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Transfusion reactions in neonates and pediatrics: How and why are they different?

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Abstract:

Neonates and children are physically as well as physiologically different from adults. They are immunologically vulnerable, and the effects of transfusion can be longstanding, including with respect to their development. The transfusion reactions in children differ from those in adults in the type of reactions, incidence, and severity. The incidence is more than that in adults for the common type of reactions noted in children. Transfusion reactions are most commonly associated with platelets, followed by plasma and red blood cell transfusions in children. Febrile, allergic, and hypotensive reactions or volume overload are the common types in children. Standardizing pediatric adverse transfusion reaction definitions and criteria are necessary to improve studies and reports. Several modifications are needed to be adapted for transfusing blood products in neonates and children to evade the reactions as much as possible and make transfusion safer in this vulnerable population. This article provides a brief articulation of the transfusion reactions in neonatal and pediatric populations describing how they are different from adults.

Keywords:

Hypoglycaemia, Hyperkalaemia, neonatal transfusion reactions, paediatric transfusion reactions

Introduction

A neonate is defined as an infant under 4 months of age for transfusion purposes.[1] The upper limit for a "pediatric" patient is defined variedly as 14 or even 18 years. Transfusion reactions reported from India show a lower incidence in the neonatal and pediatric age group, as low as 10%–20% of the reported rate in adults.[2,3] In contrast, there is a disproportionately high number of reports following pediatric transfusions compared to adults in the West. However, approximately two-thirds of these reports are related to errors, which should be preventable. These usually include incorrect blood component transfusions, specific requirements not met, and avoidable, delayed, or under/over transfusions.[4] Excess vulnerability to patient identification errors in this age group may be because they cannot confirm their details, share the same date of birth with other infants in the neonatal intensive care unit (ICU), or may not yet have a name.[5] Recognition and reporting of transfusion errors in neonates are hindered because age-appropriate adverse transfusion reaction (ATR) definitions and criteria are unavailable.

Immaturity of the immune system, particularly in extremely premature infants, and disorders of cellular immunity in children increase their susceptibility to transfusion-associated graft-versus-host disease (TAGVHD). In contrast, immunologically mediated reactions such as febrile or allergic hemolytic reactions are rare. Physiological differences lead to metabolic complications, which are more specific to this population. Blood product

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type, dose, infusion rate, monitoring, triggers, and complex administration processes such as warming and infusion through rate monitoring devices can lead to a new set of errors and complications. Specific blood components and indications for transfusion are also different in this group of patients. A child's long-term development, particularly neurocognitive development, also needs to be considered while monitoring long-term adverse events.

Transfusion reactions are generally classified based on pathogenesis into immunologically mediated reactions and those that are not. The classification is summarized in Table 1.

Metabolic Complications

Hyperkalemia

Plasma K^+ increases during storage of whole blood (WB) and red blood cells (RBCs) due to leakage of intracellular K^+ associated with inhibition of the membrane Na^+/K^+ ATPase pump. The plasma of a unit of CPDA-1 WB contains approximately 25 mEq/L of K + at day 35 and RBCs about 75–100 mEq/L, translating to about 8 mEq per unit. This would not pose a problem with low-volume transfusions (10–20 mL/kg), as the infant's daily requirement of K^+ is 1–3 mEq/kg/day. However, large-volume transfusions or the infant's kidneys' inability to excrete K^+ may lead to dangerous hyperkalemia.[6] Transfusion at a faster rate or through central lines delivering a high K^+ load directly to the heart may cause arrhythmias, including cardiac arrest.

Prevention

Using irradiated blood after 24 h of storage in neonates should be avoided. Care is to be taken to avoid mechanical lysis of cells during infusion. Blood transfusion tubing can be shielded with aluminum foil while the infant is under a radiant warmer or phototherapy lights. Inline potassium adsorption filters or washing have been shown to remove extracellular K^+ from RBC units, but these may not be feasible on a routine basis.[7]

Hypothermia

The higher susceptibility of infants to hypothermia is due to decreased body fat, an immature epidermal barrier, and a higher surface area-to-weight ratio. At increased risk are infants on extracorporeal membrane oxygenation (ECMO), those undergoing exchange transfusions or cardiac surgery, and children with trauma. Blood products brought to room temperature before transfusion also have been shown to decrease an infant's core body temperature by 0.7°C–2.5°C.[8,9]

Prevention

Usage of blood warmers designed explicitly for blood administration is recommended.[10] Counter-current technology for warming is the most effective.[11]

Impaired glucose homeostasis

Both hypoglycemia and hyperglycemia are linked to blood transfusion. This is probably also because the infants at risk of developing hypoglycemia or hyperglycemia are also the ones most likely to receive a transfusion. Neonates have decreased glycogen stores and mucosal G-6-phosphatase. The proposed mechanisms for altered glucose homeostasis in infants are summarized in Table 2.

Glucose concentrations are also known to decrease in stored units over time.[12] Glucose levels are reported to decrease after transfusion and are generally asymptomatic, but mild symptoms can be noted in infants, especially in children undergoing exchange transfusion. The incidence of hypoglycemia in infants with erythroblastosis fetalis ranged from 2% to 20%.[9]

Table 1: Classification of transfusion reactions in neonates and children

Immunological	Nonimmunological
Febrile nonhemolytic transfusion reactions	Metabolic
Allergic reactions	Hypothermia
Hemolytic transfusion reactions: Acute and delayed	Hyperkalemia
Transfusion-related acute lung injury	Acid–base abnormalities
Transfusion-associated graft-versus-host disease	Hypocalcemia
Transfusion-associated necrotizing enterocolitis	2,3 DPG reduction
Alloimmunization	Altered glucose homeostasis
Posttransfusion purpura	Infectious
	Viral: HBV, HIV, HCV, CMV
	Sepsis
	Parasites: Malaria and Babesia
	Others
	Transfusion-associated circulatory overload
	Iron overload

HBV=Hepatitis B virus, HIV=Human immunodeficiency virus, HCV=Hepatitis C virus, CMV=Cytomegalovirus, DPG=2,3-diphosphoglycerate

Table 2: Probable mechanisms for altered glucose homeostasis in infants during transfusion

Hypoglycemia	Hyperglycemia
In exchange transfusion: Islet cell hyperplasia, inactivation of circulating insulin by increasing levels of reduced glutathione released from hemolysis of red cells, leading to compensatory stimulation of beta cells	Infants requiring surgical procedures under general anesthesia: Stress from induction of anesthesia leading to release of epinephrine and norepinephrine
Decreased rate of glucose infusion during transfusion	Mobilization of endogenous glucose stores
	Intolerance to exogenous glucose by smaller and premature infants
	Intrauterine transfusion blunts the hyperinsulinemic response by reducing circulating glutathione

Prevention

Infants at risk are to be recognised and monitored. Blood products should be transfused through a second iv line, with maintenance fluids being administered at a slower rate to avoid fluid overload. The glucose concentration of the fluid may need to be increased if the infusion rate is reduced.

Reduced 2,3-diphosphoglycerate

During storage, the amount of 2,3-diphosphoglycerate diminishes rapidly. This shifts the hemoglobin–oxygen dissociation curve to the left, thereby reducing the ability of RBCs to release oxygen into tissue. It takes between 3 and 8 h to be regenerated after one unit of RBCs has been transfused. Infants younger than 4-month-old cannot compensate as effectively as older patients that can compensate for the resulting hypoxia by increasing their heart rate.[13]

Prevention

For neonates undergoing large-volume transfusions, fresher blood units are preferred.

Hypocalcemia

The use of sodium citrate as an anticoagulant that binds ionized calcium is the cause of hypocalcemia in neonates. Small-volume transfusions are unlikely to cause it, but the load infused during exchange transfusion can reach high levels. Most citrate is metabolized in the liver, kidney, and skeletal muscles. The kidney and liver are not fully functional, and muscle mass is low in neonates. Hypothermia and acidosis, if present, can also reduce the clearance of citrate. Transient hypoparathyroidism relates to the gestational and postnatal age of the neonate. The presence of hypomagnesemia can also blunt the parathyroid hormone response. Early neonatal hypocalcemia has also been attributed to the presence of hypercalcitoninemia and inducing calciuria.[13,14]

Prevention

Seizure activity during exchange transfusion where hypocalcemia is suspected should be treated with 10% calcium gluconate (2 ml/kg). Ionized calcium levels should be monitored in infants undergoing exchange transfusion.

Transfusion-associated circulatory overload

The available definitions of the Centers for Disease Control and Prevention/International Society of Blood Transfusion do not define cutoffs for age-adapted vital sign values. These definitions also ignore the effect of critical illness that can influence vital signs. Transfusion-associated circulatory overload is mentioned to be more frequent in children younger than 3 years.[15] The higher risk is probably because of comparatively fast infusion in the background of their smaller size.

Prevention

Identify patients at-risk such as premature infants, infants with cardiac and pulmonary conditions or on mechanical ventilation/vasopressors, and transfuse them at a rate as reasonably low as possible.

Transfusion-transmitted infections

Given their small size, neonates are often transfused with small-volume aliquots and could be exposed to multiple donors. On average, premature infants weighing <1 kg are exposed to more than five donors during a single hospital stay if an opened port system is utilized for aliquot production instead of multiple aliquot Pedi-pack systems.[16] There is a high risk of cytomegalovirus transmission for low-birth-weight infants born to seronegative mothers.[13]

Prevention

One strategy is to reduce multiple donor exposure, which can be achieved by using sterile collecting devices to use the same units for repeated transfusion for the infants, Pedi-packs with prior aliquoting, or a dedicated donor donates every time the patient wants.

Bacterial sepsis

It is more frequently associated with the transfusion of platelets than with any other blood product. The source of infection can be the donor or contamination of the product post collection, especially during manipulation for pediatric use and administration in open systems.[17]

Prevention

Appropriate usage of platelets and proper and reduced storage duration are beneficial in reducing these events.

Iron overload

Iron overload is observed in chronically transfused children with thalassemia major, congenital anemias, and sickle cell disease. Each milliliter of red cells contains

roughly about 1 mg of iron. Transfusion-dependent patients usually require 200–300 ml/kg/year of blood, whereas an average nonmenstruating person absorbs and loses only about 0.01 mg Fe/kg/day.[18] With no physiologic means of excreting, iron overload is inevitable in this population.

Prevention

Iron chelation should be initiated in children who have received approximately ten transfusions or a total of about 180 ml/kg of packed RBCs or have a serum ferritin level over 1000 ng/ml.[19]

Immunological Transfusion Reactions

An infant's immune system is less mature; thereby, its lymphocytes are unable to present foreign antigens effectively. Hence, immunological transfusion reactions tend to be less common in this age group.

Hemolytic transfusion reactions

These are rare in neonates. Maternal isohemagglutinins are sometimes detected in the first 2 months of life. However, infant alloantibodies are rare before 6 months of age. There is a risk of a relatively large amount of incompatible blood being transfused in neonates before acute hemolysis is recognized.[20]

Prevention

Pediatric antibody tests that include screening for clinically significant antibodies in the recipient can be done. Components should be screened for clinically significant blood group antibodies (including high-titer anti-A and anti-B), and an indirect antiglobulin test is performed.[5]

Alloimmunization

Alloimmunization to RBCs is particularly frequent in those with sickle cell disease receiving transfusions.[21] Incidence of alloimmunization and platelet refractoriness appears to be lower in children than in comparable adult populations.[22] Posttransfusion purpura can develop due to platelet-specific alloantibody developing after blood transfusion, most commonly human platelet antigen-1a.

Prevention

Transfusion of phenotype matched and leukoreduced blood, especially for those needing regular transfusions.

Febrile and allergic reactions

This is the most common type of reaction reported in the neonatal and pediatric age groups. Storage-generated biological response modifiers (BRMs) and recipient antihuman leukocyte antigens (HLA) antibodies are the two well-described mechanisms for the causation of these reactions. A higher volume of blood product per kg body weight, a higher dose of pyrogenic cytokines or allergens in blood product, and undiagnosed IgA deficiency are the causes that put these groups at higher risk for the reaction. The most common product implicated is platelets.[13,23]

Prevention

Leukoreduction, washing, and fresher blood product administration are a few strategies. Premedication can help in repeated reactions.

T-antigen activation-induced hemolysis

T-antigen activation is reported in about 0.6% of all infants in ICU and in 9%–27% of the infants with necrotizing enterocolitis (NEC).[24] The red cell membrane glycoproteins carry O-linked oligosaccharides that are disialylated tetrasaccharides. Bacterial neuraminidases released by anaerobic and aerobic organisms remove these sialic acid residues, exposing a T-antigen which is usually hidden (T cryptantigen). This T-antigen binds with anti-T immunoglobulin present in most adult plasma, and hemolysis can happen.[13,20]

Prevention

Infants with sepsis or NEC who need plasma-containing components should be minor crossmatched. Avoid transfusion of plasma or use low anti-T titres plasma. RBC products may be washed before transfusion.

Transfusion-associated necrotizing enterocolitis

The association between RBC transfusions and NEC in neonates is controversial, and severe anemia itself may predispose to the development of NEC. A recent meta-analysis of randomized controlled trials even suggested a protective effect of a recent RBC transfusion on the development of NEC, while another meta-analysis of observational data did not find any association.[25,26] In theory, intestinal injury either from feeding, intestinal ischemia, or bacterial colonization in susceptible infants combined with exposure to biologically active mediators such as free hemoglobin, increased cytokines, and broken red cell fragments within the transfused blood may trigger an immunologic response within the intestinal mucosa. Altered angiogenesis within the intestine due to platelet-activating factor acetylhydrolase and reperfusion associated with transfusion has also been described as possible mechanisms for gut injury. Prematurity, low birth weight, and hypoxic-ischemic events are known to be risk factors for the development of transfusion-associated necrotizing enterocolitis.[27,28]

Prevention

The traditional practice has been to withhold feeds during (or for a few hours after) RBC transfusion to reduce the risk of NEC, but a recent Cochrane review noted the paucity of evidence, and many units currently do not withhold feeds.[29] Washed red cells

may be provided to neonates with NEC to reduce complement-dependent antibodies that can cause hemolysis of neoantigen-labeled RBCs.

Transfusion-related acute lung injury

This condition is more challenging to differentiate from other pulmonary pathologies. The current definition is not suitable for the pediatric and neonatal population. There are two peaks noticed concerning its occurrence, one in infants <1 year and the other in those more than 14 years.[30] Two events cause transfusion-related acute lung injury: the generation of biologically active compounds related to stress that activates the pulmonary vascular endothelium and primes the neutrophils, and the infusion of biological response modifiers and antibodies in stored blood components. Infants may be vulnerable because a respiratory injury has already happened in many hospitalized ones.

Prevention

Avoid using plasma products from multiparous women donors. Rational use of plasma products is to be practised.

Transfusion-associated graft-versus-host disease

The population at risk are immunocompromised patients, extreme preterm infants, infants who receive intrauterine transfusions, those with neonatal alloimmune thrombocytopenia, and those on ECMO. Many initial cases were reported in severe combined immunodeficiency or Wiskott–Aldrich syndromes, newborns with erythroblastosis fetalis, sepsis, or ARDS. The inability of these recipients to mount an immune response against donor T-lymphocytes is fundamental to the pathogenesis of TAGVHD.[20]

Prevention

Avoid blood from blood relatives. If absolutely necessary to be used then irradiate those blood products. Pathogen inactivation has also been known to reduce the risk.

Transfusion-related immunomodulation

The development of immunity in premature infants is not complete, and they generally have complicated clinical conditions. Hence, transfusion-related immunomodulation is difficult to define in premature patients than in adults. Effects like increased risk of short-term mortality (up to 3 months), increased risk of postoperative bacterial infections, and recurrence of resected malignancies have been described. More studies are required to elucidate this issue.[31,32]

Prevention

Prestorage leukoreduction and pathogen reduction have some preventive benefits as leukocytes, and their soluble mediators mediate these effects. Washing also helps by removing soluble HLA molecules, autoantibodies, and factor concentrate.

Conclusion

Due to the numerous difficulties in classifying and studying transfusion reactions in children, standardizing pediatric ATR definitions and criteria is necessary to improve studies and reports. Several modifications are needed to be adapted for transfusing blood products in neonates and children to evade the reactions as much as possible and make transfusion safer in this vulnerable population.

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Conflicts of interest

There are no conflicts of interest.

References

1. Wong EC, Punzalan RC. Neonatal and pediatric transfusion practice. In: Cohn CS, Delaney M, Johnson ST, Katz L, editors. Technical Manual. Bethesda, Maryland: AABB Press; 2020. p. 673-703.
2. Bisht A, Marwaha N, Kaur R, Gupta D, Singh S. Haemovigilance Programme of India: Analysis of transfusion reactions reported from January 2013 to April 2016 and key recommendations for blood safety. Asian J Transfus Sci 2018;12:1-7.
3. Bisht A, Marwaha N, Kaur R, Gupta D, Chhabra R. Haemovigilance Programme of India: Comparative analysis of transfusion reactions reported over a 5-year period through two reporting formats and key recommendations for blood safety. Asian J Transfus Sci 2020;14:103-16.
4. 2018 SHOT Annual Report – Individual Chapters – Serious Hazards of Transfusion. Available from: https://www.shotuk.org/shot-reports/report-summary-and-supplement-2018/2018-shot-annual-report-individual-chapters/. [Last accessed on 2021 Nov 29].
5. Stainsby D, Jones H, Wells AW, Gibson B, Cohen H; SHOT Steering Group. Adverse outcomes of blood transfusion in children: Analysis of UK reports to the serious hazards of transfusion scheme 1996-2005. Br J Haematol 2008;141:73-9.
6. Hall TL, Barnes A, Miller JR, Bethencourt DM, Nestor L. Neonatal mortality following transfusion of red cells with high plasma potassium levels. Transfusion 1993;33:606-9.
7. Balasubramanyam P, Basavarajegowda A, Hanumanthappa N, Negi VS, Harichandrakumar KT. Irradiating stored blood and storing irradiated blood: Is it different? – A study of serial changes in biochemical parameters of red blood cell units. Asian J Transfus Sci 2021;15:172-8.
8. Laptook AR, Salhab W, Bhaskar B; Neonatal Research Network. Admission temperature of low birth weight infants: Predictors and associated morbidities. Pediatrics 2007;119:e643-9.
9. Jackson JC. Adverse events associated with exchange transfusion in healthy and ill newborns. Pediatrics 1997;99:E7.
10. Jorgenson M. Administration of blood components. In: Cohn CS, Delaney M, Johnson S, Katz L, editors. Technical Manual. Bethesda, Maryland: AABB Press; 2020. p. 537-51.
11. Uhl L, Pacini D, Kruskall MS. A comparative study of blood

warmer performance. Anesthesiology 1992;77:1022-8.
12. Goodstein MH, Locke RG, Wlodarczyk D, Goldsmith LS, Rubenstein SD, Herman JH. Comparison of two preservation solutions for erythrocyte transfusions in newborn infants. J Pediatr 1993;123:783-8.
13. Kallan J, Capocelli KE. Adverse reactions. In: Sesok-Pizzini DA, editor. Neonatal Transfusion Practices. Philadelphia: Springer; 2017. p. 81-102.
14. Luban NL. Neonatal red blood cell transfusions. Curr Opin Hematol 2002;9:533-6.
15. De Cloedt L, Emeriaud G, Lefebvre É, Kleiber N, Robitaille N, Jarlot C, *et al.* Transfusion-associated circulatory overload in a pediatric intensive care unit: Different incidences with different diagnostic criteria. Transfusion 2018;58:1037-44.
16. Kakaiya RM, Morrison FS, Rawson JE, Lotz LL, Martin JW. Pedi-pack transfusion in a newborn intensive care unit. Transfusion 1979;19:19-24.
17. Hillyer CD, Josephson CD, Blajchman MA, Vostal JG, Epstein JS, Goodman JL. Bacterial contamination of blood components: Risks, strategies, and regulation: Joint ASH and AABB educational session in transfusion medicine. Hematology Am Soc Hematol Educ Program 2003;3:575-89. Available from: https://pubmed.ncbi.nlm.nih.gov/14633800/. [Last accessed on 2022 02 21].
18. Angelucci E, Brittenham GM, McLaren CE, Ripalti M, Baronciani D, Giardini C, *et al.* Hepatic iron concentration and total body iron stores in thalassemia major. N Engl J Med 2000;343:327-31.
19. Taher AT, Porter JB, Viprakasit V, Kattamis A, Chuncharunee S, Sutcharitchan P, *et al.* Defining serum ferritin thresholds to predict clinically relevant liver iron concentrations for guiding deferasirox therapy when MRI is unavailable in patients with non-transfusion-dependent thalassaemia. Br J Haematol 2015;168:284-90.
20. Fasano R, Paul W, Pisciotto P. Complications of neonatal transfusion. In: Popovsky MA, editor. Transfusion Reactions. Maryland: AABB Press; 2012. p. 471-509.
21. Balbuena-Merle RI, Nazario-Delgado CM, Rosario-Rosado RV, Millán-Tapia D, Climent-Peris C. Red blood cell alloimmunization in pediatric sickle cell disease population of Puerto Rico: An observational study. Ann Lab Med 2020;40:187-9.
22. Hogge DE, McConnell M, Jacobson C, Sutherland HJ, Benny WB, Massing BG. Platelet refractoriness and alloimmunization in pediatric oncology and bone marrow transplant patients. Transfusion 1995;35:645-52.
23. Gente V, Basavarajegowda A, Kulkarni R, Basu D. Recipient hemovigilance at a tertiary care hospital in Southern India: A cross-sectional study. Int J Adv Med Health Res 2018;5:66.
24. Moncharmont P. Adverse transfusion reactions in transfused children. Transfus Clin Biol 2019;26:329-35.
25. Rai SE, Sidhu AK, Krishnan RJ. Transfusion-associated necrotizing enterocolitis re-evaluated: A systematic review and meta-analysis. J Perinat Med 2018;46:665-76.
26. Garg P, Pinotti R, Lal CV, Salas AA. Transfusion-associated necrotizing enterocolitis in preterm infants: An updated meta-analysis of observational data. J Perinat Med 2018;46:677-85.
27. Paul DA, Mackley A, Novitsky A, Zhao Y, Brooks A, Locke RG. Increased odds of necrotizing enterocolitis after transfusion of red blood cells in premature infants. Pediatrics 2011;127:635-41.
28. Josephson CD, Wesolowski A, Bao G, Sola-Visner MC, Dudell G, Castillejo MI, *et al.* Do red cell transfusions increase the risk of necrotizing enterocolitis in premature infants? J Pediatr 2010;157:972-8.e1.
29. Yeo KT, Kong JY, Sasi A, Tan K, Lai NM, Schindler T. Stopping enteral feeds for prevention of transfusion-associated necrotising enterocolitis in preterm infants. Cochrane Database Syst Rev 2019;2019:CD012888.
30. Lieberman L, Petraszko T, Yi QL, Hannach B, Skeate R. Transfusion-related lung injury in children: A case series and review of the literature. Transfusion 2014;54:57-64.
31. Muszynski JA, Spinella PC, Cholette JM, Acker JP, Hall MW, Juffermans NP, *et al.* Transfusion-related immunomodulation: Review of the literature and implications for pediatric critical illness. Transfusion 2017;57:195-206.
32. Chao YH, Wu KH. Transfusion-related immunomodulation in pediatric patients. Pediatr Neonatol 2019;60:483-4.