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Red Blood Cells: Exchange, Transfuse, or Deplete

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Keywords

Transfusion · Red blood cell exchange · Erythrocytapheresis · Red blood cell depletion · Sickle cell anemia · Hematopoietic stem cell transplantation · ABO phenotype · Malaria · Babesiosis

Abstract

Erythrocytapheresis, red blood cell (RBC) depletion, and RBC exchange transfusions are apheresis techniques used to rapidly lower the circulating RBC mass or to exchange the patient erythrocyte mass with donor RBC. Automated RBC exchange is performed using an apheresis device, while manual RBC exchange is based on sequential phlebotomies and isovolemic replacement. Compared to simple RBC transfusions, RBC exchange offers several advantages, e.g., a lower risk for iron accumulation and efficient control of pathological erythrocyte populations. Disadvantages are the higher costs of the procedure, the increased use of donor RBC, and the requirement of apheresis devices and trained hospital staff. The most frequent indication for RBC exchange is sickle cell disease (SCD). RBC exchange transfusions are standard treatment in SCD patients with a history of or a risk for acute stroke and are clinical options for other acute complications of SCD. The most common indication for RBC depletion is the removal of donor RBC from the bone marrow grafts in major ABO-incompatible allogeneic hematopoietic stem cell transplantation to avoid immediate hemolysis. Rare indications for RBC exchange are severe infections with intraerythrocytic pathogens such as malaria or babesiosis and severe erythrocytosis or hereditary hemochromatosis where the aim is to rapidly decrease RBC populations or the iron content. However, only few high-quality studies are available looking at the efficacy of RBC exchange in the different disease entities, and treatment is often based on low levels of evidence and should therefore be decided in close collaboration with a transfusion medicine specialist. © 2019 S. Karger AG, Basel

Introduction

Red blood cell (RBC) exchange is the replacement of a patient's RBC with homologous donor RBC and can be performed either manually or automated. It has the advantage over simple transfusions that the patient's RBC are replaced without increasing the hematocrit or exposing the patient to the risk of fluid overload or hyperviscosity [1]. RBC depletion in patients describes a procedure where RBC are removed and replaced with crystalloid or colloid solution, when necessary. This can be performed by different techniques, including sedimentation and apheresis. Erythrocytapheresis is a procedure in which RBC are removed from whole blood during the apheresis procedure and replaced by crystalloid or colloid solution [2]. In contrast, RBC depletion in stem cell products is indicated to avoid immediate hemolysis of the transplanted erythrocytes in the product during transplantation. Although the terms RBC exchange, RBC depletion, and erythrocytapheresis in the medical literature are often used interchangeably, they describe different therapeutic procedures. The main indications and the corre-

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Table 1. Level of evidence for RBC exchange transfusions [2]

Disease	Therapeutic apheresis modality	Level of evidence[1]	Indication category[2]
Sickle cell disease, acute complications			
Acute stroke	RBC exchange	1C	I
Acute chest syndrome	RBC exchange	1C	II
Priapism	RBC exchange	2C	III
Multiorgan failure	RBC exchange	2C	III
Splenic/hepatic sequestration	RBC exchange	2C	III
Sickle cell disease, chronic complications			
Stroke prophylaxis	RBC exchange	1A	I
Pregnancy	RBC exchange	2B	II
Recurrent vaso-occlusive pain crisis	RBC exchange	2B	II
Preoperative management	RBC exchange	2A	III
Allogeneic HSCT			
Minor, prevention PLS	RBC exchange	2C	III
Infections			
Malaria	RBC exchange	2B	III
Babesiosis	RBC exchange	2C	II
Polycythemia vera	Erythrocytapheresis	1B	I
Secondary erythrocytosis	Erythrocytapheresis	1C	III
Hereditary hemochromatosis	Erythrocytapheresis	1B	I
Prevention and treatment of RhD alloimmunization	RBC exchange	2C	III
Erythopoietic porphyria, liver disease	RBC exchange	2C	III

[1] Level of evidence. 1A: strong recommendation, high-quality evidence; 1B: strong recommendation, moderate-quality evidence; 1C: strong recommendation, low or very low-quality evidence; 2A: weak recommendation, high-quality evidence; 2B: weak recommendation, moderate-quality evidence; 2C: weak recommendation, low or very low-quality evidence. [2] Indication category. I: disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment; II: disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment; III: optimum role of apheresis therapy is not established. Decision making should be individualized.

sponding level of evidence for these procedures are listed in Table 1.

Manual RBC exchange implies sequential phlebotomies and isovolemic replacement with crystalloids and donor RBC. It has been frequently used in the past. However, with the introduction of automated cell separators, it has lost some of its importance, but still might be applied in selected situations [3, 4]. Automated RBC exchange is based on an apheresis procedure that separates RBC from other blood components. The RBC are selectively removed and replaced with donor RBC alone and/or colloid/crystalloids solutions [2]. Automated apheresis instruments have substantially facilitated the collection and replacement procedures. Based on clinical data such as body weight, height, gender, age, initial and final hematocrit as well as average replacement fluid hematocrit and the fluid balance, the instruments calculate the exchange volumes [5]. Moreover, automated systems allow to determine the percentage of the patient's remaining erythrocytes (fraction of the remaining cells), which is of particular interest for the calculation of the remaining pathological erythrocytes in patients with sickle cell disease (SCD), but also in malaria and babesiosis. The introduction of the automated RBC exchange procedure has substantially improved the standardization of the exchange procedures and can be performed with similar results on recent apheresis devices.

Table 2 lists the major advantages and disadvantages of the different transfusion methods. Simple transfusions are widely accessible and usually require peripheral venous access only. They can be performed without specialized technical equipment and specifically trained transfusion service staff. Therefore, they are very cost-effective and may be the only available option in many countries and smaller centers. Moreover, not all centers are able to offer RBC exchange transfusions as an emergency treatment, thus simple transfusions may still be the method of choice in these situations.

The main advantage of RBC exchange transfusions is the rapid reduction of pathological erythrocytes without increasing the hematocrit, fluid overload, and a reduced risk of iron accumulation, particularly in patients requiring chronic transfusion therapy. The procedure is faster and is associated with less hemodynamic stress for the

Table 2. Comparison of transfusion methods [21]

	Simple transfusions	Manual RBC exchange	Automated RBC exchange
Availability	Widespread	Widespread	Limited
Staff training	Minimal	Required	Required
Blood consumption	Low	Intermediate	High
Costs	Low	Intermediate	High
Hyperviscosity	Significant	Minimal	Minimal
HbS control	Limited	Intermediate	Best control
Procedure duration	Long	Long	Rapid
Procedure intervals	Short	Intermediate	Long (4-6 weeks)
Iron accumulation	High risk	Intermediate risk	Low risk
Alloimmunization	Lower risk	Intermediate risk	Higher risk
Venous access	Single venous	Double or single venous	High volume (CVC not mandatory)

CVC, central venous catheter.

patients. The main problems with RBC exchange are the high costs and the requirement for equipment and specialized staff. Adequate vascular access might be an issue, especially in patients with long-term exchanges and children of young age. Although most procedures can be performed using peripheral venous access, some patients may require a permanent central venous catheter or an arterio-venous fistula [6–8]. The question is of particular relevance for small pediatric patients, for whom simple transfusions are more frequently used than exchange transfusions, while the contrary is observed in adult patients [9]. RBC exchange transfusions require anticoagulation during the procedure, generally performed using citrate dextrose solutions.

RBC exchange transfusions are associated with a significantly higher blood requirement, because some erythrocytes transfused early are subsequently removed again by the apheresis procedure [9]. As a consequence of the higher blood consumption, some studies suggest a higher risk of alloimmunization and hemolytic transfusion reactions in patients receiving RBC exchange transfusions, although there are conflicting results in this regard [10–12]. In addition to the abovementioned disadvantages of RBC exchange, patients undergoing therapeutic apheresis are at risk for several general side effects of the apheresis procedure.

RBC Exchange in Patients with SCD

Sickle Cell Disease

SCD is an inherited disorder caused by a single mutation in the β-globin gene and encompasses homozygous mutations (S/S) as well as combined hemoglobinopathies such as a heterozygous mutation with a β^0-thalassemia (S/β^0) or other mutations (e.g., HbSC), which may have a similar clinical presentation. It results in the formation of abnormal hemoglobin polymers when deoxygenated [13–15], with decreased deformability and the typical sickle form of the erythrocytes. Sickled erythrocytes possess many unfavorable physiologic properties and induce vascular changes that promote vaso-occlusion, infarction, hemolysis, and inflammation. SCD is a multisystem disorder associated with repetitive episodes of acute illness, organ damage, and often devastating pain attacks [16]. Acute manifestations of SCD are vaso-occlusive crisis, acute pain syndrome, organ infarction, and hemolytic anemia.

Transfusion Therapy in SCD

The current pillars in the treatment of SCD are hydroxyurea and RBC transfusions, which are increasingly used both in pediatric and adult patients [17–19]. The main objectives of RBC transfusions in SCD patients are (1) correction of anemia, (2) reduction of sickle cell hemoglobin (HbS), (3) suppression of defective RBC and thus HbS production, and (4) reduction of hemolysis. Sickle cell blood has an intrinsically increased viscosity, especially if the HbS is deoxygenated and oxygenation is improved at lower hemoglobin levels. Hence, to avoid hyperviscosity the posttransfusion, the hemoglobin value should not exceed the baseline value of the patient. Moreover, aged RBC concentrates might increase storage lesions of the transfused erythrocytes, suggesting that transfusion of fresh blood might be beneficial in patients with SCD [17, 18]. However, data regarding the impact of age for erythrocyte transfusions is somewhat controversial [19, 20]. For a thorough review of transfusion therapy in SCD we refer to the excellent recently published literature and guidelines [21–23].

The potential benefits of RBC transfusions should be carefully balanced against the risks, e.g., iron overload

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and alloimmunization. To reduce the latter risk, all SCD patients should have an extended RBC phenotype (ABO, Rhesus, Kell, MNS–, Duffy–, and Kidd) before initiating transfusion therapy [24]. Many institutions recommend transfusion of ABO compatible, extended Rhesus and Kell antigen matched, leukocyte-depleted RBC products, while others try to consider additional antigens (i.e., MNS–, Duffy–, and Kidd blood groups) at the expense of increased costs. A recent review analyzing the genotyping strategy of the *RHD* and *RHCE* system shows a high frequency of partial Rh antigens in the French population, indicating a benefit of genotyping in patients with newly diagnosed SCD or known high-responders (patients with high probability to develop allo-antibodies due to multiple transfusions [25]. In some countries with high SCD prevalence sickle cell testing is recommended in all blood donors. In patients on chronic transfusion therapy, the transfusion history should be evaluated regularly, at least once a year, and patients should receive appropriate vaccinations against hepatitis B infections [23].

The decision for simple or RBC exchange transfusion requires a close collaboration with the transfusion service. The choice of the appropriate method should take into consideration the risk for hyperviscosity and alloimmunization, the iron balance, the venous access, and the availability of the respective therapy modalities. The final decision often depends on the current hemoglobin level, the steady state hemoglobin level of the patient's preexisting anemia, the percentage of HbS, as well as the general clinical condition [23]. A recent consensus conference held by the American Society for Apheresis on the role of RBC exchange transfusions in the management of patients with SCD evaluated the level of consensus among different specialists in transfusion medicine in SCD patients [26].

In patients with pretransfusion anemia below their individual hemoglobin baseline values, simple transfusions might be the best, easiest, and cheapest option aiming at a posttransfusion hemoglobin value not exceeding 100 g/L, or 10–20 g/L above the baseline level. RBC exchange transfusions are indicated in patients with increased HbS without severe anemia compared to the baseline hemoglobin level. The best posttransfusion hemoglobin level should be analyzed in each individual patient based on the clinical situation and the previous history of SCD-related complications [23].

Acute Stroke

Acute stroke is one of the most devastating complications in SCD patients, often already affecting patients at pediatric age. Without preventive measures, approximately 11% of the patients experience a stroke by 20 years of age [27]. Stroke in SCD is associated with a vasculopathy of the distal carotid and the cerebral arteries, and transcranial duplex sonography of the carotid or cerebral arteries is the method of choice for early detection of the increased vascular flow velocity [28].

RBC transfusions to decrease and maintain a low HbS level are essential for both preventing first and recurrent stroke episodes [29, 30]. In the stroke prevention trial in SCD (STOP), asymptomatic patients with increased mean blood flow as measured by transcranial Doppler sonography were randomized to receive either standard of care or regular transfusions with the aim of maintaining HbS at ≤30% and hemoglobin not higher than 120 g/L before transfusion [29]. Simple RBC transfusions or RBC exchange transfusion were both allowed in this trial. The RBC transfusion strategy resulted in an impressive 92% reduction of the risk of stroke, leading to early termination of the trial. In this regard, it is of interest that although the costs for automated RBC exchange transfusions are considerable, its use leads to cost savings for global health costs due to a reduction of hospitalization days due to SCD-associated complications [31].

Likewise, in children with silent intracerebral infarctions diagnosed on magnetic resonance imaging, chronic transfusion therapy can reduce the risk of secondary strokes [30, 32]. In the Silent Cerebral Infarct Transfusion (SIT) multicenter clinical trial, children with SCD-related silent cerebral infarcts received either standard of care (observation) or chronic transfusion therapy with the aim of maintaining hemoglobin >90 g/L and the HbS ≤30%. The observation group had more secondary episodes, both clinical strokes and new or enlarged silent cerebral infarctions. Moreover, fewer cases of acute vaso-occlusive pain, acute chest syndromes, priapism, and avascular bone necrosis were observed in the transfusion group. Not surprisingly, however, patients on chronic transfusion therapy had a five-fold higher risk of transfusion complications and a fourteen-fold higher risk of iron overload.

Discontinuation of transfusions once established has proved to be difficult. In the STOP II trial children with initially abnormal blood flow who had received at least 30 months of transfusion therapy and had a normalization of cerebral blood flow were randomized to continue or discontinue chronic transfusion therapy [33]. The trial had to be stopped early because of an increased stroke rate in the discontinuation group. A recently published phase III noninferiority study analyzed the switch to hydroxyurea in children on chronic transfusion therapy [34]. Patients with abnormal vascular flow, but without severe vasculopathy, who had received at least 1 year (mean 4 years) of transfusion therapy were randomized to continue transfusion therapy or hydroxyurea at the maximally tolerated dose. Hydroxyurea proved to be noninferior to transfusion therapy and thus can replace transfusions in patients without severe vasculopathy. In line with that,

some patients with normalization of transcranial Doppler velocity might be switched to hydroxyurea provided there is trimestral Doppler follow-up and immediate restart of transfusions in the case of reversion [35].

Taken together, these studies indicate that the current standard of care for prevention of primary and secondary stroke is to maintain HbS at <30% by long-term transfusions both in children and in adult patients. Since RBC exchange transfusions seem to be associated with a lower risk of subsequent stroke episodes, it is the method of choice in patients with acute stroke episodes [36]. Hydroxyurea treatment should be considered for the primary prevention of stroke in children with high transcranial Doppler velocity without severe vasculopathy after at least 1 year of transfusion therapy. RBC transfusions should also be offered to patients with silent cerebral infarctions.

Acute Chest Syndrome and Other SCD Complications

Acute chest syndrome is one of the most common and serious clinical complications and a frequent cause for hospitalization of SCD patients [37]. The full clinical picture, defined by respiratory problems (chest pain, fever, tachypnea, wheezing, or cough) and a pulmonary alveolar infiltrate on a chest X-ray may develop only during hospitalization [37]. Primary treatment involves broad-spectrum antibiotics, bronchodilators, and oxygen support as well as hydroxyurea. RBC transfusions are usually not indicated as first-line treatment but are a therapeutic option in resistant acute chest syndrome. To date, it is not clear whether RBC exchange transfusions are preferable to simple transfusions [38].

The frequency of acute painful crises is individual and reflects the current disease activity. They often cause prolonged hospitalization, as well as important morbidity and increased mortality in patients with SCD. Both in the STOP and the SIT trial, the incidence of acute painful crises was reduced by RBC transfusions. However, hydroxyurea is also very effective in reducing the painful crises and therefore should be considered as first-line therapy. Simple or RBC exchange transfusions should be considered in patients resistant or intolerant to hydroxyurea. Transfusions might be life-saving in acute aplastic crisis, splenic or hepatic sequestration, as well as multiorgan failure. The transfusion can be administered as simple or exchange transfusion depending on the clinical condition of the patient and the pretransfusion hemoglobin values.

Perioperative Management of SCD Patients

Surgery and anesthesia are associated with an increased risk for acute SCD complications. Many sickle cell crises are caused by vascular alterations due to acute or chronic inflammation. Surgical interventions including anesthetic procedures may cause hypotension, local hypoxia, acidosis, and inflammation, thereby triggering sickling of erythrocytes and vaso-occlusive crises in approximately 20% of all patients with a 1-month overall mortality of 1.1% [39]. Therefore, patients with SCD undergoing a surgical intervention should be rigorously hydrated.

The main objective of perioperative management of patients with SCD is to prevent the development of vaso-occlusive crises, stroke, and acute coronary syndromes during and after surgical interventions. There is a broad consensus that patients before elective surgery should receive RBC transfusions. The Transfusions Alternatives Preoperatively in Sickle Cell Disease (TAPS) study clearly demonstrated that preoperative transfusions are associated with an almost four-fold decrease of the risk of perioperative SCD-related complications, in particular acute coronary syndrome [40]. In patients with hemoglobin <90 g/L, simple transfusions are preferred over exchange transfusions aiming at a posttransfusion hemoglobin level of >100 g/L. A randomized controlled study showed that a conservative perioperative management (objective: hemoglobin >100 g/L) was as effective in preventing perioperative complications as an aggressive preoperative transfusion management (objective: HbS < 30%), and the conservative strategy resulted in only half the number of transfusion complications [41].

ABO-Incompatible Hematopoietic Stem Cell Transplantation

Since HLA and ABO antigens are independently inherited, allogeneic hematopoietic stem cell transplantation (HSCT) is routinely performed across the ABO blood group barrier [42, 43]. Three groups of ABO mismatch can be distinguished in HSCT: minor, major, and bidirectional ABO incompatibility. Minor ABO incompatibility, e.g., from an O-type donor to an A-type recipient, is characterized by the ability of donor B-lymphocytes to produce anti-recipient isohemagglutinins. In contrast, major ABO-incompatible HSCT, e.g., from an A-type donor to an O-type recipient, is characterized by the presence of preformed anti-donor isohemagglutinins. In bidirectional ABO incompatibility, e.g., A-type donor to a B-type recipient, a combination of both the major and minor ABO blood group barriers must be overcome [44].

Major ABO-incompatible HSCT may be complicated by severe hemolysis immediately after the infusion of the stem cell product. This immediate hemolysis is caused by preexisting isohemagglutinins in the recipient that bind to and eventually eliminate transplanted donor erythrocytes. Isohemagglutinins can be removed from the recipient prior to HSCT by plasmapheresis and/or by slow infusions of incompatible donor-type RBC [45]. Alterna-

tively, RBC can be removed from the stem cell product by RBC depletion. Stem cell products collected by peripheral blood apheresis usually contain small amounts of donor erythrocytes and, due to the low risk of hemolysis, do not require further processing. In contrast, bone marrow-derived stem cell products contain approximately 25–35% donor erythrocytes. Here, RBC depletion is a standard procedure to avoid hemolysis and can be achieved by density centrifugation (sedimentation) or automatically using an apheresis device [46, 47]. While this technology has been used for many years in major ABO-incompatible bone marrow transplant recipients, it has partially lost its importance in the last decade due to the preferential use of peripheral blood stem cell products. However, with the renewed interest in bone marrow stem cell products in the context of haploidentical HSCT, the processing of ABO-incompatible bone marrow products will be increasingly used again [48]. The choice of the technique largely depends on the center's experience. While historically many centers have used sedimentation for RBC depletion, currently RBC depletion is predominantly done by apheresis as it is less complicated and laborious. Comparison of different depletion technologies has shown that there are slight differences with regard to erythrocyte depletion and the recovery of mononuclear cells [46]. Throughout the years, several apheresis devices have been used to perform RBC depletion prior to stem cell transplantation, achieving robust erythrocyte depletion [49–52].

An important immunohematological complication after minor or bidirectional ABO-incompatible HSCT is delayed hemolysis due to donor-derived passenger lymphocyte syndrome (PLS), which produces antibodies against the patient's remaining erythrocytes [53, 54]. It is characterized by a delayed hemolysis, 2–4 weeks (typically 7–10 days) after HSCT, and occurs in 10–15% of patients after minor ABO-incompatible HSCT. Although rare, it can cause severe hemolysis and may lead to multiorgan failure and eventually death of the patients. Hemolysis persists until the residual recipient RBC are destroyed or replaced by donor type and by transfused RBC. Risk factors for PLS include peripheral blood stem cells, a donor with blood group O and recipient with blood group A, cyclosporine alone as GVHD prophylaxis, and reduced-intensity conditioning.

To avoid PLS, patient erythrocytes can be prophylactically removed by RBC exchange and substituted with O erythrocytes with a goal of less than 35% of residual RBC. This concept has been tested in a single-center study analyzing minor or bidirectional ABO-incompatible HSCT receiving prophylactic RBC exchange transfusions with historical controls [55]. All patients were transplanted with reduced-intensity conditioning and mostly peripheral blood stem cells. To avoid immediate hemolysis, plasma was reduced from bone marrow products. The incidence of PLS was high in the historical control (5/10 patients) and 3 patients died of transplant-related mortality during the period of hemolysis. For this reason, prophylactic RBC exchange transfusions prior to minor or bidirectional ABO-incompatible HSCT were started, replacing 1–1.5 times the patient blood volume with a median of 8 RBC concentrates. Thus, the incidence of severe hemolysis and transplant-related mortality was reduced in minor ABO-incompatible reduced-intensity conditioning HSCT undergoing RBC exchange, while there was no difference in the incidence of GVHD and overall survival.

A second retrospective single-center study analyzed prophylactic RBC exchange transfusion in minor and bidirectional ABO-incompatible HSCT. In contrast to the previous study, prophylactic RBC exchange was performed on day 4 after allogeneic HSCT and only in patients deemed to be high risk according to the presence of predefined risk factors. It is of note that in the RBC exchange group, a higher number of patients received reduced-intensity conditioning regimens due to a change in the transplant practice in this period. The latter study showed a statistically nonsignificant trend towards fewer cases of severe hemolysis in the exchange group, while there was no difference in overall survival. Patients in the RBC exchange group required twice as many RBC transfusions compared to the historical group [56].

However, although there might be a slight improvement in the incidence of severe hemolysis, RBC exchange has not been widely accepted among transplant centers due to practical reasons, the potential side effects in this particular patient population, and the relatively inefficient exchange procedure [53].

RBC Exchange in Infectious Diseases

Malaria

Malaria represents a significant health problem and is associated with a considerable mortality despite adequate treatment. While most cases with acute malaria have relatively low parasitic burden, approximately 10% of the patients are classified as severe cases with a high infectious load [57]. In these cases, the therapeutic aim is to rapidly reduce the parasitic load.

Standard treatment for malaria consists of intravenous antibiotics and supportive care. Adjunct RBC exchange transfusions may have at least 3 beneficial effects: (1) the rapid reduction of parasitemia, (2) improvement in the rheologic properties of the blood and oxygen delivery, and (3) reduction of intravascular hemolysis and cytokines. RBC exchange in malaria patients has been introduced more than 40 years ago for

patients with severe parasitemia (>10%), mostly with plasmodium falciparum. However, to date no randomized clinical trial has ever been performed. Several case reports or smaller case series analyzed the benefit of added RBC exchange with variable results. In 2002 a meta-analysis concluded that there was no benefit of the adjunct therapy and the authors did not recommend the use of RBC exchange in these clinical situations [58]. A more recent case series has looked again at the issue. A single-center study retrospectively analyzed 146 cases of malaria diagnosed at the Vienna University Hospital from 2002 to 2010 [57]. Of these, 16 patients were classified as having severe malaria, and 11 patients were candidates for and 5 patients underwent RBC exchange. The procedure was safe and led to a rapid reduction of the parasitic load. However, a thorough analysis of the efficacy of the procedure was not possible due to the low number of patients.

In 2013 the Center for Disease Control and Prevention (CDC) performed a retrospective analysis, in which 101 patients receiving RBC exchange transfusions were matched to 314 patients not receiving exchange transfusions [59]. Despite faster parasite clearance, there was no evidence for efficacy and, as a consequence, the CDC no longer recommends RBC exchange transfusions as an adjunct procedure for the treatment of malaria due also to the availability of highly efficient antimalarial drugs. Moreover, most of the patients with severe malaria live in countries without medical access to RBC exchange procedures and/or pathogen-free (i.e., *Plasmodium*) blood products.

Babesiosis

Babesiosis is a tick-borne infectious disease caused by intraerythrocytic protozoa [60]. More than 100 different *Babesia* species are known, but mostly they infect wild and domestic animals, while only few cause infections in humans. In the USA, most cases are caused by *Babesia microti*, while in Europe, many cases have been attributed to infection with *Babesia venatorum*. Transmission in humans is mainly caused by ticks, but in some cases it may also arise during pregnancy and as a transfusion-associated event [61]. *Babesia* infect red cells causing hemolysis and hypoxia. The clinical manifestations vary considerably, ranging from subclinical infections to life-threatening acute infections with acute respiratory failures, acute hemolysis, and disseminated intravascular coagulation. Immunocompromised patients are at risk for severe and relapsing or persistent forms of babesiosis and require extensive antibiotic treatments [62].

The primary treatment for babesiosis is an antibiotic combination, e.g., atovaquone and azithromycin or clindamycin and quinine for 7–10 days [63]. Adjunct RBC exchange is indicated in immunocompromised or splenectomized patients with high parasitic load (>10%) and a severe clinical picture consisting of hemolysis, or end-organ disease in the liver, kidney, or lungs [64]. Some reports suggest performing RBC exchange in elderly, pregnant, or pediatric patients with severe babesiosis and in the presence of concomitant disseminated intravascular coagulation or coma. A recent review of blood bank charts from 19 patients receiving RBC exchange transfusions for babesiosis showed that the procedure could reduce the parasitic load by 75%. However, there was no evidence that RBC exchange transfusions could reduce the number of hospital days or mortality [65]. Hence, the available data for adjunct RBC exchange in patients with babesiosis is even less than in patients with malaria, therefore the indication and treatment procedures are poorly defined and mostly deduced from malaria [64, 66]. In patients with post-babesiosis warm-antibody autoimmune hemolytic anemia, RBC exchange does not seem to have an impact on the outcome [67].

Rare Indications

Polycythemia vera is a malignant disease belonging to the myeloproliferative neoplasms. The absolute increase in RBC results in hyperviscosity and tissue hypoxia. Polycythemia vera patients are generally treated with isovolemic phlebotomy and low-dose aspirin, and high-risk patients require cytoreductive therapy. Repetitive phlebotomies gradually lower the disease-associated symptoms and the risk of thromboembolic complications [68]. Some rare patients may present with severe microcirculatory symptoms or hemodynamic instability and require rapid lowering of the hematocrit. Erythrocytapheresis, like isovolemic phlebotomy, corrects the hyperviscosity by lowering the hematocrit value, but removes a higher erythrocyte volume than isovolemic phlebotomy and therefore reduces the time and number of procedures required to achieve the target hematocrit [69–71]. Hence, it may be considered in hemodynamically unstable patients or in patients who require an efficient and fast decrease of red cell mass.

Hereditary hemochromatosis is the most common inherited genetic disease in Europe and is often associated with a mutation in the *HFE* gene, although several others may also be involved [72, 73]. Patients with a homozygous *HFE* mutation are at risk for iron accumulation resulting in chronic iron overload and if untreated, eventually organ damage.

The standard therapy for hereditary hemochromatosis is repetitive isovolemic phlebotomy, which in general efficiently lowers the iron overload. However, erythrocytapheresis removes erythrocytes more efficiently and therefore might offer a possibility to reduce the iron

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overload faster in patients with symptomatic iron overload. Two randomized trials compared phlebotomy and erythrocytapheresis as initial therapy in patients with newly diagnosed hereditary hemochromatosis or during maintenance phase after having reached the therapeutic range [74, 75]. Both studies showed that the number of treatment procedures could be significantly reduced using erythrocytapheresis (9 vs. 27 treatment procedures during initial therapy, and 3.3 vs. 1.9 treatment procedures/year during the maintenance phase). Given the clearly lower number of treatment procedures during the initial phase, the overall costs of the two treatments were similar, while the costs with erythrocytapheresis were higher during maintenance. Another study analyzed asymptomatic blood donors with elevated ferritin levels. Upon confirmation of hereditary hemochromatosis, patients underwent either phlebotomies or erythrocytapheresis [76]. This study did not show a benefit for erythrocytapheresis, but a higher risk of procedural complications.

Summary

Erythrocytapheresis, RBC depletion, and RBC exchange transfusions are efficient therapeutic modalities to lower the hematocrit or to transfuse without increasing the hematocrit or causing iron overload. The most important indications for RBC exchange transfusions are patients with stroke in the setting of SCD. RBC depletion by sedimentation or apheresis is mainly used during processing of ABO-incompatible bone marrow products. Most indications are based on few studies in the literature and decisions have to be based on personal experience, availability of staff and equipment, and the individual patient situation. The transfusion medicine specialists should be integrated early in the decision process.

Disclosure Statement

The authors declare no financial conflicts.

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