matched program, the incidence of alloimmunization is 6.4%. Unfortunately, this estimate is confounded by the fact that the number of persons transfused at other institutions cannot be accurately confirmed. Despite this limitation, a number of conclusions can be drawn. As is apparent from the data presented in Table 7, the individuals who were sensitized despite receiving Ag-matched blood have developed far fewer antibodies. In addition, these antibodies have more commonly been of undetermined specificity or directed against low frequency Ags. Importantly, despite the need for chronic transfusions in four of these seven patients, none has manifested antibody-related complications. This is

Table 7. Alloimmunization, Children’s Hospital Experience

<table>
<thead>
<tr>
<th>Patient</th>
<th>Antibodies*</th>
<th>Notes†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>E, K, HTLA</td>
<td>Sensitized elsewhere</td>
</tr>
<tr>
<td>2</td>
<td>C, E, Fy*, McCoy*</td>
<td>Sensitized elsewhere</td>
</tr>
<tr>
<td>3</td>
<td>E</td>
<td>Sensitized elsewhere</td>
</tr>
<tr>
<td>4</td>
<td>C, E, Le*, Le*</td>
<td>Prior exposure elsewhere</td>
</tr>
<tr>
<td>5</td>
<td>C, K, Bg, HTLA</td>
<td>Prior exposure</td>
</tr>
<tr>
<td>6</td>
<td>C, E</td>
<td>Prior exposure</td>
</tr>
<tr>
<td>7</td>
<td>E, K</td>
<td>Prior exposure</td>
</tr>
<tr>
<td>8</td>
<td>C, Kp*, Jk*, Le*</td>
<td>Prior exposure</td>
</tr>
<tr>
<td>9</td>
<td>C*, E, s, Fyb</td>
<td>Prior exposure</td>
</tr>
<tr>
<td>10</td>
<td>c, C*, E, K, Kp*</td>
<td>Prior exposure</td>
</tr>
<tr>
<td>11</td>
<td>E, M, S, Le*, Jk*</td>
<td>Prior exposure</td>
</tr>
<tr>
<td>12</td>
<td>K</td>
<td>Prior exposure</td>
</tr>
<tr>
<td>13</td>
<td>Fy*</td>
<td>Prior exposure</td>
</tr>
<tr>
<td>14</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>C, S, Fy*</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>V, S</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Kp*</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>?Jk*</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>?Jk*</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Bg</td>
<td></td>
</tr>
</tbody>
</table>

* Antibodies against the antigens listed (see text for abbreviations); HTLA, high titer low avidity.
† See text.
in marked contrast to those immunized before Ag matching began, whose subsequent transfusion management has been far more difficult.

As illustrated by the cases of accidental exposure to Rh(C)-positive blood, strict quality control is essential. Furthermore, our data underscore the importance of a multi-institutional approach to this problem. To prevent exposure to mismatched units at other centers, attempts must be made to educate patients, families, and the medical community at large. We agree with the recommendation that persons with SCD carry medical identification information that includes their RBC phenotype and antibody specificities.178

Cost. The expenditure in labor and money to establish and maintain such a program is significant. There are increased demands in regard to donor recruitment, typing and screening, and cryopreservation. Cell washers and a -80°C freezer are required. Finally, the deglycerolizing process takes about an hour per unit, which limits the speed with which blood can be made available. As a result of this increase in labor, supplies, and equipment, the cost of an Ag-matched deglycerolized unit at our institution is about 60% greater than that for standard PRBCs. National laboratories charge even more. Certain costs can be minimized, for example, by restricting Ag screening to African-American donors.179 If regional resources were pooled in this effort, overall expenditures could be decreased and labor efficiency increased.

Similar experience has been reported by others. Ambrosio et al180 suggest that closely matching donor and recipient for extended RBC Ags lowers the rate of subsequent antibody formation in previously alloimmunized patients. Notably, three of the four new antibodies formed resulted from technical errors in the transfusion program. In a larger series of patients with β-thalassemia major and HbS/β-thalassemia, Spanos et al181 found prophylactic matching for Rh and K Ags at the onset of transfusion to be associated with a significant decrease in the incidence of primary alloimmunization (3.7% vs 15.7%).

Although there is controversy about the necessity and cost effectiveness of prophylactic extended matched blood transfusion,170,179-182 our experience with alloimmunized patients, the apparent benefits of our transfusion program, and the reports of Ambrosio et al171 and Spanos et al181 lead us to our current policy. Given the risks associated with antibody formation, we do not believe that it is prudent to reserve Ag-matched blood only for those patients known to be alloimmunized. It is possible that prophylactic matching restricted to the most commonly involved Ags (eg, C, E, K) may eventually prove to be a more practical approach for most blood banks. However, without question, when there is a history of sensitization, every effort should be made to provide the most extended matched blood available. Furthermore, in light of the potential for severe hemolysis after large volume transfusion, we recommend using well-matched units for RBC exchange.

ALTERNATIVES TO HOMOLOGOUS TRANSFUSION

Given the problems associated with exposure to homologous blood, recent efforts have focused on alternative approaches to therapy.

Autologous cryopreservation. RBCs from persons with SCD can be frozen and deglycerolized with modifications of standard techniques.183 In theory, autologous transfusion could be used in the management of nonvascular complications of SCD. However, this is for the most part impractical. Blood donation in patients with SCD is potentially hazardous. Furthermore, reinfusing RBCs that contain HbS would be undesirable in many situations where transfusion is needed. Nonetheless, such blood could conceivably be used, for example, in the management of severe anemia or alloimmunization.184,185 Small aliquot donations or blood removed during exchange transfusion might be saved for use at a later date. Pretreatment with erythropoietin and/or hydroxyurea might improve the feasibility of autologous donation in the future.

Antisickling agents. Pharmacologic attempts to alter the propensity of RBCs to sickle date back to the early 1960s.1 Recent reviews of the effects and limitations of such therapies are available.8,186 Currently, there are no agents approved for the treatment of SCD and only a single drug, hydroxyurea, is undergoing large-scale human trials. The influence of hydroxyurea on HbF production and the intraerythrocyte environment form the basis for the hope that this agent may prove efficacious.187

Bone marrow transplantation. Bone marrow transplantation and gene transfer techniques offer potentially curative approaches to this genetic disorder.188 As our understanding of the determinants and predictors of clinical severity improves,19,189 it may become possible to select patients early in life who would merit such an aggressive curative approach. A collaborative study of marrow transplant for patients severely affected with SCD is in the early stages at this time.190

CONCLUSIONS

RBC transfusion has long been and currently remains an integral part of the management of SCD. The judicious use of blood can be both life-saving and life-prolonging in a variety of clinical settings. Nonetheless, given the multitude of transfusion-related complications, as well as the unique properties of HbS, the approach to RBC transfusion in this group of disorders merits special consideration. Taking into account the particular clinical state, the various methods of transfusion, and the interactions of Hct, HbS, and viscosity, allows an improved strategy. Although new methods of treatment may someday supplant this form of therapy, clinicians of tomorrow will undoubtedly share in the frustrations and victories associated with the use of transfusions in SCD.

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