CME/SAM

Red blood cell exchange in patients with sickle cell disease—indications and management: a review and consensus report by the therapeutic apheresis subsection of the AABB

Elizabeth Biller,[1] Yong Zhao,[2] Mary Berg,[3] Lisa Boggio,[4] Kelley E. Capocelli,[5] Deanna C. Fang,[6] Scott Koepsell,[7] Lejla Music-Aplenc,[8] Huy P. Pham,[9,] Angela Treml,[10,†] John Weiss,[11] Geoffrey Wool,[10] and Beverly W. Baron[10]*

BACKGROUND: A prior practice survey revealed variations in the management of patients with sickle cell disease (SCD) and stressed the need for comprehensive guidelines. Here we discuss: 1) common indications for red blood cell exchange (RCE), 2) options for access, 3) how to prepare the red blood cells (RBCs) to be used for RCE, 4) target hemoglobin (Hb) and/or hematocrit (Hct) and HbS level, 5) RBC depletion/RCE, and 6) some complications that may ensue.

STUDY DESIGN AND METHODS: Fifteen physicians actively practicing apheresis from 14 institutions representing different areas within the United States discussed how they manage RCE for patients with SCD.

RESULTS: Simple transfusion is recommended to treat symptomatic anemia with Hb level of less than 9 g/dL. RCE is indicated to prevent or treat complications arising from the presence of HbS. The most important goals are reduction of HbS while also preventing hyperviscosity. The usual goals are a target HbS level of not more than 30% and Hct level of less than 30%.

CONCLUSION: Although a consensus as to protocol details may not be possible, there are areas of agreement in the management of these patients, for example, that it is optimal to avoid hyperviscosity and iron overload, that a target Hb S level in the range of 30% is generally desirable, and that RCE as an acute treatment for pain crisis in the absence of other acute or chronic conditions is ordinarily discouraged.

Sickle cell disease (SCD) occurs in approximately one in 500 African Americans in the United States.[1,2] A single-nucleotide substitution in the β-globin chain of hemoglobin (Hb; valine instead of glutamic acid at position six) results in an abnormal Hb (HbS) that polymerizes at low oxygen concentrations,

ABBREVIATIONS: CPB = cardiopulmonary bypass; RCE = red blood cell exchange; SCD = sickle cell disease.

From the [1]Department of Pathology, Ohio State University Wexner Medical Center, Columbus, Ohio; the [2]Departments of Medicine and Pathology, UMass Memorial Medical Center, Worcester, Massachusetts; the [3]Department of Pathology, University of Colorado Hospital, Aurora, Colorado; the [4]Rush University Medical Center, Chicago, Illinois; the [5]Department of Pathology, Children's Hospital Colorado, University of Colorado Anschutz Medical Center, Aurora, Colorado; the [6]Department of Laboratory Medicine and Pathology, Mayo Clinic, Jacksonville, Florida; the [7]Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, Nebraska; the [8]Children's Mercy Hospitals and Clinics, Kansas City, Missouri; the [9]Department of Pathology, Division of Laboratory Medicine, University of Alabama at Birmingham, Birmingham, Alabama; the [10]Department of Pathology, University of Chicago, Chicago, Illinois; and the [11]Department of Pathology and Laboratory Medicine, University of Wisconsin School of Medicine, Madison, Wisconsin.

Address reprint requests to: Elizabeth Biller, MD, Department of Pathology, Ohio State University Wexner Medical Center, Columbus, OH 43210; e-mail: elizabeth.biller@osumc.edu.

**Current address:* Keck School of Medicine, University of Southern California, Los Angeles, CA.

†Current address: Blood Center of Wisconsin, Milwaukee, WI.

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causing deformation and sickling of the red blood cell (RBC).[1] SCD is associated with numerous potential complications related to both the anemia and the presence of the abnormal Hb. RBC transfusion to improve oxygen-carrying capacity and to treat or decrease the risk of complications due to sickling has been an important part of the treatment for many years. A practice survey performed by Dunbar and colleagues[3] in Florida, which has one of the largest SCD populations in the United States, revealed variations in the management of these patients, and the authors indicated that "the study underscores the need for the development and dissemination of comprehensive sickle cell transfusion guidelines and protocols."

MATERIALS AND METHODS

Fifteen physicians in the active practice of apheresis from 14 institutions representing different geographic regions within the United States discussed how they manage RBC exchange (RCE). The material discussed here represents a consensus of the authors.

RESULTS

Simple transfusion versus RCE

Transfusion in SCD generally is performed to accomplish two goals: first, to increase oxygen-carrying capacity by improving anemia, and second, to help prevent or treat complications related to the presence of HbS.[4–6] Most institutions perform either simple transfusions or automated RCEs, depending on the clinical situation and the desired result. Simple transfusions are recommended when symptoms are primarily due to anemia and Hb level is less than 9 g/dL, whereas exchange transfusions are indicated in an effort to prevent or treat complications arising from the presence of HbS.[5] If automated RCE is being performed, HbS percentage can be decreased without a significant increase in hematocrit (Hct) or blood viscosity, and this also can help to prevent iron overload.[7,8] If simple transfusions are being performed to improve anemia, care must be taken to avoid hyperviscosity.[4]

Indications for RCE

The vast majority of RCEs performed by apheresis services are for the prevention or treatment of complications of SCD. Most commonly, RCEs are used to treat complications such as acute stroke, severe acute chest syndrome with hypoxia and rapid progression of symptoms, severe sickle cell hepatopathy, and acute multiorgan failure syndrome.[5,6,9]

Most institutions discourage RCE as an acute treatment for uncomplicated pain crisis. Guidelines support this recommendation, and there is no evidence that transfusion leads to faster recovery in this situation.[5,10] Chronic simple transfusions or exchange transfusions, however, may be helpful in patients who have frequent pain crises and are unable to take or do not respond to hydroxyurea.[5] Transfusions can reduce the frequency of pain events[11,12] and may help reduce hospital readmission rates. A study examining hospital discharge records of Medicaid patients hospitalized with sickle cell crisis found that patients who received a simple transfusion during their hospitalization had a greater than 20% decrease in the 30-day readmission rate.[13] A chronic exchange transfusion program, especially if continued over several years, can decrease total days spent in the hospital and decrease the annual cost of care for patients with SCD.[12,14]

The indications for chronic RCEs (and chronic transfusions in general) with the most evidence-based support are primary and secondary stroke prevention.[5] Transcranial Doppler ultrasonography is helpful in assessing children to determine their risk of stroke.[15] Chronic transfusions also are effective for preventing recurrent strokes and silent cerebral infarcts in children[16] and may be useful in adults as well.[5,17] The optimal duration of treatment is unknown,[18] but many centers continue transfusion treatment indefinitely for patients who have had a previous stroke.[19] Chronic transfusion programs also have been used to prevent recurrent acute chest syndrome and vasoocclusive pain crises.[11]

Some institutions perform RCEs for the prevention and treatment of priapism. Some small recent studies have shown that exchange to a low HbS level (in one study ≤30%[20] and in another study ≤16%[21]), with Hb level of approximately 10 g/dL in the acute setting, has been helpful in resolving priapism.[20–22] One institution represented by the authors noted that chronic RCEs seemed to be helpful in preventing recurrent episodes of priapism in at least two patients.

RCE may be considered before surgery, as both anesthesia and surgery increase the risk of SCD-related complications, particularly acute chest syndrome.[5,23–25] Fewer sickle-related complications have been noted in transfused (either simple or exchange) versus nontransfused patients undergoing low- and moderate-risk surgical procedures.[25] In low- and moderate-risk surgical procedures, there does not seem to be a significant difference in the rate of complications when using an aggressive (maintaining preoperative Hb level of approximately 10 g/dL and HbS of ≤30%) versus a conservative (achieving a preoperative Hb level of approximately 10 g/dL) transfusion strategy.[26] Generally, simple transfusion has been suggested in preparation for low- and moderate-risk surgeries when the patient's Hb level is less than 9 g/dL (to increase it to 10 g/dL),[27] and exchange transfusion has been suggested when a patient is having high-risk surgery, has severe SCD, or had other comorbid conditions.[5]

As the life expectancy of patients with SCD improves, care providers increasingly are confronted with hematologic malignancies and other neoplasms that may develop in these patients who may benefit from autologous

hematopoietic stem cell transplantation. However, granulocyte–colony-stimulating factor (G-CSF) may precipitate severe, even fatal, vasoocclusive crises when used for mobilization of hematopoietic progenitor cells for autologous transplantation in patients with SCD.[28,29] RCE before G-CSF administration may, based on rare case reports, be an effective approach to prevent this potential life-threatening complication.[30–32] RCE may be considered before administering intravenous (IV) contrast dye for cerebral angiography, as the dye is viscous and has been shown to cause increased sickling in vitro.[10,24]

SCD is associated with an increased risk of complications during pregnancy for both the mother and the fetus.[33] Maternal complications include acute pain crisis, pulmonary complications, hypertensive disease, infection, thrombotic events, and delivery necessitating additional interventions such as Cesarean section.[34,35] Fetal complications include increased risks of intrauterine growth restriction, low birthweight, preterm birth, and stillbirth/intrauterine fetal demise.[34,35] The prevalence of these complications can vary with sickle cell genotype; for example, pain crises and preterm delivery have been reported more frequently in pregnant women with HbSS, whereas postpartum hemorrhage has been reported as more likely to occur in women with HbSC.[35] Hydroxyurea is contraindicated during pregnancy, and thus additional treatment options are needed. A recent publication by Berthaut and colleagues[36] presents evidence for detrimental effects of hydroxyurea on sperm. Studies evaluating the use of simple and exchange transfusion during pregnancy have shown mixed results.[5,37–40] However, most sources agree that prophylactic transfusion (simple or exchange) should be considered for pregnant women with a history of severe SCD-related complications who were on a chronic transfusion program before pregnancy or who have had repeated pain crises or worsening of anemia during pregnancy.[5,6,24,35] A meta-analysis of studies evaluating the use of transfusion during pregnancy found that prophylactic transfusion (vs. on-demand transfusion) significantly reduced the odds of vasoocclusive pain episodes, pulmonary complications, pulmonary embolism, pyelonephritis, maternal mortality, perinatal mortality, neonatal death, and preterm birth.[34]

Complications of SCD for which the role of RCE is not determined include pulmonary hypertension, end-stage renal disease either before or after renal transplant, and progressive sickle retinopathy.[5,9,24,41] The use of RCE in these conditions should be determined on a case-by-case basis.[5,8,24] At least one study reported rapid improvement in patients with pulmonary hypertension who were treated with RCE.[22]

Vascular access

Ideally, RCEs are performed using peripheral veins, as these are usually one-time procedures. However, many patients lack adequate peripheral veins, and thus other means of access must be used, such as central venous catheters specifically designed for dialysis or apheresis or implantable high flow ports. Many patients undergoing urgent RCE for critical illness will require placement of a temporary central venous catheter.[9] For long-term access, choices include tunneled central venous catheters, implantable ports, and (used less commonly) arteriovenous fistulas.[1] Tunneled central venous catheters have a higher rate of complications in patients with SCD compared to other patient groups.[4] Patients requiring long-term access often prefer implantable ports because they are easier to care for and place fewer restrictions on their activity.

RBC units

Whenever possible, thought should be given early to the potential transfusion needs of patients with SCD who are admitted to the hospital, as their clinical condition may sometimes deteriorate rapidly.[5] This will permit time to perform ABO and Rh typing, antibody screening, RBC phenotyping, and molecular typing for patients who may need it (e.g., those with warm autoantibodies, multiple alloantibodies, or recent transfusions) and allow the blood bank to assess the availability of RBC units before they are needed. Communication among hospitals also is important to check for antibody history.

Alloimmunization can be a significant complication associated with SCD. Alloantibodies can prolong the time needed to complete a serologic workup, make it difficult to locate compatible units, and cause acute and delayed hemolytic transfusion reactions, which can be severe.[42,43] A recent case series suggests that RBC alloimmunization itself can contribute to decreased survival in patients with SCD.[43] Patients with SCD have a higher incidence of alloimmunization than the general population and most other patient populations, with approximately 25% to 40% of chronically transfused patients developing RBC antibodies.[44–47] There are multiple contributing factors, including differences between the antigen makeup of SCD patients and blood donors, the immune response of the patient, age at first transfusion, and the number of transfusions.[1,42,45,46,48,49] Most commonly, alloantibodies are directed against antigens in the Rh and Kell blood group systems.[1,45,48]

To help reduce the rate of alloimmunization, many centers establish a RBC phenotype on their patients with SCD and provide RBCs that are not only negative for antigens to which the patient already has antibodies, but also that are prophylactically matched for the C, E, and K antigens (considered the most immunogenic).[44,48] This has helped to significantly reduce the rate of alloimmunization.[4,47,48] However, patients expressing variants of the Rh antigens may still develop antibodies against parts of the antigen that they lack,[4,50,51] and these variants are not detected with standard serologic testing.[50,51] There is a significant amount of *RH* diversity in African Americans, and

despite matching for the Rh antigens, Rh antibodies still are seen frequently.[51] For example, in a 15-year retrospective analysis of 182 patients with SCD at The Children's Hospital of Pennsylvania who received transfusions from African American donors, a total of 91 antibodies with unexplained Rh specificities were identified in 78 patients; 56 of the antibodies occurred in patients whose RBCs were phenotypically positive for the corresponding Rh antigen, and 35 occurred in patients whose RBCs lacked the antigen and were transfused with Rh-matched RBCs. High-resolution *RH* genotyping showed variant alleles in 87% of the patients.[51]

Fewer centers perform prophylactic extended matching to include such antigens as Duffy, Kidd, and Ss.[45,52] While a prophylactic extended matching protocol is likely to prevent formation of more alloantibodies, it creates issues such as not being able to find enough compatible units in a timely manner and results in a significant cost increase.[45,47] A cost-effectiveness study using a decision tree model to evaluate four different antigen-matching strategies in a hypothetical sickle cell cohort found that prospective extended antigen matching (prophylactic antigen matching regardless of alloimmunization history) would be expected to cost almost $2 billion more than history-based extended matching (only providing antigen-matched blood after the patient developed an alloantibody) over 10 years and prevent 2424 alloimmunization events.[53] More specifically, it would cost between $369,482 and $769,284 to prevent one alloimmunization event.[53] However, these numbers likely do not represent the whole picture, as the study did not analyze the potential cost savings as a result of prophylactic antigen matching or take into account some factors such as the actual availability of the needed matched units.[54] Some centers do not antigen match until the patient develops an alloantibody.[47] Among the institutions represented by the authors, all prophylactically match for the C, E, and K antigens; additionally, two institutions perform a full match (refers to Duffy, Kidd, and S/s blood groups) prophylactically, and two perform a full match after a patient develops an antibody.

Units selected for transfusion should be HbS negative and leukoreduced.[1,2,7,41,49] Leukoreduction helps to decrease the incidence of febrile transfusion reactions and lessens the risk of alloimmunization against HLA antigens. HLA alloimmunization needs to be taken into consideration because bone marrow or stem cell transplants are possible curative treatments for SCD and should be seriously considered at an early age in symptomatic patients with a matched sibling donor.[24,55]

Institutions take several different approaches to determine how many RBC units to exchange. The number of units needed depends on the volume and Hct of the individual units[2] as well as the patient's preprocedure Hct and HbS levels, height, weight, and the desired HbS and Hct targets. RBC units are routinely labeled with volume, but this varies from unit to unit. Units are not generally labeled with Hct, and it can be difficult to obtain this information from blood suppliers. On average, RBC units with additive solution produced from a whole blood donation have a volume of approximately 330 mL and a Hct level of approximately 55% to 60%, whereas RBC units from apheresis donations have a volume of approximately 300 mL and a Hct of approximately 60%.[2] Some institutions use an estimate of 56% to 57% Hct (i.e., an approximate average) for each unit. One author's institution asks its blood suppliers for information about Hct levels on their units and then averages them. Terumo BCT has created a RCE calculator for use with the Spectra Optia apheresis system, which can be accessed from their website and is available as an app for phones and tablets (https://www.terumobct.com/therapeutic-apheresis/protocols/rbcx/calc-tool).

Target Hb and/or Hct

Hyperviscosity is of particular concern in patients with SCD. Sickle cells, particularly deoxygenated sickle cells, have a higher viscosity than normal RBCs.[6,56] Increased viscosity negatively affects oxygen delivery, which in turn contributes to further sickling.[4,6] The presence of nonsickled RBCs decreases viscosity but does not entirely normalize it.[4,43] The risk of hyperviscosity is affected by both the Hct and the percentage of HbS.[4,6] Therefore, if simple transfusion is performed, the oxygen-carrying capacity of the blood increases, but the overall increase in Hct leads to increased viscosity, which hinders improvement in overall oxygen delivery.[56] RCE decreases viscosity, which improves blood flow.[57] Additionally, the increase in HbA after RCE leads to increased affinity of Hb for oxygen, along with increased oxygen saturation.[57]

Most patients with SCD have a lower baseline Hb and/or Hct compared with normal individuals, and in the absence of symptoms, they do not require transfusion.[5] Keeping the Hct level at less than 30% or Hb level at less than 10 g/dL aids in preventing hyperviscosity.[4,23,56]

Target HbS level

A target HbS level after RCE of not more than 30% has been recommended for clinical conditions such as acute chest syndrome, but in very sick patients a lower HbS level may be desirable.[5,7] HbS level of less than 30% is also a recommended target in the treatment of additional acute complications of SCD, such as ischemic stroke and multiorgan system failure.[4,6,55] It is generally agreed that a target HbS in the range of 30% after chronic exchange transfusion is helpful in reducing the incidence of stroke, acute chest syndrome, priapism, and other conditions.[4,5,7] For primary stroke prevention in children, the recommended target HbS level is less than 30%.[5,15] It appears that even if this goal is not met, prior transfusions can continue to confer benefit, as no strokes were reported in the children who

occasionally did not reach the HbS goal of less than 30%.[15] For secondary prevention of silent cerebral infarctions in children, the Silent Cerebral Infarct Multi-Center Clinical Trial (SIT) demonstrated that children who received monthly transfusions with a goal Hb level of more than 9 g/dL and HbS level of not more than 30% had a relative risk reduction of recurrent infarction of 58% compared to children in the standard of care group.[16]

For prevention of recurrent ischemic strokes in both adults and children, chronic transfusion to maintain a HbS level of less than 30% has been recommended.[5,58] It is unknown how long chronic transfusion should be performed, but the risk of recurrence appears to be highest in the first 3 to 4 years after the initial stroke.[17,58] Some small studies suggest that it may be possible, if patients have been stable neurologically for at least 4 years after the first stroke, to maintain them at a goal HbS level of less than 50% without significantly increasing their risk.[7,19,59]

Currently there is no consensus on the transfusion strategy that should be used for patients with SCD undergoing surgery.[23] Evidence-based guidelines recommend preoperative transfusion to bring Hb level to 10 g/dL.[8] A comparison of conservative (endpoint—transfusion to a Hb level of 10 g/dL) and aggressive (achieving HbS level of <30%) transfusion strategies found no significant difference in the incidence of perioperative complications, and the conservative transfusion approach was associated with fewer complications related to transfusions.[23] One study of orthopedic surgery patients suggested that HbS levels of 50% to 60% still may be effective in decreasing sickling episodes and sickle-related complications.[26] In some special surgical circumstances, such as procedures requiring cardiopulmonary bypass (CPB), lower HbS goals (e.g., in the range of 10%-20%) may be considered, but the optimal HbS goal is unknown.[60,61]

During cardiac surgery, multiple conditions can be present that are conducive to RBC sickling, including hypothermia, cold cardioplegia, stress, vasoconstriction, acidosis, and CPB itself.[61,62] Pre- or intraoperative RCE can decrease the concentration of HbS as well as improve oxygenation, both of which are beneficial in a surgical setting.[61] In some case reports, particularly in pediatric cardiac surgery, the priming of the bypass circuit itself functions as a partial or complete RCE and can effectively lower HbS levels without the need for a separate exchange.[63,64] Multiple case series have reported successful surgical outcomes after reducing HbS to between 4 and 20% with the use of RCE or the bypass circuit.[61–64] However, a study of children and adults reported good outcomes without the use of perioperative RCE, but HbS levels were not provided in this study.[65] Specific details of the surgery to be performed may influence the choice of target HbS level, with some authors suggesting that a lower HbS goal may be beneficial in surgeries using moderate or deep hypothermia, low-flow CPB rates, or circulatory arrest.[66]

RBC depletion/RCE

RCE can be modified to include an initial phase of isovolemic hemodilution (or "depletion"—removing RBCs to a specified Hct while instilling saline [or 5% albumin], which is then followed by RCE).[67,68] This procedure can reduce the volume of RBCs needed for the exchange and thus reduce donor exposure[7,67]—that is, for the same volume of RBCs used, the efficiency of HbS removal is improved because fewer RBCs need to be removed.[69] However, this is not an option for all patients, as the preprocedure Hct must be taken into account. One study selected only patients with preprocedure Hct levels of more than 26% and stable hemodynamic status.[69] A second study required a preprocedure Hct level of 23% or more and decreased the patient's Hct up to 6% during the isovolemic hemodilution phase (if baseline Hct level was 23%-31%) or 8% (if baseline Hct level was ≥32%).[70] The procedures generally were well tolerated.[69,70]

Complications

In addition to the risks associated with venous access, particularly central venous access, there are also multiple risks associated with the blood products used. These include iron overload, alloimmunization, acute and delayed hemolytic and nonhemolytic transfusion reactions, transfusion-transmitted infections, and allergic reactions.[42]

Warm autoantibodies may develop as a complication of SCD, occurring in approximately 8% to 10% of patients.[45] These autoantibodies may be panreactive, or they may show specificity for a particular blood group antigen, commonly one in the Rh system (usually e).[45,48] Most patients with SCD do not have clinically significant hemolysis as a result of their autoantibodies.[45,71] Autoantibody formation may be associated with alloimmunization.[48]

Hyperhemolysis syndrome is a potentially life-threatening type of delayed hemolytic transfusion reaction that can be seen in SCD[1,4] in which there is destruction of both the patient's own cells and the transfused cells, which can lead to severe anemia.[4,45,72,73] Although hyperhemolysis is more common in previously alloimmunized patients, it can also occur in patients without previous alloimmunization.[45] A characteristic finding is a posttransfusion Hb level that is lower than the pretransfusion level.[73–75] Other common symptoms and laboratory findings include pain, fever, elevated lactic dehydrogenase, hyperbilirubinemia, hemoglobinuria, decreased or absent percentage of HbA, and decreased reticulocyte count.[4,45,72,74] The direct antiglobulin test is often negative,[4] and new RBC antibodies often are not identified.[74] The etiology is not well understood,[45,75] and the optimal treatment is unknown.[73] As additional transfusions may exacerbate the hemolysis, they should be avoided unless absolutely necessary.[1,4,74,76] Common initial treatments include steroids and/or intravenous immune globulin.[74] Erythropoietin may be given to compensate for the suppression of erythropoiesis in these patients.[73,75,77–79]

In severe cases, rituximab treatment has been used successfully.[77] There has been a report of successful treatment with plasma-to-RBC exchange (removal of the patient's plasma using a commercial cell separator operating the plasma exchange program and tubing and replacement with donor RBCs); the goal of this procedure was to conserve patient RBCs and improve oxygen-carrying capacity while maintaining isovolemia.[73] More recently, eculizumab, a C5 inhibitor, has been tried to inhibit complement-mediated intravascular hemolysis, with mixed results.[78–80] If anemia is severe and/or refractory to these treatments, transfusion with antigen-matched, crossmatch-compatible units may be unavoidable.[4,78] Extended antigen matching does not appear to prevent hyperhemolysis.[45]

Transition of care from pediatric to adult

There is no evidence-based guidance currently available to help manage the transition of a patient with SCD from pediatric to adult care.[5] Some institutions continue to perform prophylactic exchanges in adults whom they inherit from pediatrics who are currently asymptomatic but who had been in a prior crisis situation. Studies suggest that if an adult patient has previously had a stroke, the risk of recurrence remains high without treatment,[17] and thus common practice is to continue chronic transfusion/RCE in these patients.[5]

DISCUSSION

Patients with SCD are prone to numerous complications for which RCE may be urgent and lifesaving, including stroke, acute chest syndrome, and sickle hepatopathy. Although a consensus as to protocol details may not be possible, there is general agreement that RCE rather than chronic transfusion is beneficial in limiting iron overload, a target HbS level in the range of 30% (or even lower in some critically ill patients) is desirable, hyperviscosity is to be avoided, pain crisis in the absence of other complications is ordinarily not a sufficient indication to perform a RCE, and periodic RCEs on a long-term maintenance basis may help to prevent recurrences of some conditions to which patients may be prone (e.g., stroke). A prior practice survey indicated that there are variations in the clinical management of these patients. While every case must be evaluated individually, we have presented some common practices.

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CONFLICT OF INTEREST

LB was a consultant for Grifols (research apheresis study). The other authors have disclosed no conflicts of interest.

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