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PATIENT BLOOD MANAGEMENT IN PEDIATRICS

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INTRODUCTION

When we think about patient blood management (PBM), we often think of routine transfusions in adults. However, PBM encompasses more than adult transfusions. It includes a series of medical and surgical strategies designed to optimize the care of any patient who may need a blood transfusion. When it comes to pediatric patients needing a blood transfusion, additional considerations must be taken into account. Unlike adults, pediatric patients have unique physiological characteristics and medical needs that necessitate specialized approaches to PBM.

With 40% of children worldwide and 15-20% in industrialized countries presenting with preoperative anemia, PBM programs aimed at identifying anemia in infants and children are essential.[1] The judicious use of blood products in these scenarios impacts immediate health outcomes, long-term recovery and overall well-being. Therefore, understanding and implementing effective PBM strategies in pediatrics is a medical and moral imperative.

TRANSFUSION THRESHOLDS

Transfusion guidelines for neonates, infants and children can be somewhat controversial and are constantly evolving. For example, historically, a more liberal strategy was employed because it was linked to improved neurodevelopmental outcomes. It was later found that a restrictive threshold (<7g/dL) showed no difference in outcomes when compared with the liberal threshold (<9g/dL).[2,3] This includes the TIC-TOC trial, which showed no increased risk of adverse outcomes when comparing the restrictive vs. liberal thresholds[4], and the TOP trial, which showed no significant difference in survival without neurodevelopmental impairment between the restrictive and liberal groups.[5] These studies, amongst others, have shown that restrictive thresholds were non-inferior.

Data supports restrictive transfusion thresholds in infants, children and adolescents. A hemoglobin threshold of 7g/dL in hemodynamically stable patients is sufficient and lower than the previous recommendation of >9g/dL.[2,3] It should be noted that neonates have a more complex approach to transfusion thresholds due to their varying hemoglobin levels, varying hemoglobin types

(i.e., proportion of hemoglobin A and F) and their inability to handle stress responses. Due to these considerations, factors other than hemoglobin levels must be considered for neonates.[6]

Current guidelines for neonatal transfusions take into account age, comorbidity and respiratory status. For example, if a neonate has clinical instability, such as a need for vasopressor support, mechanical ventilation, acute sepsis or necrotizing enterocolitis, a more liberal transfusion threshold is recommended, as shown in Table 1.[6] Transfusion thresholds for stable neonates can be seen in Table 2.[7,8]

ALTERNATIVE MODALITIES

Iron deficiency anemia is common in adults, and the strategies employed to treat it in adults can often also be used for pediatric patients.[9,10] This includes administering oral or parenteral iron two to four weeks before a surgical procedure, with serum iron and ferritin being measured during treatment to help determine if iron treatment is sufficient.[9] In patients with chronic inflammatory conditions, a ferritin level may be misleading since it is an acute phase reactant that elevates during inflammatory conditions. In these cases, percent transferrin saturation can be used to determine iron stores. Additionally, reticulocyte hemoglobin concentration can be used to measure iron incorporation in erythrocytes and can be used to determine if iron therapy is sufficient.

Oral iron is the first line of therapy for most patients with iron deficiency anemia. Oral iron, such as ferrous sulfate, can cause gastrointestinal side effects, including nausea, vomiting, and constipation. A meta-analysis in pediatric patients showed that iron hydroxide polymaltose complex had similar bioavailability as ferrous sulfate but was much better tolerated due to decreased side effects. Additionally, ferrous gluconate formulations can be used if iron hydroxide polymaltose complex is unavailable, as it is also associated with fewer side effects when compared with ferrous sulfate.[10]

Erythrocyte-stimulating agents (ESA) have also been studied as an alternative to blood transfusion to increase red cell production. Limited studies involve children; however, a few studies on Jehovah's Witnesses showed benefits with ESA administration.[11,12] Additionally, a single study showed that administering ESAs seven days before a procedure effectively reduced the need for allogeneic blood transfusion.[13]

Acute normovolemic hemodilution (ANH) has been explored as a potential strategy in children to reduce the need for a blood transfusion. ANH involves removing blood directly before a procedure and replacing the volume with a crystalloid solution.[14] This dilutes the blood that is shed during the procedure. The blood removed during the beginning of the procedure is then transfused back into the patient. Research has shown that in adult patients, the risk for myocardial ischemia or poor tissue perfusion is not elevated among those who have had ANH done during a procedure.[14]

Though data supports ANH in adults, limited studies in children have been published. A single-center retrospective cohort study including pediatric patients up to 36 months of age undergoing surgical repair or palliation of their cardiac defect with the use of cardiopulmonary bypass performed ANH on patients with a mean weight of 6.2 +1.9 kg. Patients below 6 kg of body weight required blood priming of the cardiopulmonary circuit; however, ANH was still performed with the intention of minimizing platelet activation and improving the preservation of native coagulation factors.[15]

IDENTIFICATION OF ANEMIA

Identifying anemia is challenging in the pediatric population, depending on the age of onset. Symptoms of anemia include fatigue, lethargy, pallor, irritability, poor feeding and tachypnea. Clinicians should focus on the appearance of patients' skin, eyes, mouth, chest and mucous membranes when considering anemia.[9] Pallor can be sensitive to anemia but usually only persists when hemoglobin levels are very low (<7g/dL). If hemolytic anemia is present, scleral icterus, jaundice and/or hepatosplenomegaly may be present, which should initiate an evaluation.[16,17]

In the surgical setting, healthy pediatric patients having minimally invasive procedures usually do not require preoperative laboratory testing. However, a comprehensive physical exam must be performed in this population to catch the signs and symptoms of anemia. If necessary, laboratory testing should be performed two to four weeks before the procedure for those undergoing invasive procedures or with comorbidities to allow time for adequate treatment if needed.[17]

SPECIAL REQUIREMENTS

There has been a long debate about using fresh or stored red cell units in pediatric patients. In 2019, Spinella et al. published the results of a randomized controlled trial exploring using fresh vs. standard-issue red cell units in critically ill pediatric patients.[18] Biochemical markers were used to check for organ dysfunction and tissue perfusion. The results demonstrated that there was no increase in mortality or progressive organ dysfunction in the standard-issue group compared to using fresh units.

Irradiation of cellular components is done to prevent transfusion-associated graft-vs-host disease (TA-GVHD). When cellular products are irradiated at a certain dose, donor T cells are inactivated, which prevents TA-GVHD.[19] Due to their immature immune systems, premature neonates weighing less than 1,200 g at birth should receive irradiated cellular components.[20] Guidelines for irradiated cellular components, published by the British Society for Haematology in 2020,[19] states that non-irradiated cellular products are appropriate for preterm and term infants with no history of intrauterine transfusion. The guidelines state that blood needs to be irradiated for both intrauterine transfusion and exchange transfusion and should be transfused within 24 hours to prevent hyperkalemia.[19] Pathogen-reduced platelets do not need to be irradiated as this inactivates residual lymphocytes.[21]

Transfusion-transmitted disease is an issue with any patient population. Specific to those with compromised immune systems, including neonates, cytomegalovirus (CMV)-seronegative blood has been recommended due to the ability of the virus to contribute to morbidity and mortality in these patient populations.[22,23] With the spread of universal leukocyte reduction across blood suppliers, CMV testing may be overkill. Since CMV normally resides in leukocytes, leukoreduced products are considered CMV-safe. The results of a 2014 study on CMV transmission in blood and breast milk demonstrated that leukocyte-reduced blood was less likely to transmit CMV compared with breast milk.[23]

CONCLUSION

PBM in pediatrics is a complex yet essential aspect of medical care that requires tailored approaches to meet children's unique physiological and medical needs. The evolving guidelines and evidence support more restrictive transfusion thresholds, which have been shown to be non-inferior in terms of outcomes compared to liberal thresholds. This approach not only reduces the risk associated with transfusions but also emphasizes the importance of individualized care, particularly for neonates who require specific considerations beyond just hemoglobin levels.

Moreover, alternative modalities such as iron supplementation, ESAs, and ANH offer promising strategies to manage anemia and reduce the need for transfusions in pediatric patients. These methods highlight the ongoing advancements in PBM that aim to optimize patient outcomes while minimizing exposure to blood products. Identifying and managing anemia early, through both clinical evaluation and laboratory testing, remains a critical component of preoperative care in pediatrics.

Table 1: Recommended transfusion thresholds for neonates with clinical instability[6]

Preterm Neonates <35 weeks	Hemoglobin
0-7 days	<11 g/dL
8-14 days	<10 g/dL
>= 15 days	<8 g/dL
Neonates >= 35 Weeks	**Hemoglobin**
0-7 days	<11 g/dL
>= 8 days	<7 g/dL

Table 2: Recommended transfusion thresholds for stable neonates[7,8]

Preterm Neonates <35 weeks	Hemoglobin
0-7 days	<10 g/dL
8-14 days	<8 g/dL
>= 15 days	<7 g/dL
Neonates >= 35 Weeks	**Hemoglobin**
0-7 days	<10 g/dL
>= 8 days	<7 g/dL

1. Goobie SM, Gallagher T, Gross I, Shander A. Society for the advancement of blood management administrative and clinical standards for patient blood management programs. 4th edition (pediatric version). *Paediatric Anaesthesia*. 2019;29(3):231-236. **doi:10.1111/pan.13574**
2. Goel R, Cushing MM, Tobian AAR. Pediatric patient blood management programs: not just transfusing little adults. *Transfusion Medicine Reviews*. 2016;30(4):235-241. **doi:10.1016/j.tmrv.2016.07.004**
3. Valentine SL, Bembea MM, Muszynski JA, et al. Consensus recommendations for RBC transfusion practice in critically ill children from the Pediatric Critical Care Transfusion and Anemia Expertise Initiative. *Pediatric Critical Care Medicine*. 2018;19(9):884-898. **doi:10.1097/pcc.0000000000001613**
4. Nishijima DK, VanBuren JM, Linakis SW, et al. Traumatic injury clinical trial evaluating tranexamic acid in children (TIC-TOC): A pilot randomized trial. Academic Emergency Medicine. 2022;29(7):862-873. **doi:10.1111/acem.14481**
5. Kirpalani, H., et al. "Transfusion of prematures (TOP) trial: does a liberal red blood cell transfusion strategy improve neurologically-intact survival of extremely-low-birth-weight infants as compared to a restrictive strategy?." Study protocol 2012. Accessed: June 4, 2024. **Transfusion of Prematures (TOP) Trial: (nih.gov)**
6. Sawyer AA, Wise L, Ghosh S, Bhatia J, Stansfield BK. Comparison of transfusion thresholds during neonatal extracorporeal membrane oxygenation. *Transfusion*. 2017;57(9):2115-2120. **doi:10.1111/trf.14151**
7. Lacroix J, Hébert PC, Hutchison JS, et al. Transfusion strategies for patients in pediatric intensive care units. *New England Journal of Medicine*. 2007;356(16):1609-1619. **doi:10.1056/nejmoa066240**
8. Muszynski JA, Guzzetta NA, Hall MW, et al. Recommendations on RBC transfusions for critically ill children with nonhemorrhagic shock from the Pediatric Critical Care Transfusion and Anemia Expertise Initiative. *Pediatric Critical Care Medicine*. 2018;19(9S):S121-S126. **doi:10.1097/pcc.0000000000001620**
9. Baker RD, Greer FR. Diagnosis and prevention of iron deficiency and Iron-Deficiency anemia in infants and young children (0–3 years of age). *Pediatrics*. 2010;126(5):1040-1050. **doi:10.1542/peds.2010-2576**
10. Yasa B, Agaoglu L, Unuvar E. Efficacy, Tolerability, and Acceptability of Iron Hydroxide Polymaltose Complex versus Ferrous Sulfate: A Randomized Trial in Pediatric Patients with Iron Deficiency Anemia. *International Journal of Pediatrics*. 2011;2011:1-6. **doi:10.1155/2011/524520**
11. Smith SN, Milov DE. Use of erythropoietin in Jehovah's Witness children following acute gastrointestinal blood loss. *J Fla Med Assoc*. 1993;80(2):103-105. **https://pubmed.ncbi.nlm.nih.gov/8455008**
12. Waldman N. Management of severe anemia without transfusion in a pediatric Jehovah's witness patient. *The Journal of Emergency Medicine (S.l Online)*. 1994;12(6):872-873. **doi:10.1016/0736-4679(94)90513-4**
13. Ootaki Y, Yamaguchi M, Yoshimura N, Oka S, Yoshida M, Hasegawa T. The efficacy of preoperative administration of a single dose of recombinant human erythropoietin in pediatric cardiac surgery. *The Heart Surgery Forum*. 2007;10(2):E115-E119. **doi:10.1532/hsf98.20061183**
14. Weiskopf RB, Viele MK, Feiner J, et al. Human cardiovascular and metabolic response to acute, severe isovolemic anemia. *JAMA*. 1998;279(3):217. **doi:10.1001/jama.279.3.217**
15. Crescini WM, Muralidaran A, Shen I, LeBlanc A, You J, Giacomuzzi C, Treggiari MM. The use of acute normovolemic hemodilution in paediatric cardiac surgery. *Acta Anaesthesiologica Scandinavica* 2018. doi. **doi: 10.1111/aas.13095**
16. Janus J, Moerschel SK. Evaluation of anemia in children. *PubMed*. 2010;81(12):1462-1471. **https://pubmed.ncbi.nlm.nih.gov/20540485**
17. Fletke, Kyle Jordan, Alexander Kaysin, and Stephanie Jones. "Preoperative Evaluation in Children." *American Family Physician* 105.6 (2022): 640-649. PMID: 35704826

18. Spinella PC, Tucci M, Fergusson DA, et al. Effect of Fresh vs Standard-issue Red Blood Cell Transfusions on Multiple Organ Dysfunction Syndrome in Critically Ill Pediatric Patients. *JAMA*. 2019;322(22):2179. **doi:10.1001/jama.2019.17478**
19. Foukaneli T, Kerr P, Bolton-Maggs PHB, et al. Guidelines on the use of irradiated blood components. *British Journal of Haematology*. 2020;191(5):704-724. **doi:10.1111/bjh.17015**
20. Goel, R, Punzalan, RC, Wong, ECC. Neonatal and pediatric transfusion practice. In: Cohn C, et al. Technical manual. 21st ed. Bethesda, MD: AABB Press, 2023.
21. Circular of Information for the use of human blood and blood components. Food and Drug Administration. 2021. Accessed June 4, 2024. **Circular of Information for the Use of Human Blood and Blood Components - Watermarked Version (aabb.org)**
22. What is CMV Negative Blood? Why Is It Important. Accessed June 4, 2024. **https://www.redcrossblood.org/local-homepage/news/article/why-cmv-negative-blood-is-so-important.html**
23. Josephson CD, Caliendo AM, Easley KA, et al. Blood transfusion and breast milk transmission of cytomegalovirus in very Low-Birth-Weight infants. *JAMA Pediatrics*. 2014;168(11):1054. **doi:10.1001/jamapediatrics.2014.1360**