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Red blood cell components: Meeting the quantitative and qualitative transfusion needs

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In this issue

Summary

Red blood cell (RBC) transfusion is a very common therapeutic intervention. However, because of multiple recent studies improving our understanding of appropriate transfusion scenarios, the total number of RBC units transfused per year is actually decreasing in the developed world and there are no longer major shortages of RBC products for general use. Nonetheless, there are an increasing number of "special" uses, which can put strains on the blood supply for particular types of products; these may produce shortages of specific types of RBCs or require collections targeting certain types of donors. This review will focus on several broad topics, including providing some examples of "special" settings that require, or could require, special types of RBC products.

Introduction

Red blood cell (RBC) transfusion is one the most common therapeutic interventions in hospitalized patients; in particular, in the United States, approximately 15 million units are transfused annually into approximately 5 million recipients [1]. Nonetheless, due to multiple clinical trials comparing clinical efficacy outcomes of liberal versus restrictive transfusion protocols [e.g., the Transfusion Requirements in Critical Care (TRICC) trial [2]], the total number of RBC units transfused per year is actually decreasing in the United States [3]. Thus, there are no longer major shortages of RBC products for general use. In addition, multiple other studies have been published, or are underway, identifying the best "transfusion trigger" and the best indications for RBC transfusions (e.g., ref. [4]); the conclusions of some of these studies are sure to lead to decreases in RBC utilization in

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certain specific settings. However, other such studies may actually increase the utilization of RBC products [5]. Some of the latter studies may also identify "special" uses, which can put strains on the blood supply for particular types of products; as a result, these may produce shortages of specific types of RBCs or require targeted collections. One example of this issue encompasses using group O, Rh-negative RBCs for uncrossmatched emergency transfusions [6]. Another example involves patients with sickle cell disease, in which Rh-genotypically matched RBCs can be provided to patients with existing alloantibodies recognizing unusual Rh antigens; similarly these types of RBC units can be provided to other such patients to prevent potential alloimmunization [7,8].

In addition, there is a broad consensus that having better RBC products and better indications for RBC transfusions would decrease the number of transfusions required, in general, and in the chronic transfusion setting (e.g., for patients with sickle cell disease or beta-thalassemia), in particular [9]. Decreased numbers of RBC transfusions would also limit a recipient's exposure to various acute and chronic adverse effects [e.g., transfusion-associated acute lung injury (TRALI), alloimmunization, hemolytic transfusion reactions, iron overload, transfusion-transmitted infections].

Therefore, although this review will focus on several broad topics, which are outlined below, there are complex interrelationships between these somewhat artificially separated topics. In addition, this review will identify some examples of "special" settings that require, or could require, special types of RBC products.

Why do we transfuse RBCs?

To provide the appropriate context, it is important to understand the indications for RBC transfusions. The most common, generally accepted, rationale is to improve oxygen delivery and, concomitantly, improve carbon dioxide removal. In addition, RBC transfusions, particularly exchange transfusions, are used to replace or dilute "bad" circulating RBCs, such as in the setting of acute chest syndrome in patients with sickle cell disease. A similar rationale is used in patients with malaria or babesiosis, who, if they present with high levels of parasitemia, are at-risk for significant morbidity and mortality. A final example in this category includes neonates with clinically severe hemolytic disease of the fetus and newborn.

An additional, less appreciated indication for RBC transfusions is to promote hemostasis. Thus, RBC transfusions can improve hemostasis in anemic, thrombocytopenic patients, even in the absence of platelet transfusions, presumably by improving laminar flow and decreasing the width of the "cell-free zone," thereby increasing the probability that the circulating platelets will interact with the vessel wall [10–12]. It is also possible that, following prolonged RBC storage, phosphatidylserine-expressing RBCs and RBC-derived microparticles, may enhance hemostasis (see below). In addition, recent studies highlighted the beneficial role that RBCs play in clot architecture [13,14]. Nonetheless, as will be seen below, this is a two-edged sword, and transfusions of refrigerator storage-damaged RBCs may actually enhance pathological thrombosis.

Finally, chronic RBC transfusions can repress endogenous erythropoiesis, either in settings of ineffective erythropoiesis (e.g., in beta-thalassemia and myelodysplastic syndrome) or those involving production of abnormal RBCs (e.g., in sickle cell disease). Again, this approach can have negative consequences, particularly if the transfused RBCs have a suboptimal lifespan; the major adverse outcome in this regard is chronic iron overload, potentially producing significant organ dysfunction.

Glossary

RBC	red blood cell
TRICC	transfusion requirements in critical care
TRALI	transfusion-related graft-versus-host disease
HLA	human leukocyte antigen(s)
G6PD	glucose-6-phosphate dehydrogenase
CMV	cytomegalovirus

What are the consequences of transfusing RBCs?

Alloimmunization

Although RBC transfusions are therapeutically beneficial, they are not without risk. For example, because it is not yet possible to transfuse patients with genotypically completely identical RBCs (other than in the setting of autologous transfusion or in the very rare case of the donor being an identical twin), a major potential consequence of RBC transfusion is alloimmunization to blood group antigens. Alloimmunization can result in acute or delayed hemolytic transfusion reactions [15], potentially producing significant morbidity and mortality. In addition, it is more difficult, time consuming, and costly to identify compatible RBC units for alloimmunized patients. Other than phenotype/genotype matching, it is not at all clear how to prevent alloimmunization, and the overall phenomenon remains poorly understood; nonetheless, there is general agreement that the probability of alloimmunization increases somewhat in proportion to the number of units a patient receives over their lifetime [16,17]. In addition, abundant evidence in animal models demonstrates that certain types of inflammation in the recipient enhance alloimmunization following RBC transfusion [18]. However, it remains controversial whether this is relevant in humans [16,19–21]. Furthermore, in accord with our understanding of basic immunology, blood group alloantigens need to be presented by appropriate human leukocyte antigens (HLA) of the major histocompatibility