REVIEW ARTICLE

Use of Fresh-frozen Plasma in Newborn Infants

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Abstract

Nearly 10% of premature and critically ill infants receive fresh-frozen plasma (FFP) transfusions to reduce their high risk of bleeding. The authors have only limited data to identify relevant clinical predictors of bleeding and to evaluate the efficacy of FFP administration. There is still no consensus on the optimal use of FFP in infants who have abnormal coagulation parameters but are not having active bleeding. The aims of this review are to present current evidence derived from clinical studies focused on the use of FFP in neonatology and then use these data to propose best practice recommendations for the safety of neonates receiving FFP.

Keywords: Coagulation tests, Disseminated intravascular coagulation, Fresh-frozen plasma, Hemorrhages, Plasmapheresis, Relative risk, Whole-blood donor units.

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Key Points

- Fresh-frozen plasma is prepared by freezing plasma obtained either from single whole-blood donor units or through plasmapheresis; it contains high levels of soluble pro-coagulation factors, natural anticoagulants, and the tissue plasminogen activator inhibitor.
- Premature and critically ill infants frequently receive FFP transfusions due to high risk of bleeding; clinical studies show records of such treatment in up to 10% of these infants.
- Infants longer clotting times than adults which may be developmentally appropriate, and the risk of bleeding may not be proportionate to these deviations.
- Current evidence suggest that the use of FFP should be directed primarily to neonates with active bleeding and associated coagulopathy.
- Further information from controlled studies is needed to accurately identify neonates who are truly at risk for bleeding complications requiring FFP administration.

Introduction

Up to 10% of all premature and critically ill infants receive FFP transfusions.[1] These patients comprise a fragile population at risk of hemorrhagic complications, but the data to identify clinical predictors of bleeding and to evaluate the efficacy of FFP administration are limited.[2] Consequently, despite continued efforts to develop clinical guidelines on FFP administration in neonates, the recommendations remain under-supported with low-quality evidence, and there is a lack of consensus on its optimal use.[3,4] Not surprisingly, FFP continues to be administered to asymptomatic neonates who do not have any clinical evidence of bleeding. In many instances, FFP might be administered just to correct "prolonged" values in coagulation tests that might actually be developmentally appropriate. A large proportion of FFP transfusions in these infants cannot be easily justified based on risk or prior confirmed hemorrhage [5,6]

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To optimize FFP transfusions in neonates, we need better understanding of the developmental changes in various physiological markers of hemostasis and the interpretation of coagulation tests to detect coagulopathy. The levels of most coagulation proteins in premature infants change with gestational development , resulting in wide ranges of standard coagulation screening tests such as the prothrombin time (PT) and activated plasma thromboplastin time (APTT, Fig. 1).[7] Furthermore, the risk of bleeding may not be proportionate to these deviations. There is a need for reference ranges appropriate for accurate/corrected gestational age to evaluate/interpret these maturational changes and coagulation tests in newborns.[2,8–11] Figure 2 shows the changes in fibrinogen levels and the change in PT/aPTT seen with development.

This review presents current evidence on the use of FFP in neonatology and a set of best practice recommendations for the safety of neonates receiving FFP. We have included evidence from an extensive literature search in databases PubMed, EMBASE, and Scopus. To avoid bias in identification of studies, keywords were short-listed prior to the actual search from anecdotal personal experience and from PubMed's Medical Subject Heading (MeSH) thesaurus. For primary evaluation, we modified the Grading of Recommendations Assessment, Development, and Evaluation

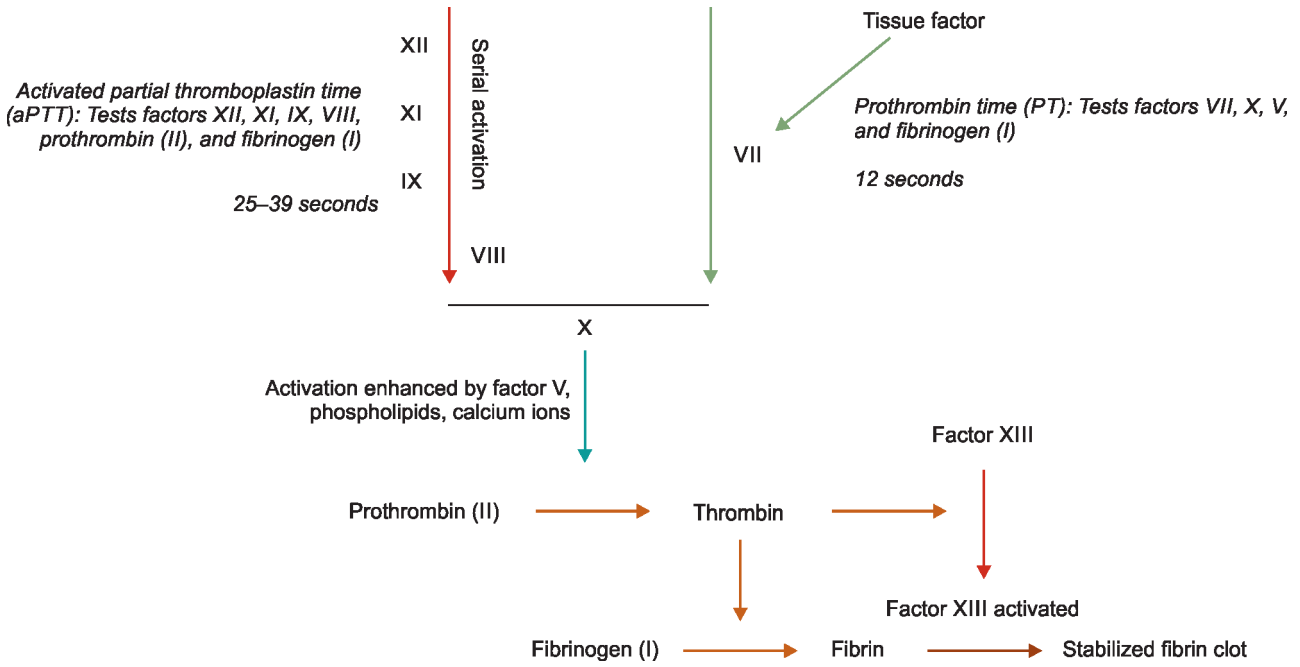
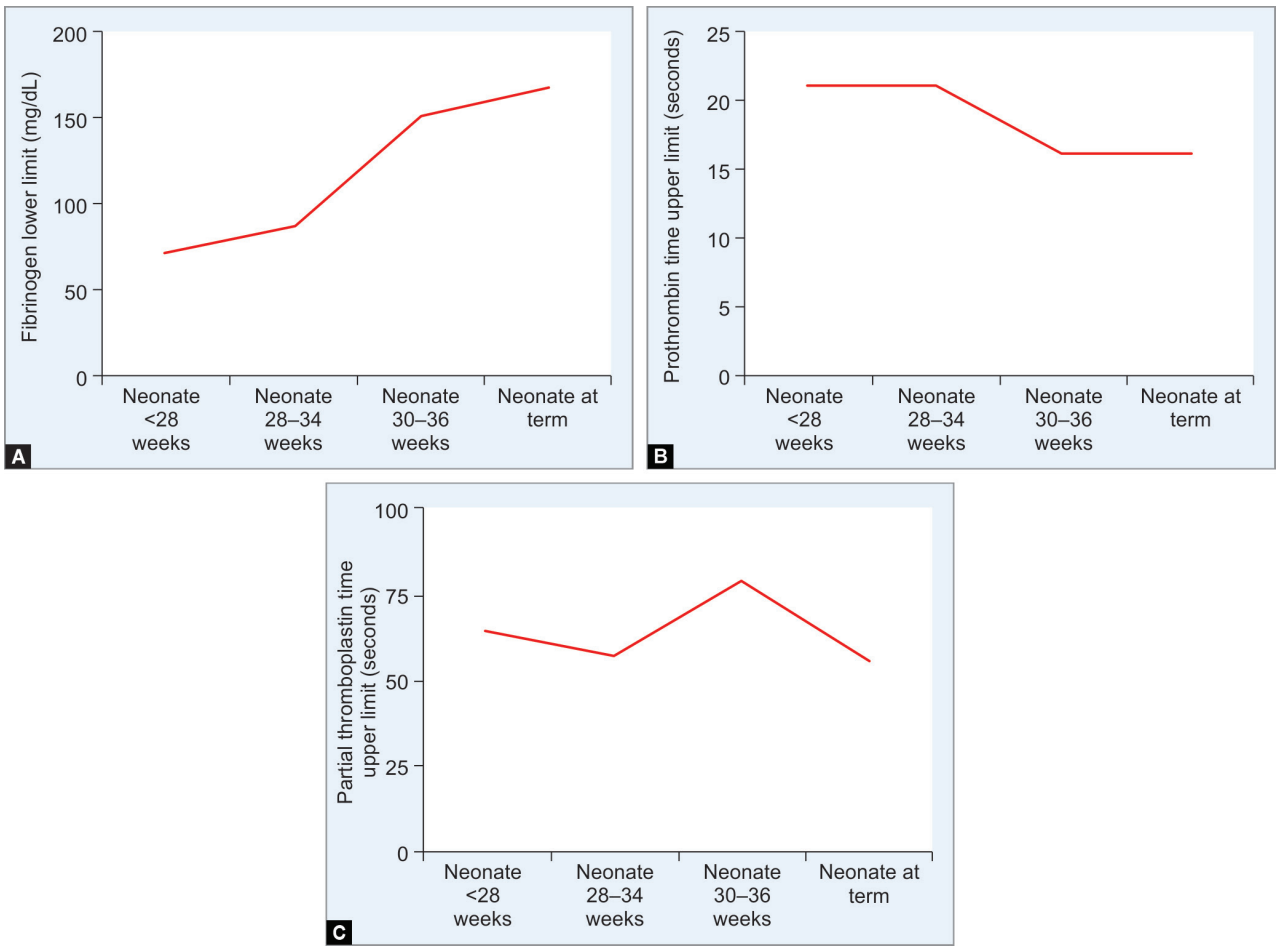


Fig. 1: Coagulation cascades and the traditionally used tests for evaluation in critically ill infants



Figs 2A to C: Line diagram in panel (A) show low plasma fibrinogen levels in extremely premature infants that rise toward term gestation. Panels (B and C) show the high degree of variability in prothrombin and PTTs across gestational maturation (adapted from Girelli et al. Blood Transfus 2015;13:484–497)

Table 1: Criteria for assigning grade of evidence and strength of recommendations

Quality of evidence	*Type of clinical study*	*Consistency of results*
A = High	Randomized trial without important limitations	Considerable confidence in the estimate of effect
B = Moderate	Randomized trial with important limitations or exceptionally observational studies with strong evidence	Further research likely to have impact on the confidence in estimate, may change estimate
C = Low	Observational studies or case series	Further research is very likely to have impact on confidence, likely to change the estimate
Strength of recommendations	Balance between benefits and harms	
1 = Strong	Certainty of imbalance	
2 = Weak	Uncertainty of imbalance	

The grading scheme classifies the quality of evidence as high (grade A), moderate (grade B), or low (grade C) according to the study design and to the consistency of results. The strength of recommendations was further classified as either strong (1) or weak (2) according to the balance between desirable and undesirable outcomes. Strong recommendations (1) are made when there is confidence that the benefits either do or do not outweigh the harm and costs of treatment. Where the magnitude of benefit or not is less certain, a weaker (1) recommendation is made. Grade I recommendations can be applied uniformly to most patients, whereas grade II recommendations require a more individualized application

Table 2: Choice of donors by blood groups for FFP transfusion therapy

ABO phenotype of the recipient	*ABO phenotype of units to transfuse (in order of preference)*
O	O, A, B, AB
A	A, AB
B	B, AB
AB	AB

(GRADE) system to assess the quality of evidence and strength of recommendations (Table 1). In addition, we also used the conventional grading systems of recommendations and the levels of evidence defined by the Oxford Centre for Evidence-based Medicine (Supplemental tables 1–2).[12,13]

Preparation, Characteristic, and Storage of FFP

Fresh-frozen plasma is prepared by freezing plasma separated from single whole-blood donor units or during plasmapheresis.[1] It is usually separated by centrifugation at 1000–2000gm at 4°C or is isolated during plasmapheresis.[14] There are newer techniques where whole blood is passed through semipermeable membranes and do not require *centrifugation*. These bags are usually stored frozen at 30°C. When needed for clinical use, FFP is thawed by placing the bags in a water bath at a temperature of 30–37°C for 20–30 minutes or in an FDA-approved device for 1–6 minutes.[15] After thawing, plasma should be used within 1–6 hours, and if not, then it was stored at 1–6°C. If not frozen, the product should be discarded after 24 hours of preparation. Ideally, FFP should not be frozen once it has been thawed.

The plasma used must be compatible with the recipient in terms of the ABO blood groups (Table 2).[8] A standard dose of 10–20 mL/kg administered intravenously over 60 minutes (grade of evidence C, strength of recommendation typically raises circulating levels of the coagulation factors by approximately 20%, which is more than the 10% rise that is usually needed to correct hemostasis.[16] Prior to FFP administration, standard precautions that include matching of blood types to confirm ABO compatibility need to be undertaken. The bags should be carefully inspected to ensure that the product is not expired and also for any leaks. The product should not contain any blood clots.

Table 3: Coagulation factors in FFP

Coagulation factor	*Plasma concentration required for hemostasis (units/mL). Transfusion of 10 mL/kg typically contains amounts of coagulation factors to achieve hemostasis. Factor levels in donor plasma can be assumed to be approximately 1 U/mL*
I (fibrinogen)	100–160 mg/dL
II (prothrombin)	0.5
V	0.1–0.3
VII	0.05–0.25
VIII	0.1–0.45
IX	0.1–0.4
X	0.1–0.25
XI	0.15–0.35
XIII	0.1–0.6
vWF (von Willebrand Factor)	0.25–0.6

Fresh-frozen plasma preparations should be leukodepleted (white blood cells $<1 \times 10^6$/unit), preferably at the time of collection (prestorage, grade of evidence C, strength of recommendation 1). These measures may prevent nonhemolytic febrile reaction, reduce the risk of alloimmunization, and lower the risk of transmission of viral infection such as cytomegalovirus (grade of evidence B, strength of recommendation 1).[17]

Fresh-frozen plasma contains higher levels of soluble coagulation factors than whole blood.[18] It contains 400–900 mg/unit of fibrinogen, which is much higher than normal whole blood levels of 200–400 mg/dL; there are also high levels of factors VIII, II, VII, V, IX, X, XI, XII, and XIII (Table 3, data from our hospital laboratory).[19,20] There are also high levels of albumin, immunoglobulins, and of naturally occurring anticoagulants such as proteins C and S, antithrombin, and the tissue plasminogen activator inhibitor.[21,22] Maintenance of the frozen state is the most important for factor VII.[13] The activity of factors V and VIII also declines, although at a slightly slower rate.[23] These details are important for the choice of therapeutic measures to prevent/treat hemorrhages in a critically ill infant; other preparations such as cryoprecipitate are richer in

fibrinogen, factor VIII and von Willebrand factor but may not be as effective volume expanders.[13,14,18]

Some centers have applied viral inactivation methods to FFP.[24] Solvent/detergent treatment of plasma pooled from about 1000 units allows a high degree of standardization, shows known concentration and activity of key bioactive proteins, has reduced immunological risks related to antibodies and leukocytes, and eliminates pathogens such as hepatitis A and parvovirus.[24–26] Treatment of FFP with methylene blue, a phenothiazine dye, can also be virucidal.[27] There is more biological variability as it is derived by addition of an inactivation method to single units of plasma. Viral inactivation methods may reduce the concentrations of some clotting factors and inhibitors of coagulation.[27]

Indications for FFP Administration in Infants

The use of FFP in newborn infants have been reported across different clinical setting. Fresh-frozen plasma corrects coagulopathy by replacing deficient/defective clotting factors,[28]and it is usually used in active bleeding as replacement therapy in conditions associated with coagulopathy. We have summarized the current information in favor of FFP administration in various clinical situations:

- Volume expansion in very preterm infant

Premature ill infants are at high risk of bleeding, particularly intraventricular, and are frequently treated prophylactically with FFP administrations.[19,29] Four studies have investigated prophylactic administration of FFP transfusions in pre-term neonates to decrease the incidence of IVH: One showed FFP to reduce IVH, but the other three reported no change in similar IVH rates,[13,30–32] and a meta-analysis found no differences in grade of IVH or mortality.[33] We suggest that the routine use of FFP should be avoided in preterm infants in the absence of active bleeding (grade of evidence A, strength of recommendation 1).

- Cardiac surgery/cardiopulmonary bypass

About a fifth of all infants with congenital heart defects (CHD, 2–3/1000 births) may require surgery.[34] Up to 40% of infants with surgical CHD may show severe complications in the postoperative period,[35] with mediastinal blood losses as high as 100 mL/kg. Hypofibrinogenemia and inadequate reversal of heparin effects may contribute to perioperative bleeding. Fresh-frozen plasma, platelets, cryoprecipitate, RBCs, and antifibrinolytic drugs are often administered to prevent/stop bleeding; the concerns are higher because surgical re-exploration of the chest in infants with severe bleeding was successful in controlling the hemorrhage in less than half of all the cases.[35] Infants with excessive bleeding may exhibit hypofibrinogenemia at the end of CPB and are frequently treated with FFP/cryoprecipitate;[36] hypofibrinogenemia is known to alter clot formation.[8] Bleeding risk is increased with concurrent thrombocytopenia, and hence platelet transfusion is appropriate in these settings.[37] The contribution of fibrinolysis to bleeding during CPB is still unclear.[38] Ongoing fibrinolysis seems to exacerbate bleeding; antifibrinolytics may help reduce perioperative bleeding after cardiac surgery in some, but not in all cases.

During CPB complex coagulopathy occurs and the predictive value of routine tests such as PT, partial thromboplastin time (PTT), and platelet counts may not always be useful.[39] The importance of FFP administration has been investigated in several trials that have compared the effectiveness of giving FFP before and after undergoing CPB.[40] Studies that evaluated FFP usage in infants, as part of the priming prior to the initiation of CPB, did not reduce blood loss or the need for transfusions in all cases.[41]

Current guidelines from the Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis[42] suggest the addition of fresh frozen plasma to the CPB prime in neonates undergoing cardiac surgery (grade of evidence B, strength of recommendation 1).

- Surgery and trauma

Surgical intervention and/or trauma frequently leads to hemorrhages.[43] Blood loss and metabolic changes such as acidosis and hypothermia can also accentuate bleeding.[44] Inadequate volume resuscitation and low tissue perfusion can increase the tissue expression of procoagulant mediators and lead to disseminated intravascular coagulation (DIC), lactic acidosis, and further disrupt vascular integrity and perfusion to set up a feed-forward loop.[45] Newborns and small infants do not compensate for hypovolemia in all conditions as well as adults; 10% loss of intravascular volume can disrupt vasomotor balance, peripheral tissue perfusion, and homeostasis in cardiac output. Hypothermia enhances many of these effects. Respiratory compromise can further accentuate these changes.

We need to carefully evaluate our strategies to minimize transfusions in elective surgical procedures. The benefits of FFP transfusions are not clear.[46] The use of prophylactic FFP prior to surgical procedures in infants who have abnormal clotting tests, but no active bleeding, is not supported in clinical studies. A detailed family history of bleeding, therapeutic history, and data on risk of bleeding in various surgical or other invasive procedures are more important than the results of *in vitro* clotting tests when assessing the risk of clinically significant bleeding. For infants who have abnormal clotting tests and other factors that indicate a significant bleeding risk during a procedure, FFP administration can be considered, although this is not evidence-based (grade of evidence C, strength of recommendation 2).[33]

- Congenital factor deficiencies

Congenital coagulation disorders are inherited conditions characterized by abnormally low levels of coagulation factors.[47] Hemophilia A and B, and von Willebrand disease, comprise nearly 80–85% of all cases with inherited bleeding disorders.[48] Hemophilia A and B can rarely present with bleeding symptoms in newborn period, as can homozygous deficiency of coagulation factors II, V, VII, X, and XIII.[47] Some of these inherited coagulation factor deficiencies may present in the neonatal period with intracranial and/or scalp hemorrhages, although most infants with these conditions do not have bleeding except with invasive procedures.[49] The other 15% result from deficiencies of fibrinogen, prothrombin, factors V, and combined factors V/VIII, VII, X, XI, and XIII.[50] These conditions can vary in severity from just a few cutaneous bleeds to potentially life-threatening hemorrhages.

The first line of treatment of inherited bleeding disorders is replacement of the deficient factor, using specific plasma-derived or recombinant products.[51] Single coagulation factors are available for the majority of deficient factors except for factors II,V, and XI.[52] For factor II deficiency, prothrombin complex concentrates (PCCs) can be used; these contain specific coagulation factors obtained from pooled normal plasma, namely factors II, IX, X, and VII in varying amounts depending on the product.

Fresh-frozen plasma can be administered in newborns and young infants with active bleeding during the initial hospital stay until the specific disorder has been identified, when specific products are not available or in resource limited countries (grade of evidence C, strength of recommendation 1). Large doses of FFP are

required in severe hemophilia and 15–25 mL/kg may be required to raise the FVIII/FIX concentration to hemostatic levels (grade of evidence C, strength of recommendation 1).

- Disseminated intravascular coagulation

Disseminated intravascular coagulation can occur in neonates with severe perinatal asphyxia, sepsis, shock, severe hypothermia, or necrotizing enterocolitis. These infants are usually critically ill and may bleed from multiple sites. Laboratory tests may show low platelet counts; prolonged PT and PTT; and decreased fibrinogen. Fibrin degradation products, such as d-dimers, can be elevated. The primary condition needs to be treated aggressively; the bleeding disorder can be controlled using FFP (grade of evidence C, strength of recommendation 1; other products such as cryoprecipitate and platelet concentrates may also be necessary. FFP/other blood products can bring temporizing relief while the primary condition is treated.[53] There may not be any strong, clinically relevant differences in the coagulation tests, outcomes of DIC, or in mortality.

- Vitamin K deficiency

Neonates express coagulation factors II, VII, IX, and X, which are vitamin K-dependent, at only about half the levels seen in adults.[54] Premature infants have even lower levels. Deficiency of vitamin K presents as hemorrhagic disease of the newborn (HDN) and can be associated with life-threatening intracranial hemorrhages.[55] There are two presentations:

1. Classical HDN occurs in the first week after birth due to a transient deficiency of vitamin K-dependent factors, and it is characterized by cutaneous bruising and/or intestinal hemorrhages in neonates. In infants born to mothers treated with drugs that suppress vitamin K metabolism, HDN can appear within the first 24 hours after birth. Routine administration of vitamin K soon after birth is effective in preventing classical HDN.[56]
2. Late HDN appears between 2 and 8 weeks after birth and is usually associated with vitamin K malabsorption. Vitamin K supplementation is effective within a few hours.[57] In addition to vitamin K, FFP can also help control severe bleeding or intracranial hemorrhage.[57]

Neonates who present with acute bleeding due to vitamin K deficiency should be treated upon suspicion with intravenous vitamin K, which will reverse the coagulopathy.[58] However, because vitamin K typically takes longer to show therapeutic effect, FFP should also be administered immediately to reduce the risk of devastating intracranial hemorrhages (grade of evidence C, strength of recommendation 1).

- Liver disease

Infants with acute or chronic liver disease may manifest with coagulopathy. Acute liver failure in neonates can occur due to birth asphyxia, sepsis, viral infections, and metabolic diseases. There may be decreased synthesis of pro- and anticoagulant factors, hypo- and dysfibrinogenemia, thrombocytopenia and platelet dysfunction, reduction of gamma-carboxylation of vitamin K-dependent proteins, and hyperfibrinolysis. To correct the coagulopathy, these infants require FFP and cryoprecipitate transfusions in addition to the treatment of the primary liver disease (grade of evidence C, strength of recommendation 2).[59]

- Extracorporeal membrane oxygenation (ECMO)

Extracorporeal membrane oxygenation is used to provide life support in infants with severe cardiorespiratory failure. These infants may already have coagulopathy due to sepsis, shock, or profound hypoxia, which may increase the risk of intracranial hemorrhage. The foreign surface of the ECMO circuit can activate the coagulation cascade; heparinization can prevent clot formation, but this also increases the risk of bleeding.[60] FFP support may be needed in infants after surgery and in those with sepsis. Some infants who have been on prolonged ECMO and need frequent transfusions, FFP has been used to treat possible microhemorrhages.[61] However, in a clinical study, scheduled FFP administrations did not increase circuit life or reduce the need for blood product transfusions.[62] Patients in the intervention group had similar hemorrhagic and thrombotic complications as the control group.

As limited data are available on the transfusion practice of neonatal ECMO patients, the recommendations are based on expert opinion provided by different ECMO centers.[63]

- Exchange transfusion

Infants with severe unconjugated hyperbilirubinemia may need exchange transfusion to prevent bilirubin encephalopathy/kernicterus. Many centers use blood reconstituted from FFP and packed erythrocytes for exchange transfusions, although the evidence of benefit from the use of reconstituted blood is limited.[64]

Partial exchange transfusion (PET) is traditionally used as the method to lower the hematocrit and treat hyperviscosity in neonatal polycythemia. Three randomized clinical trials conducted to compare the efficacy of crystalloid solutions versus plasma used for PET to treat neonatal polycythemia showed variable results.[65–67] Two meta-analyses, which included all these three studies, showed no significant difference in the reduction of post-exchange hematocrit.[68–70] Fresh-frozen plasma should not be used to treat polycythemia unless there is a coexistent coagulopathy (grade of evidence A, strength of recommendation 1).

Adverse Effects

Fresh-frozen plasma can have several adverse effects:[71]

- Immunological reactions, including early events due to innate immune reactions or delayed events such as alloimmunization to various circulatory antigens.
- Nonimmunologic complications seen with blood transfusions such as infections, circulatory overload, and metabolic derangements can also be seen with FFP administration. FFP lacks leukocytes, and therefore the transmission of cytomegalovirus is less frequent. However, human immunodeficiency virus (HIV) and hepatitis can be transmitted.[72] Circulatory overload can be seen in infants with pre-existing pulmonary edema or congestive heart failure. Metabolic complications like citrate toxicity and consequent hypocalcemia are rare but have been noted.

Conclusions

Administration of FFP is a frequent intervention in premature and critically-ill infants. Current evidence suggests that FFP should be used primarily in neonates with active bleeding and associated coagulopathy, or for deficiency of congenital factors for which no specific concentrated coagulation factors are available. In the setting of neonatal acquired coagulopathy, evaluation and interpretation of the standard coagulation test (PT, APTT) should be based on reference ranges appropriate for gestational and post-natal age. More information from controlled studies is needed

to accurately identify infants who are truly at risk for bleeding complications and who actually need FFP transfusions.

Supplementary Material

The supplementary tables are available online on the website of www.newbornjournal.org.

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