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Transfusion Medicine Problems and Solutions for the Pediatric Hematologist/Oncologist

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Abstract

Blood component transfusion is an integral part of the care of children with oncologic and hematologic conditions. The complexity of transfusion medicine may however lead to challenges for pediatric hematologists/oncologists. In this review, three commonly encountered areas of transfusion medicine are explored. The approach to the investigation and management of suspected platelet refractoriness is reviewed. The unique transfusion related challenges encountered by children undergoing stem cell transplantation are also discussed. Finally, issues arising out of the care of children with hemoglobinopathies are explored, with an emphasis on the incidence of allo- and autoimmunization.

Keywords

Alloimmunization; Blood transfusion; Platelet refractoriness; Review; Sickle Cell Disease; Stem Cell Transplantation; Thalassemia

INTRODUCTION

The transfusion of blood components is a critical part of the care of children with hematologic and oncologic diagnoses. Evidence however suggests discomfort among practitioners when confronted with clinical transfusion medicine problems. Marked deficits in transfusion knowledge have been demonstrated among resident trainees and practicing physicians(1, 2); analogous deficits in pediatric haematologists/oncologists have not been systematically investigated. These deficits may impair patient care; a systematic review found that improper transfusion practices, resource use and patient harm could all be reduced through transfusion medicine educational interventions(3).

In this review, we explore three areas of transfusion medicine relevant to the general pediatric hematologist/oncologist. Platelet refractoriness is commonly encountered; the approach to its investigation and management is explored. Children undergoing hematopoietic stem cell transplantation have unique transfusion challenges which are also

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reviewed. Finally, children undergoing chronic transfusion therapy may develop allo- and autoimmunization; strategies for prevention and management are presented. Readers interested in a more basic introduction to blood components and their uses are referred to several general resources(4, 5).

PLATELET REFRACTORINESS

Platelet transfusion is an important part of the supportive care provided to hematology and oncology patients. However, with few data or guidelines in children, significant variability exists in product selection, dosing and approach to platelet refractoriness(6).

Platelet Products

Platelet products are prepared from either whole blood or apheresis donations(7, 8). In the United States whole blood is separated into components using the Platelet Rich Plasma production method. This results in individual units of platelets with an average volume of 60mL and $0.55\text{--}0.7 \times 10^{11}$ platelets, which can then be transfused either individually or as a pooled product. Apheresis platelet units on the other hand contain an average of 250mL and $3\text{--}4 \times 10^{11}$ platelets and account for 75–95% of platelet products in the United States(7, 9). In Canada and Europe, the Buffy Coat production method is used for whole blood, resulting in a pooled platelet product with an average volume of 325mL and $1.5\text{--}4.5 \times 10^{11}$ platelets.

Dose Response

Platelets are often transfused as prophylaxis against thrombocytopenic bleeding in children; in this situation, the expected increment for a 10mL/kg or 1 PRP unit/10kg transfusion is generally accepted to be $50 \times 10^9/\text{L}$ (6, 10). Platelet refractoriness is defined as the failure to mount an expected rise in the platelet count following a platelet transfusion. This has been standardized using the Corrected Count Increment (CCI) measured 1 hour following a platelet transfusion. The CCI is calculated as follows(11):

$$\frac{[(\text{Platelet value post} - \text{treatment}) - (\text{Platelet value pre} - \text{treatment})] \times \text{BSA}(\text{m}^2)}{\text{Number of platelets transfused} \times 10^{11}}$$

Practically, the platelet content of the transfused product is commonly estimated as $0.7 \times 10^{11}/\text{PRP}$ platelet unit and $4 \times 10^{11}/\text{apheresis}$ platelet unit(12). The Trial to Reduce Alloimmunization to Platelets (TRAP) study group defined refractoriness as a CCI of less than $5 \times 10^9/\text{L}$ measured 1 hour after transfusion of ABO matched, fresh (<72h) platelets on two separate occasions(13). This definition was endorsed by the American Society of Clinical Oncology. Among adults, refractoriness is reported in up to 50% of transfusions and up to 70% of patients receiving multiple transfusions; very little pediatric specific data are available(14).

A general approach to the investigation can be seen in Figure 1. It should be emphasized that concurrent with this approach, effective communication between bedside caregivers and the blood bank/transfusion service is crucial. Such communication ensures the best possible platelet transfusion practice, timely investigation of inadequate response, and appropriate product selection for refractory patients(15).

ABO Groups

Platelet surfaces express several antigen groups: A and B blood group antigens, Human Platelet Antigens (HPA) and Class I Human Leukocyte Antigens (HLA -predominantly HLA-A and HLA-B). The presence of normal anti-A and/or anti-B antibodies in the

recipient may cause a faster clearance of ABO mismatched platelets, resulting in decreased recovery. The definition of platelet refractoriness therefore requires the transfusion of ABO compatible platelets(16–18). Carr and colleagues showed that patients transfused ABO incompatible platelets had higher rates of refractoriness (69% vs 8%) but also developed higher rates of anti-HLA (38% vs 8%) and anti-HPA antibody formation (31% vs 8%)(19). It is also important to remember that platelets are suspended in plasma which contains donor anti-A and/or anti-B antibodies. These antibodies can cause significant, life threatening hemolysis when transfused to a group incompatible recipient (e.g. group O- donor, group A-recipient)(20, 21). Despite the problems associated with ABO mismatched platelets, platelet availability and an excess of group O donors frequently result in out of group transfusions. In a retrospective pediatric cardiac surgery population, 26% of platelet transfusions were ABO incompatible(21).

In order to reduce the risk of hemolysis of recipient red cells from passive anti-A and/or anti-B antibodies, platelets from group O donors can be tested for high titre anti-A/anti-B isohemagglutinins and, if present, excluded from out of group transfusions. Alternatively, plasma reduction of minor mismatched platelet products can be undertaken(22–24). A Biomedical Excellence for Safer Transfusion (BEST) collaborative international study recently reported that nearly 20% of hospital transfusion services surveyed had no policy for how to approach ABO non-identical platelet transfusion(25).

Non-immune causes of refractoriness

Refractoriness to platelet transfusions is often due to non-immune causes; even in the presence of antibodies against HLA or HPA, up to 30% of patients will not respond to antigen matched platelet transfusions(8). Recipient factors which decreased platelet transfusion response in the TRAP study included fever, splenomegaly, bleeding, and Amphotericin treatment (13). The same group also found older (>48h) platelet products and gamma irradiation to be associated with a decreased platelet increment. (26)

HPA and HLA antibodies

Antibodies to human platelet antigens are an infrequent cause of platelet refractoriness, and when present, are often accompanied by anti-HLA (or lymphocytotoxic) antibodies(12, 27). HLA antibodies are usually formed in multiply transfused patients because of exposure to donor white blood cells and the HLA Class I and Class II antigens on their surface(8). The removal or inactivation of white cells from blood components would therefore theoretically decrease rates of alloimmunization and platelet refractoriness. This hypothesis was tested in the large randomized multi-center TRAP trial. The investigators found that both leukofiltration (white cell removal) or UVB radiation (white cell inactivation) resulted in a significant decrease in lymphocytotoxic antibody detection and platelet refractoriness. While none of the 3 treatment groups (leukofiltered pooled PRP, UVB irradiated pooled PRP or leukofiltered apheresis products) were found to be superior over one another, all were superior to the lack of any leukoreduction/inactivation(13).

Prevention of platelet refractoriness

Based on the TRAP trial, the current ASCO recommendation is that all AML patients, and possibly other patient groups who require multiple platelet transfusions, receive leukoreduced platelet (and red cell) transfusions in an effort to prevent platelet alloimmunization. A strong argument can be made for the adoption of universal leukoreduction as a standard of care. UVB irradiation is not clinically available at the current time.

Investigation and Management

If alloimmunization is suspected, three equally effective approaches to management are possible, each with the aim of avoiding antibody-antigen interaction(8, 15). When an anti-HLA antibody is detected in a recipient, donors lacking the corresponding antigen can be sought. With this strategy however, mismatched antigens between donors and recipients may still be present. Another method involves matching donors and recipients for the 4 HLA-A and HLA-B antigens. Unlike antigen avoidance, this strategy requires HLA typing of the recipient and a substantially larger pool of HLA typed donors. It should be remembered that with either of these approaches ABO compatibility may be sacrificed in order to obtain HLA compatibility, potentially leading to poor response even after HLA matched platelet transfusion(28). A third approach with increasing availability involves crossmatching donor platelets with the recipient's serum(8, 27). Whatever the strategy, it is important to note that lymphocytotoxic antibodies are transient in up to 60% of cases; repeat testing and a re-trial of random donor platelets should therefore be attempted after a period of time(15).

STEM CELL TRANSPLANT PATIENTS

Pediatric patients in the stem cell transplant (SCT) period have specific transfusion needs which differ from those of both the general pediatric population and of non-SCT pediatric oncology patients. Among the most important considerations discussed in this review are: indications for cytomegalovirus (CMV)-negative and/or irradiated blood products, potential hemolytic complications, and "rules" for ABO/Rh matching around SCT. Though several of issues discussed have relevance to other patient populations (neonates, congenital immunodeficiencies), their consideration is outside of the scope of this review.

CMV-Negative Blood Products

North American seropositivity for CMV varies regionally from approximately 30% to 80%(29, 30). In CMV-positive individuals, the virus survives within white blood cells, chiefly monocytes(31, 32). Some of these cells remain in cellular blood products (i.e. RBCs and platelets), even when those products are leukoreduced(32). Intact mononuclear cells are not present in frozen plasma preparations(32) but are present in fresh plasma units.

The risk of transfusion associated (TA) CMV infection in an immunocompetent CMV-negative recipient is negligible(31). In allogeneic SCT patients, however, the transfusion of CMV-untested, non-leukoreduced blood products results in rates of TA-CMV infection as high as 30–60%(29). Leukoreduction alone reduces this risk to approximately 2.5%(33, 34), a level which has been described as "CMV safe"(35). Leukoreduction combined with the use of products exclusively from CMV-seronegative donors reduces the risk to approximately 1.5%(33, 34). Though this difference in risk has been a matter of some dispute, a 2005 meta-analysis concluded that the "receipt of CMV-seronegative (compared with leukoreduced) components was associated with a 58% reduction in risk" for CMV infection. The absolute difference was however once again small(34).

Based on these data and due to other advantages, it is now widely accepted that leukoreduction is absolutely required for SCT patients. Indeed, as mentioned above many blood suppliers practice universal leukoreduction. The added utility and cost effectiveness of CMV negative product in the setting of leukoreduction continues to be controversial, requiring balancing limited supplies of CMV-negative product with growing demands for added safety. While the reduction in CMV transmission seems to be real, it is small in absolute terms. Thus, it remains true that CMV-negative products appear to be the safest choice for CMV-negative SCT patients with CMV-negative donors. However, when limited

CMV-negative supplies preclude this option, the next best choice is leukoreduced only, which can still be considered to be safe in terms of CMV infection.

Many hospitals use guidelines like those illustrated in Table I, from the B.C. Children's Hospital in Vancouver, Canada. These guidelines reinforce the points that (i) CMV-negative oncology patients who are candidates for SCT should receive CMV-negative products even before their SCT has begun, and (ii) CMV-negative products are generally reserved for CMV-negative patients who receive stem cells from CMV-negative donors(36).

Irradiated blood products

As noted above, passenger white blood cells (WBCs) are universally present in cellular blood products: leukoreduction reduces but does not remove them entirely. Though donor T cells are usually destroyed by a recipient's immune system, this may not occur in severely immunocompromised recipients. Viable donor T cells may thus proliferate, target recipient HLA antigens and destroy recipient cells in a phenomenon known as transfusion associated graft versus host disease (TA-GVHD). TA-GVHD is usually lethal(37, 38).

The overall risk of TA-GVHD is difficult to quantify, depending on a variety of factors including a population's HLA distribution. Its incidence has been quoted as 1/1,600–7,900 transfusions in Japan, and 1/17,700–39,000 transfusions in the USA(39). The Serious Hazards of Transfusion program in the United Kingdom (SHOT-UK) notes that TA-GVHD comprised 0.8% of serious pediatric transfusion reactions(40).

For at-risk patients, including those undergoing SCT, cellular products must be irradiated. Irradiation damages the DNA of passenger WBCs and prevents their proliferation. Frozen plasma does not need to be irradiated as the freezing/thawing process kills passenger lymphocytes. Irradiation is not without consequence: RBC maximum storage time is reduced from 42 to 28 hours and free potassium is increased. Irradiation does not appear to affect platelet viability. Guidelines for irradiation in pediatric oncology are shown in Table I.

Hemolytic complications of stem cell transplant

SCT recipients are at risk of hemolysis from the transplant itself. This is most commonly seen in the setting of either major or minor ABO-mismatched SCT. In the case of major ABO mismatch, the recipient has antibodies against the graft's ABO group. This may have two consequences: first, hemolysis of donor RBCs due to recipient ABO antibodies may occur. The risk of this can be reduced by RBC-depleting SCT products before infusing or freezing. Second, the presence of high titre anti-ABO antibodies may lead to delayed RBC reconstitution in the recipient, resulting in a rare type of pure red cell aplasia(41–43). While engraftment itself is not delayed, it may take years for the patient to become transfusion-independent(44).

In minor ABO mismatch, plasma in the graft contains antibodies against the recipient, which may cause hemolysis of recipient RBCs. Plasma depletion of SCT product may help in prevention (42). In addition, minor ABO mismatches may result in the passenger lymphocyte syndrome, in which recipients develop severe and even fatal hemolytic anemia one to three weeks after SCT (42, 43, 45). This condition is similar to TA-GVHD, though in passenger lymphocyte syndrome it is passenger B cells which proliferate within the recipient and generate anti-A or anti-B antibodies. The DAT is typically positive, though this may be delayed until several days after hemolysis begins. Conversely some recipients of minor ABO mismatch SCT may develop a positive DAT without significant hemolysis(42, 46). Passenger lymphocyte syndrome occurs in up to approximately 15% of minor or bidirectional mismatch SCT(47, 48). It is more common with peripheral blood than bone marrow stem cell sources, and with non-myeloablative conditioning(43, 45). It has been

rarely reported in cases of mismatch for non-ABO antigens(49). Passenger lymphocyte syndrome requires a high degree of clinical vigilance and aggressive monitoring (e.g., daily LDH, CBC, DAT). In the event of hemolysis, aggressive transfusion support with donor compatible RBCs is warranted.

ABO/Rh matching

Prior to SCT, transfusions should be ABO matched in the usual fashion. Post-SCT, there are two general approaches to ABO matching of RBCs. One may choose RBCs which are compatible with both the donor and the recipient: for example, an A recipient with an AB donor should receive either group A or group O cells. Alternatively, one may always choose type O cells. Unless the donor is group O, this may also facilitate following the patient's RBC engraftment status.

Rh matching is even more straightforward; RBCs for transfusion need only to be compatible with the donor Rh group(50). For example, a patient receiving an Rh positive SCT, irrespective of the recipient's Rh group, may receive Rh positive cells. Note that in this scenario, if the recipient was Rh negative pre-SCT, it may be easier for the blood bank and its Laboratory Information System to continue to provide only Rh negative cells until the patient's Rh group is formally changed.

It is worth noting that other RBC antigen families (non-ABO, non-Rh) do not require routine matching to either recipient or donor. However, should a patient be found to have circulating RBC antibodies, the usual crossmatching must be performed.

Platelets for SCT patients should be chosen to avoid ABO-mediated hemolysis of recipient or donor cells; the plasma containing the platelets should be compatible with both donor and recipient RBCs. The same approach should be used for plasma products.

TRANSFUSION ISSUES IN HEMOGLOBINOPATHIES

Indications for Transfusion

Patients with Sickle Cell Disease (SCD) receive transfusions with RBCs to improve their oxygen carrying capacity, reduce the percentage of RBCs with sickle hemoglobin and to improve vasculopathy. This is accomplished by modulating whole blood viscosity, decreasing sickle cell adhesion and altering the plasma microenvironment. In addition, chronic transfusion can inhibit erythropoiesis thereby decreasing peripheral blood reticulocytes and nucleated RBCs. Different transfusion practices are used for different clinical scenarios in SCD. Options include simple transfusions of 10–15 mL/kg of RBC, manual partial exchange, or either automated or manual single volume exchange transfusion.

Automated exchange, or erythrocytapheresis (ECP), is most often used for acute complications like decompensated acute chest syndrome or evolving stroke. It can also be used as part of a chronic transfusion program for 1) primary and secondary stroke prophylaxis as demonstrated in the STOP I and II trials(51, 52) 2) chronic acute chest syndrome, 3) preparation for major surgical interventions, or 4) multisystem organ failure. A target of 30% of cells containing sickle hemoglobin is usually programmed into the ECP equipment. Controversial indications for simple transfusion include priapism, leg ulcers, pulmonary hypertension, chronic pain and reversing end organ damage.

In the thalassemias and other congenital hemolytic anemias (CHA), the decision to initiate and maintain transfusion is based on different criteria and rationales. Transfusion normalizes hemoglobin concentration, improves oxygen delivery and inhibits erythropoiesis, thus improving the ineffective erythropoiesis associated with CHA. Clinically, simple

transfusions of 10–15 mL/kg at 3–4 week intervals improve growth and development, decrease splenomegaly and prevent the bony changes associated with marrow hyperplasia secondary to ineffective erythropoiesis. Normalization of the hemogram is dramatic, with lower reticulocytes, decreased immature reticulocyte fraction, fewer nucleated RBCs and less anisocytosis and poikilocytosis.

Complications of transfusion should be disclosed to parents and patients before initiating a chronic transfusion program. Iron overload and subsequent organ damage, allo- and autoantibody formation, transfusion-associated infections, acute or delayed hemolytic transfusion reactions (AHTR and DHTR) and immune dysregulation are among the most significant. When indwelling ports or peripheral intravenous catheters are used, central venous line thrombosis can occur. Families should also be aware that ECP involves a 4–6 fold greater number of transfused RBCs per episode, thereby increasing donor exposures(53). On the other hand, ECP is effective in reducing iron overload over time(54).

Alloimmunization in Chronically Transfused Children

The development of RBC alloimmunization is problematic, particularly for patients with multiple alloantibodies. Over time, this can result in the inability to obtain RBCs and consequent morbidity and mortality from AHTR unless alternate therapies such as hydroxyurea or HSCT can be offered.

Alloimmunization occurs more frequently in SCD than in CHA, with rates ranging from 10–40% versus 0.2 – 8% respectively(55, 56). Multiple factors contribute to this discrepancy, including RBC antigenic differences between predominantly Caucasian donors and recipients, the “foreignness” of the RBCs resulting from antigen discrepancies, the degree of antigenic exposure, concomitant acute inflammation at time of transfusion, HLA type, co-inheritance of certain HLA-specific genes, and immune function of the recipient at the time of transfusion (Figure 2).

Turning to potentially modifiable factors, among patients with CHA, rates of alloimmunization may be increased by splenectomy and decreased by the exclusive use of leukoreduced blood (57). While all transfusion services honor the major blood group antigens (ABO and D[Rh]) when matching blood products, matching for minor blood group antigens (Ee, Cc, Kk, Fya, Jka, Jkb, others) is not always possible due to limitations in transfusion product inventory(58). Using older serological methods, prospective matching has been found to reduce alloantibody development from 3 to 0.5% in 63 children in STOP matched for Cc, Ee, D and K(55, 59); this phenomena has been confirmed in concept by other studies(60, 61). Complicating matters further, some recipients never develop RBC antibodies despite hundreds of transfusions. Indeed, identifying the responder versus non-responder phenotype would greatly improve the assignment of better matched donor to recipient RBC transfusions, preserving rare inventory for those at highest risk or those who have already developed one or more antibodies.

There appears to be a higher rate of RBC autoantibodies among patients with SCD (4–8%) and CHA (1–3%) who have pre-existing alloantibodies(62). While the clinical significance of autoantibody development remains uncharacterized, its presence makes serological crossmatching very difficult. DHTR also appears to be more prevalent in patients with pre-existing alloantibody; the pathophysiology of this phenomenon is beyond this brief review. Molecular RBC phenotyping of donors and recipients may, in the future, make prospective RBC matching more precise but cannot be recommended without FDA approval of the method(s), evidence of efficacy and identification of specific recipient groups that would most benefit from the testing and blood inventory management required.

A critical issue that faces those caring for SCD patients in urban areas arises when patients are seen at multiple facilities, including ones where the transfusion history and presence of a pre-existing RBC allo- or autoantibody is unrecognized. As these antibodies wane over time from antigenic exposure, patients may present without serological evidence of an alloantibody and receive antigenically positive RBCs, stimulating a brisk anamnestic response and leading to either AHTR or DHTRs. National or regional patient registries with timely serological information and more widespread use of Medic-Alert identification systems should therefore be instituted.

CONCLUSION

Transfusion medicine impacts upon patients in a multitude of ways; the above discussion highlights only three areas that the hematologist/oncologist may encounter. Perhaps the main take home point is thus the importance of effective communication between caregivers and transfusion services, which ensures the prompt and appropriate investigation and management of transfusion related issues. Such communication is therefore essential to the delivery of high quality care to patients.

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Figure 1.

Figure 2.

Table 1

Guidelines for provision of irradiated and/or CMV-negative cellular blood products in pediatric hematology and oncology patients *

Diagnosis	<u>Special transfusion requirements</u>	
	Irradiated	CMV-negative
New oncology patient with unconfirmed diagnosis	✓	✓
Allogeneic SCT or on SCT list	✓	✓**
Autologous SCT	✓	
ALL – standard risk	✓	
ALL – high risk	✓	✓***
ALL – relapsed	✓	✓***
AML	✓	✓***
Aplastic anemia/undiagnosed pancytopenia	✓	✓***
Burkitt's lymphoma/leukemia	✓	✓***
Hodgkin lymphoma	✓	
Non-Hodgkin lymphoma	✓	
Solid tumors	✓	
Histiocytosis X	✓	

* All such patients should receive leukoreduced red blood cell and platelet products;

** If both donor and recipient are CMV-negative or CMV status is unknown;

*** If CMV-negative or CMV status unknown; Adapted from Wadsworth L, Au N, Herd S. B.C. Children's Hospital special requirements for blood components, revised 2004. B.C. Children's Hospital, Vancouver, Canada