Review of the literature on allogeneic red blood cell and plasma transfusions in children

Heather A. Hume,* MD, FRCPC; Jonathan B. Kronick, MD, PhD, FRCPC; Victor S. Blanchette, MD, FRCP(UK), FRCPC

Abstract

Objective: To review the published research on allogeneic red blood cell (RBC) and plasma transfusions in children over 4 months of age.

Evidence: Search of MEDLINE database between January 1966 and July 1996 and manual search of relevant textbooks. Articles addressing guidelines for administration, evaluation of appropriateness of therapy, utilization and indications for transfusion were selected for review.

Results: Most publications containing guidelines for RBC and plasma transfusions do not cover pediatric patients. We identified 18 articles that addressed blood utilization or appropriateness of RBC or plasma transfusions in children; only 6 were randomized or controlled trials. These, as well as observational studies are reviewed.

Conclusion: There is a paucity of controlled data on which to base transfusion decisions for pediatric patients.

A review of existing recommendations and guidelines was carried out to assist in the development of guidelines for the transfusion of red blood cells (RBCs) and plasma.1,2 It revealed that published reports primarily address blood transfusions in adults. Therefore, a further review was performed to identify evidence-based reports on allogeneic RBC and plasma transfusions in children. These formed the basis for the development of guidelines for RBC and plasma transfusions in children.

Methods

General systematic review

The literature search began with the results of the search and selection process carried out for the development of guidelines for RBC and plasma transfusions in adults.1,2 Those citations were reviewed by 1 of the authors to determine if they were applicable to pediatric transfusions. If this could not be clearly determined from the title, the abstract was reviewed.

This review addresses RBC and plasma transfusions in children over 4 months of age. Readers interested in neonatal transfusions are referred to recent reviews and guidelines.3,4 The review does not address autologous blood transfusions, the complications of blood transfusions or transfusions for children requiring long-term support (e.g., patients with thalassemia, sickle-cell anemia or diamond blackfan anemia).

Pediatric systematic review

An additional search of MEDLINE from January 1966 to July 1996 was constructed using the medical subject headings (MeSHs) erythrocyte transfu-
sion, blood transfusion or blood component transfusion combined with child as keywords and text words in the titles and abstracts of all citations. Animal studies and studies addressing newborns under 1 month old were excluded.

In addition, MEDLINE searches for the same period were conducted using the MeSHs blood transfusion, blood component transfusion, erythrocyte transfusion, fresh frozen plasma, blood transfusion practice and transfusion practices combined with each of the following journal titles: Journal of Pediatrics, Pediatrics, Archives of Diseases in Childhood, Pediatric Research and, for 1979–96, the American Journal of Pediatric Hematology/Oncology. The abstracts of each of the citations retrieved by this search were reviewed by 1 of the authors.

Finally the bibliographies of relevant chapters of two pediatric textbooks7,8 and two transfusion medicine textbooks3,9 were searched.

Criteria

Publications retrieved by these search strategies were selected for inclusion in this review if they addressed patients over 4 months and under 18 years of age and 1 of the following aspects of RBC or plasma transfusion therapy:

- guidelines for administration (a guideline was defined as a manuscript which made specific recommendations about transfusion therapy and included a review of the literature)
- studies evaluating the appropriateness of transfusion therapy
- reports of utilization (either aggregate or in specific clinical settings)
- studies (observational or controlled) addressing indications for transfusion.

All original studies addressing the indications for transfusion were reviewed by at least 2 of the authors.

Results

Previously published guidelines for RBC and plasma transfusion

The general systematic review of the literature revealed 13 articles (1 with an accompanying background article) with guidelines for the administration of blood components and 1 additional article with guidelines for conducting blood utilization reviews.12–26 (Transfusion guidelines and audit criteria, although similar, are not identical. Guidelines are developed to help a practitioner decide whether to administer a transfusion, whereas audit criteria are designed to permit rapid distinction, either prospectively or retrospectively, between a transfusion episode that is likely appropriate and one that is likely inappropriate.) The pediatric systematic review did not uncover any additional guideline articles fulfilling the definition, although two publications related to blood utilization reviews that addressed pediatric transfusions were identified.27,28

The recommendations of the guideline articles and an evaluation of the methods used to develop these guidelines are reviewed in a companion article.2 Of the 13 guideline publications, 6 do not indicate whether they address pediatric patients,12,13,15–18 4 do not necessarily apply to children,19–22 1 addresses coronary artery bypass surgery only,23 1 addresses obstetric and gynecologic patients only24 and 1 explicitly states that it addresses both adult and pediatric patients25 (Table 1).

Pediatric transfusions are addressed in the most detail (Table 2) by the American Association of Blood Banks (AABB) to help institutions perform audits (blood utilization reviews).26 Their criteria include 3 sections for RBC transfusions: for pediatric patients under 4 months of age; for pediatric patients over 4 months of age; and for adult patients. Audit criteria for fresh-frozen plasma (FFP) transfusions were the same for all 3 groups. A background document discussing the rationale for the neonatal and pediatric criteria was published,27 although a description of how the literature review was conducted and evaluated was not included. An evaluation of the acceptability of the neonatal and pediatric audit criteria to the AABB membership was published in 1993.28 In general, members

<table>
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<tr>
<th>Table 1: Summary of guidelines of the British Committee for Standards in Haematology25</th>
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<tbody>
<tr>
<td><strong>Summary</strong></td>
</tr>
<tr>
<td>Fresh-frozen plasma (FFP) should only be use to treat bleeding episodes or prepare patients for surgery in certain defined situations.</td>
</tr>
<tr>
<td><strong>Definite indications for the use of FFP</strong></td>
</tr>
<tr>
<td>1. Replacement of single coagulation factor deficiencies, where a specific or combined factor concentrate is unavailable</td>
</tr>
<tr>
<td>2. Immediate reversal of warfarin effect</td>
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<tr>
<td>3. Acute disseminated intravascular coagulation</td>
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<tr>
<td>4. Thrombotic thrombocytopenic purpura</td>
</tr>
<tr>
<td><strong>Conditional uses (FFP only indicated in the presence of bleeding and disturbed coagulation)</strong></td>
</tr>
<tr>
<td>1. Massive transfusion</td>
</tr>
<tr>
<td>2. Liver disease</td>
</tr>
<tr>
<td>3. Cardiopulmonary bypass surgery</td>
</tr>
<tr>
<td>4. Special pediatric indications*</td>
</tr>
<tr>
<td><strong>No justification for the use of FFP</strong></td>
</tr>
<tr>
<td>1. Hypovolemia</td>
</tr>
<tr>
<td>2. Plasma exchange procedures</td>
</tr>
<tr>
<td>3. “Formula” replacement</td>
</tr>
<tr>
<td>4. Nutritional support</td>
</tr>
<tr>
<td>5. Treatment of immunodeficiency states</td>
</tr>
</tbody>
</table>

* These are discussed further in the publication.26 They apply mainly to the use of FFP in neonates with disseminated intravascular coagulation, necrotizing enterocolitis or both.
agreed with the criteria for RBC and FFP transfusion, although there was some disagreement over the hemoglobin concentrations [Hb] suggested as “transfusion triggers” and modifications were frequently necessary to permit local use. (Note: FFP and frozen plasma (FP) are defined in the guidelines accompanying this review.)

In addition, the Canadian Red Cross Blood Transfusion Centres in Toronto, Vancouver and Montreal have published pamphlets or pocket cards with blood transfusion guidelines, although they do not make specific reference to pediatric patients.

In summary, except for the AABB, most associations developing transfusion guidelines have either not indicated whether their guidelines are intended to address pediatric as well as adult blood transfusion recipients or have stated that the guidelines may not be applicable to young children.

The appropriateness of RBC and plasma transfusion

Beginning in the early 1980s, studies evaluating the appropriateness of blood transfusion practices began to appear. In most of these, definitions of appropriateness were determined locally by the investigators. A critical review of 9 such studies determined that reported appropriateness rates varied widely (from greater than 97% to about 50% of RBC transfusions). The major factor in this variation appeared to be marked differences in the criteria used to define an appropriate transfusion.

We identified only 2 studies specifically addressing the appropriateness of pediatric blood transfusion practices. In 1, the criteria used were not explicitly stated as the purpose of this report was to describe the method of the transfusion review using a computer database. However, the authors did report that the charts of 11% of RBC transfusion episodes required further review after being identified as possibly inappropriate.

The second study used explicit algorithmic criteria, described in the article, to review transfusion practices in patients aged 4 months to 21 years in a tertiary-care pediatric hospital in 1985. The criteria were developed from published research, although the details of the literature search were not described. Of 138 RBC transfusions reviewed, 80% were considered to be appropriate, 12% of “unknown benefit–risk ratio,” 6% inappropriate, and in 3% of cases the charts contained insufficient information to classify the transfusions. Those considered of unknown benefit–risk ratio were mainly of RBC transfusions administered to pre- or postoperative patients or patients undergoing chemo- or radiotherapy and whose [Hb] was 80–100 g/L. Of 246 FP transfusions reviewed, only 42% were considered appropriate; 32% of “unknown benefit–risk ratio,” 18% inappropriate, and in 8% of cases there was insufficient information in the medical chart to permit an evaluation. The majority of FP transfusions considered of unknown benefit–risk ratio were administered to patients weighing 25 kg or less and in whom blood losses replaced by transfusions represented less than 50% of the patient’s total blood volume. Most RBC and FP transfusions considered to be of unknown benefit–risk ratio would likely be considered inappropriate if reviewed in 1997 using the criteria outlined in the accompanying guidelines.

Two other publications reporting blood losses and transfusion requirements for the surgical correction of craniosynostosis in infants included an evaluation of the appropriateness of the observed transfusion practices. The 2 groups of investigators, each using their own appropriateness criteria (described in the reports), estimated that excessive intraoperative and postoperative RBC transfusions were administered to about 30% and 70% of patients.

These observations suggest that, at least in the 1980s, pediatric transfusion practice was often inappropriate. No more recent studies evaluating the appropriateness of transfusion practices in children were found.

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**Table 2: Blood utilization review guidelines**

**Pediatric guidelines for RBC transfusion**
The indications for transfusion of RBCs to patients over 4 months of age may include:
- Preoperative hemoglobin concentration ([Hb]) < 80 g/L when alternative therapy is not available or postoperative [Hb] < 80 g/L with signs or symptoms of anemia
- Acute loss of 15% or more of blood volume or signs and symptoms of hypovolemia that is not responsive to fluid administration
- [Hb] < 130 g/L and severe cardiopulmonary disease
- [Hb] < 80 g/L in patients receiving chemotherapy or radiotherapy
- [Hb] < 80 g/L in patients with chronic anemia without expected response to medical therapy and signs or symptoms of anemia
- Complications of sickle-cell disease, such as cerebrovascular accident or acute chest syndrome, or for preoperative preparation
- Chronic transfusion regimen for thalassemia or other RBC

**Pediatric and adult guidelines for FFP transfusion**
Prothrombin time (PT) and partial thromboplastin time (PTT) should be measured before decision. Appropriate criteria for FFP transfusion may include:
- PT and PTT > 1.5 times the mean normal value in a nonbleeding patient scheduled for surgery or invasive procedure
- Diffuse microvascular bleeding, transfusion of 1 blood volume or more and PT and PTT > 1.5 times the mean normal value or not yet available
- Warfarin overdose with major bleeding or impending surgery

Other indications may include thrombotic thrombocytopenic purpura, emergency reversal of warfarin and treatment of plasma anticoagulant deficiencies, such as protein C, protein S, or antithrombin III when specific therapy is not available or advisable.

Source: Adapted from Stehling et al.11
**Blood utilization**

Several studies addressing blood utilization at a national or regional level have been reported; however, transfusions administered to children are either not included or not reported separately. In a survey of blood utilization in the United States, the percentage of whole blood or RBC transfusions administered as “pediatric” units represented 0.5% and 0.8% of all such transfusions in 1989 and 1992, respectively. The percentage of transfusions actually administered to children was not reported.

We identified 14 articles that describe allogeneic blood utilization in specific pediatric settings in 1 or a small number of institutions. Such reports cannot be used to develop evidence-based guidelines, particularly as several studies have shown that there is significant variability in transfusion practices for a given clinical setting among different institutions. The data from these reports are nevertheless of interest, particularly if the reporting institution’s transfusion protocol is described, in that it allows a basis for comparison of practices between institutions and an estimation of the impact of these procedures or illnesses on the blood bank. The clinical situations most commonly reported were orthotopic liver transplantation, surgical correction of craniosynostosis and open heart surgery for congenital cardiac defects (including 2 publications addressing the use of bloodless techniques).

**Allogeneic RBC transfusion in children**

We found only 3 randomized, controlled trials of allogeneic RBC blood transfusion therapy in children (excluding neonates or very young infants and patients with thalassemia or sickle-cell disease). In addition, 4 non-randomized studies addressing the indications for RBC transfusion were identified.

In the 1970s, Australian investigators conducted 2 randomized controlled trials studying the effect of RBC transfusion on the duration of neutropenia in children with malignancies. The patients were chosen at random to receive RBC transfusion to maintain a [Hb] of either 100–120 g/L or 140–160 g/L. In both studies children whose [Hb] was maintained at 140–160 g/L had a significantly more rapid rise in neutrophil count, a lower incidence of infection (defined as a fever with or without a proven infection) and a lower incidence of interruption of chemotherapy. The investigators hypothesized that suppression of erythropoiesis by hypertransfusion led to a greater influx of cells from the pluripotent stem cell compartment into the granulocytic pathway. Although these findings are interesting, given the risk associated with transfusion therapy and the potential hypercoaguable state associated with malignant disease (thus decreasing willingness to maintain [Hb] > 160 g/L), it is unlikely that they influenced transfusion practices significantly. These studies are no longer relevant as the intensity of chemotherapy has increased dramatically in recent years, and the study goals (i.e., decreased duration of neutropenia) can now be attained, if necessary, through the use of granulocyte colony-stimulating factor.

Two studies, 1 of which was a randomized, controlled clinical trial addressed the issue of blood transfusion in African children with anemia and malaria. In both, the investigators discuss the combined problems in Africa of the frequency of severe anemia associated with malaria in young children, the shortage of blood for transfusion and the high risk of transfusion-transmitted HIV infection. In this setting, it is important to determine if transfusion will actually decrease mortality.

In the randomized, controlled trial, 116 children, aged 2 months to 6 years, with malaria and hematocrit levels between 0.12 and 0.17, but without congestive heart failure or pneumonia were randomly chosen to receive either treatment for malaria and hookworm alone (n = 56) or in addition a whole blood transfusion (n = 60). Mean hematocrit at admission was 0.140 in the transfusion group and 0.144 in the no-transfusion group. There was a trend toward more hospital admissions and deaths in the no-transfusion group, although the differences were not statistically significant and the 95% confidence intervals (CI) were wide (in those with complete follow-up, 2/53 deaths in the no-transfusion group and 1/53 deaths in the transfusion group). The authors concluded that a larger trial is necessary to clarify this issue.

The other was a surveillance study in which data were collected over approximately 12 months on all children under 12 years of age (n = 2433) admitted to the pediatric ward of a Kenyan hospital. Transfusions (whole blood) were administered according to routine practice and availability. Overall, 29% (684) of patients had severe anemia ([Hb] less than 50 g/L) and 20% (483) of patients received blood transfusions. Based on laboratory criteria alone, children with [Hb] less than 39 g/L who were transfused had a lower mortality than children who were not transfused, but this finding applied only to children transfused on the day of admission (odds ratio (OR) 0.30, 95% CI 0.14 to 0.61) or the day after admission (OR 0.37, 95% CI 0.14 to 1.0). Based on a combination of laboratory and clinical criteria, children with clinical signs of respiratory distress and [Hb] less than 47 g/L who were transfused had a lower mortality than those who were not (OR 0.19, 95% CI 0.09 to 0.41).
Morbidity was not addressed in this report. Among children without respiratory distress, there was no association between receipt of blood transfusion and mortality, irrespective of [Hb] on admission. Based on these observations, the authors recommend that, in their setting, blood transfusions be administered to children with [Hb] less than 50 g/L and congestive heart failure or respiratory distress and to those without clinical complications and [Hb] less than 30 g/L.

Two studies addressed the use of RBC transfusions to improve tissue oxygen delivery (DO2) and consumption (VO2) in children with septic shock. Previous studies in children and adults demonstrated that VO2 is directly related to survival in septic shock, and in 2 studies of adults with septic shock VO2 was found to be dependent on DO2. Lucking and colleagues studied 8 RBC transfusions of 10–15 mL/kg given to 7 children (ages 4 months to 15 years, mean age 31 months) with hyperdynamic septic shock. All had [Hb] less than 110 g/L (mean 93 g/L), low tissue oxygen extraction rates (below 24%) and low VO2 (less than 180 mL/min per square metre). The RBC transfusions led to statistically significant increases in both DO2 (from 636 ± 167 to 828 ± 266 mL/min per square metre) and VO2 (from 112 ± 36 to 157 ± 60 mL/min per square metre) without significant changes in either cardiac output or oxygen extraction rate. The authors suggested that the increase in VO2 was both clinically and statistically significant. Of the 7 children, 6 survived.

However, in a study carried out in a similar setting, Mink and colleagues did not observe a beneficial effect of RBC transfusion. Hemodynamic measurements before and after RBC transfusion (8–10 mL/kg) were performed in 8 children (ages 2 months to 6 years, mean age 32 months) with septic shock and mild anemia (mean [Hb] 102 g/L). DO2 increased (from 599 ± 65 to 818 ± 189 mL/min per square metre) and the oxygen extraction rate decreased from 28% to 22%. The authors concluded that attempts to increase VO2 in children with septic shock should focus on methods other than RBC transfusion. A similar result, i.e., an absence of increase in VO2 following RBC transfusion, was also found by a third group of investigators studying septic shock in adults. Thus the effect of RBC transfusions on morbidity and mortality in children with septic shock and mild to moderate anemia remains to be defined.

Seear and colleagues studied the relation between DO2 and VO2 after cardiac bypass surgery. Of 15 children (ages 2.5 to 8 years), 8 received RBC transfusions of 10–15 mL/kg and 7 received inotropes (adrenaline infusion). Therapy was not selected at random, but according to clinical judgement. All children were well resuscitated at the time of study. The exact nature of the cardiac defects and surgeries were not described. The mean pre and post-transfusion [Hb] of the transfused children were 84 g/L and 99 g/L, respectively. RBC transfusion significantly increased DO2 (from 20.5 ± 6.4 to 26.2 ± 7.1 mL/min per kilogram) but did not alter VO2. Adrenaline infusions increased both VO2 and DO2. These investigators discussed the potential for measurement error in determining VO2 and cautioned against the use of potentially dangerous therapies, i.e., ionotropes to raise VO2 in ill children. Although not specifically discussed by the authors, these results do not support the use of RBC transfusions to raise VO2 in this setting.

**Plasma transfusion in children**

We found only 3 controlled clinical trials addressing the use of FFP in children beyond the neonatal period: examined the use of FFP for pediatric hemolytic–uremic syndrome (HUS); in the other, FFP was used as 1 of the components of reconstituted whole blood to replace blood losses following open heart surgery. We also identified review articles and observational studies that addressed FFP use for congenital deficiencies of hemostatic or anticoagulation proteins, for congenital C1 esterase inhibitor deficiency, for meningococcal septicemia, for pediatric HUS and for acquired antithrombin III deficiency.

Most studies specifically addressing the use of FFP in childhood are concerned with its use in the treatment of HUS, which is characterized by thrombocytopenia, microangiopathic hemolytic anemia and acute renal failure. In childhood, 90% of cases follow a diarrheal prodrome (classic HUS) and are linked to enterohemorrhagic *E. coli* (e.g., *E. coli* 0157:H7) infections. The remaining 10% of childhood cases are either idiopathic (and sometimes familial) or secondary to a variety of conditions, such as infections, malignancies or drugs. The clinical and pathologic characteristics of HUS are very similar to, and occasionally difficult to distinguish from thrombotic thrombocytopenic purpura (TTP), a disorder more often occurring in adults, in which fever and central nervous system involvement are more frequent and mortality is greater. Daily plasma exchange (or exchange using cryosupernatant) is now considered to be the treatment of choice for adult TTP.

In a study conducted by Loirat and colleagues, 79 children with HUS (mean age 28 months) were randomly assigned either to a group receiving plasma infusions (*n* = 39) or to a control group treated conservatively (*n* = 40). The duration of hemolysis, thrombocytopenia and anuria was similar in the 2 groups. Serum creatinine levels were similar after 1 month, but were higher in the control group at 3 months (66 ± 28 µmol/L compared with 49 ±
14 µmol/L in the plasma group; \( p < 0.02 \) and at 6 months (63 ± 21 µmol/L compared with 48 ± 13 µmol/L; \( p < 0.0005 \)). The prevalence of proteinuria was also higher in the control group at the 6-month follow-up. However, differences were no longer significant after 1 year. Renal tissue was examined in 54 cases (27 from each group). Diffuse cortical necrosis was present in 7 members of the control group, but was absent from the plasma group (\( p < 0.02 \)). Taking into consideration the higher serum creatinine levels, the higher prevalence of proteinuria during the first 6 months of follow-up and the greater prevalence of diffuse cortical necrosis in the control group compared with the plasma group, these investigators concluded that plasma infusions were beneficial.

A second randomized, controlled trial evaluating the role of FFP infusions in the treatment of classical childhood HUS was performed by Rizzoni and colleagues.\(^{66}\) They studied 32 children, ranging in age from 4 months to 6 years: 17 were in the study group (FFP administered daily until normal platelet count achieved) and 15 in the control group (no FFP given). There were no significance differences between the 2 groups for any of the clinical or laboratory characteristics studied. The only difference noted involved the presence on follow-up renal biopsies of vascular changes on electron microscopy: none were seen in 7 biopsies performed in the study group, whereas thickening of the lamina rara interna and arteriolar damage was present in 5 of 7 biopsies performed in children in the control group. These investigators concluded that FFP infusions did not significantly alter the short- and medium-term clinical outcome of classical childhood HUS and that a longer follow-up period would be necessary to determine if the renal vascular changes demonstrated by electron microscopy in children who did not receive FFP would prove to be clinically relevant.

Thus these 2 groups of researchers drew different conclusions on the beneficial effects of FFP for HUS despite similar outcomes. In light of this, a third group of investigators\(^{68}\) reviewed retrospectively the charts of 61 children treated for HUS at their institution between 1979 and 1988.\(^{68}\) Of these, 36 patients had classic HUS severe enough to warrant hemodialysis: 18 received plasma therapy and 18 did not. The 2 groups were similar with regard to the severity of HUS, the duration of hospital stay, the duration of renal dysfunction and the incidence of disease-related complications. At discharge, the prevalence of hypertension was higher in the plasma therapy group than in the control group. These investigators concluded, as have authors of more recent reviews, that plasma therapy for classic pediatric HUS does not provide sufficient benefit to outweigh the potential risks of this therapy.\(^{68}\)

No study specifically addressing the role of FFP in atypical (nondiarrhea-associated) HUS in childhood was identified, although at least 1 study has retrospectively evaluated the use of plasma exchange with purified protein fraction followed by a FFP transfusion.\(^{69}\)

Manno and colleagues\(^{67}\) studied the influence of the type of blood transfused immediately following open heart surgery in children on the volume of postoperative blood loss. In a prospective, controlled (but not randomized) study in 161 children, they compared the use of whole blood less than 6 hours old, whole blood 24–48 hours old and reconstituted whole blood, i.e., RBCs, FFP and platelet concentrates. They found that the transfusion of whole blood was associated with significantly less postoperative blood loss than the transfusion of blood components in children under 2 years of age who underwent complex cardiac surgery (56–62 mL/kg versus 110 mL/kg over 24 hours, respectively). Blood losses were not significantly different for the different transfusion strategies for other groups of children.

In light of these findings, Petäjä and co-workers\(^{47}\) conducted a retrospective review of bleeding complications and the use of blood components after open heart surgery in 73 infants under 1 year of age. Although this study cannot be directly compared with that of Manno and colleagues,\(^{67}\) as patient characteristics and management were not the same and blood losses were calculated only for the first 6 hours postoperatively (versus 24 hours in Manno’s study), they did find lower postoperative blood losses (3 to 51 mL/kg over the first 6 postoperative hours). These investigators concluded that such losses could be acceptably managed with blood component therapy (as opposed to the use of relatively fresh whole blood). These reports do not provide sufficient evidence to generate clear practice guidelines for replacement of blood losses following open heart surgery in children.

One study\(^{71}\) addressed the role of FFP in the treatment of meningococcemia, a disorder often associated with coagulopathy. It was a retrospective analysis of charts of patients aged 1 month to 80 years (mean age of 11 years) in 2 centres in Norway, conducted to determine the predictors of a fatal outcome in severe meningococcemia. Demographic and clinical variables were studied in a multiple regression analysis, and the effect of various therapeutic components was then assessed by adding them separately to the significant clinical variables. The administration of blood or plasma (as opposed to colloids alone) was found to be significantly associated with a fatal outcome. According to the authors, this was not due simply to an association between prognosis and the administration of plasma. They recommended avoiding the administration of FFP to patients with meningococcal sepsis. The retrospective na-
ture of this study and the lack of standardization of care in the 2 study centres over time make it difficult to draw firm conclusions, although the data do suggest that FFP was of no obvious benefit.

We did not find any other studies addressing the use of FFP in children with acute bleeding. In spite of the lack of studies, experts agree that the use of FFP as a volume expander alone — in the absence of clinically significant coagulation factor deficiency — or prophylactically in the setting of massive transfusion is contraindicated in the child as it is in adults.7,8,25,26,72 This approach seems reasonable for children 6 months of age or older as the levels of coagulation factors as well as the levels of natural inhibitors of coagulation generally approach adult levels by this time.73 Infants under 6 months of age have relatively lower levels of the vitamin K-dependent coagulation factors (FII, FVII, FIX, FX) as well as the 4 contact factors and the vitamin K-dependent inhibitors of coagulation. Prothrombin time (PT) and activated partial thromboplastin time (APTT) are correspondingly prolonged (Table 3). Thus, it is likely that the factors are more rapidly depleted in situations such as acute hemorrhage or disseminated intravascular coagulation, and it may be reasonable to administer plasma transfusion relatively sooner in infants under 6 months of age than in older infants or children.

FFP has been used to treat congenital deficiencies of hemostatic or anticoagulant proteins. More appropriate alternatives now exist for most of these disorders and, as new treatments are rapidly becoming available, recommendations for treatment are constantly changing.74 The care of children with these disorders should be supervised by a physician with expertise in pediatric hemostasis or thrombosis. Available alternatives are listed in Table 3 of the guidelines.7

The potential of FFP to normalize antithrombin III (ATIII) levels in children with acute lymphoblastic leukemia receiving L-asparaginase was studied in 8 patients.75 ATIII levels were significantly decreased in all the children, but there was no statistical or clinically important increase in ATIII levels following FFP infusion.

FFP has been reported to treat successfully life-threatening complications of congenital C1 esterase inhibitor deficiency (hereditary angioedema)76; however, a virally-inactivated C1 inhibitor concentrate has recently been developed and shown to be effective in the treatment of this disorder.77

Finally, FFP has been used for nutritional support. In 1985, a panel convened by the National Institutes of Health concluded that FFP is useful in infants with secondary immunodeficiency associated with severe protein-losing enteropathy and in whom total parental nutritional is ineffective.78 The current search retrieved no studies addressing this use of FFP and more recent guidelines do not recommend its use for nutritional support.25,26,72

### Conclusions

In spite of the many situations in which a physician may consider administering RBC or plasma transfusion to a child and the potentially serious complications associated with transfusion therapy, there is a remarkable paucity of controlled data on which to base decisions. Few studies address the most common pediatric problems for which transfusions are used (e.g., in surgery, oncology and for critically ill patients), and most recommendations are extrapolated from adult data. There is clearly a need for additional carefully designed studies of transfusion therapy in children.

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**Table 3: Reference values (mean followed by upper and lower boundary for 95% of the population) for coagulation tests in healthy full-term infants during the first 6 months of life**

<table>
<thead>
<tr>
<th>Test</th>
<th>Day 1</th>
<th>Day 30</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT (s)</td>
<td>13.0 (10.1–15.9)</td>
<td>11.8 (10.0–14.3)</td>
<td>12.4 (10.8–13.9)</td>
</tr>
<tr>
<td>INR</td>
<td>1.0 (0.53–1.62)</td>
<td>0.79 (0.53–1.26)</td>
<td>0.89 (0.64–1.17)</td>
</tr>
<tr>
<td>APTT (s)</td>
<td>42.9 (31.3–54.5)</td>
<td>40.4 (32.0–55.2)</td>
<td>33.5 (26.6–40.3)</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>2.83 (1.67–3.99)</td>
<td>2.70 (1.62–3.78)</td>
<td>2.78 (1.56–4.00)</td>
</tr>
<tr>
<td>FV (U/mL)</td>
<td>0.72 (0.34–1.08)</td>
<td>0.98 (0.62–1.34)</td>
<td>1.06 (0.62–1.50)</td>
</tr>
<tr>
<td>FVII (U/mL)</td>
<td>0.66 (0.28–10.4)</td>
<td>0.90 (0.42–1.38)</td>
<td>1.06 (0.67–1.43)</td>
</tr>
<tr>
<td>FVIII (U/mL)</td>
<td>1.00 (0.50–1.78)</td>
<td>0.91 (0.50–1.57)</td>
<td>0.99 (0.50–1.49)</td>
</tr>
<tr>
<td>FIX (U/mL)</td>
<td>0.53 (0.15–0.91)</td>
<td>0.51 (0.21–0.81)</td>
<td>1.09 (0.55–1.63)</td>
</tr>
<tr>
<td>FX (U/mL)</td>
<td>0.40 (0.12–0.68)</td>
<td>0.59 (0.31–0.87)</td>
<td>1.06 (0.70–1.52)</td>
</tr>
<tr>
<td>FXI (U/mL)</td>
<td>0.38 (0.10–0.66)</td>
<td>0.53 (0.27–0.79)</td>
<td>0.97 (0.67–1.27)</td>
</tr>
<tr>
<td>vWF (U/mL)</td>
<td>1.53 (0.50–2.87)</td>
<td>1.28 (0.50–2.46)</td>
<td>0.92 (0.50–1.58)</td>
</tr>
</tbody>
</table>

Note: PT = prothrombin time; INR = international normalized ratio; APTT = activated partial thromboplastin time; FV to FXI = procoagulant factors; vWF = von Willebrand factor. Procoagulant factors are expressed in units per millilitre, where pooled plasma contains 1 U/mL.

Source: Adapted from Andrew and Schmidt.7

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References


