Do Transfusions Cause Necrotizing Enterocolitis? Evidence and Potential Mechanisms

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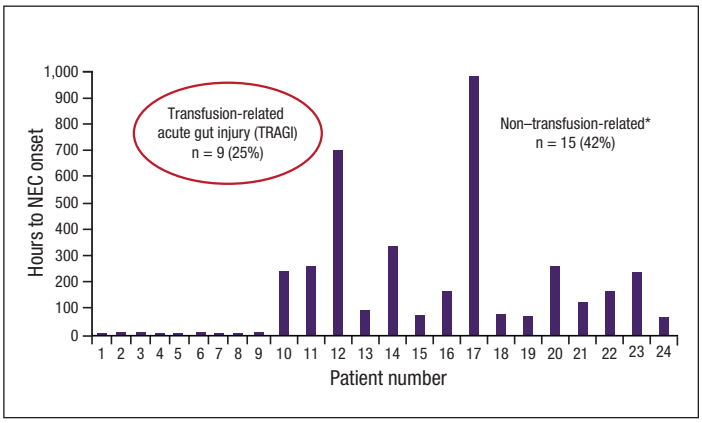
Transfusion-associated gut injury (TRAGI) refers to the temporal association (<48 hours) between packed red blood cell (PRBC) transfusion and the development of necrotizing enterocolitis (NEC) in very low birth weight neonates **(Figure 1)**.[1] Other than extreme prematurity, TRAGI cases lack many of the classical risk factors associated with NEC (eg, low Apgar scores, hypotension, hypoxia, umbilical catheters, feeding intolerance, sepsis). A comparison of several recent reports from different neonatal intensive care units (NICUs) showed TRAGI accounted for approximately 30% of all NEC cases. TRAGI was associated with lower gestational age (<28 weeks), lower birth weight (<1,000 grams), extreme anemia (hematocrit [Hct] ≤25%), and transfusion of older stored blood (>10 days). Despite the association between PRBC transfusion and NEC, there is limited evidence (ie, a lack of randomized clinical trial data, particularly regarding temporality) to support a causal relationship.[2,3]

Figure 1. Number of hours to onset of NEC after PRBC transfusion.[1]



A retrospective chart review of 65 infants in the NICU who developed NEC found that formula-fed infants accounted for 72% (n = 47/65) of NEC cases, while only 28% (n = 18/65) of infants who received breast milk developed NEC.[4] These findings suggest breast milk is protective against NEC; however, the incidence of TRAGI was similar in the infants who received formula and those who received breast milk (32% and 28%, respectively), suggesting breast milk does not protect against TRAGI. Therefore, the TRAGI injury likely originates on the vascular side, as opposed to the luminal side, of the mucosal barrier.

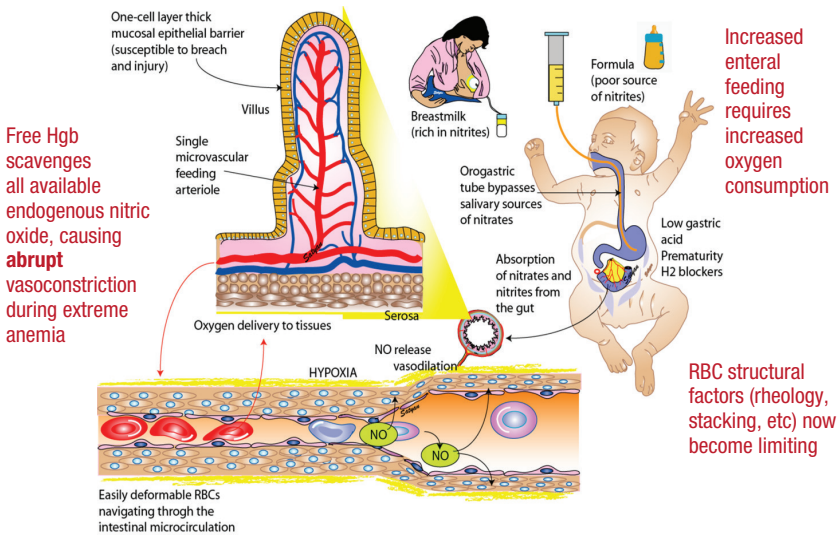
Extreme anemia (Hct <25%) has been associated with increased risk of NEC after PRBC transfusion in preterm infants.[5] PRBC transfusions also cause a failure of physiologic reflex responses to enteral feeding in anemic, very low birth weight infants.[6] Enteral feeds increase gut motility and digestion and consequently oxygen consumption; thus, they may disrupt the balance of oxygen delivery and consumption. Physiologic mechanisms to compensate for extreme anemia include increased cardiac output, increased oxygen extraction due to reduced oxygen delivery, elevated erythropoietin levels, and release of hemoglobin-bound nitric oxide.[7] These processes may result in a reaction to PRBC products due to factors associated with red blood cell (RBC) storage lesion **(Table 1)**.[8] Of these factors, only the hypoxic vasodilation effect becomes physiologically significant during extreme anemia. RBC storage lowers RBC nitric oxide and increases nitric oxide scavenging by free hemoglobin, which has a 100- to 1,000-fold higher affinity for nitric oxide than RBCs containing hemoglobin. Nitric oxide scavenging after transfusion can result in perturbations in nitric oxide–dependent hypoxic vasodilation and reduced blood flow.[8,9] Unique arteriole branching in the intestinal villi make these structures more susceptible to conditions that cause oxygen deprivation (eg, anemia, flow disturbances).[10] In addition, RBC storage causes physical and structural changes in RBCs (eg, changes in rheology, increased adhesiveness, more stiff, less malleable), which may cause injury to the intestinal microvasculature.[8] Thus, RBC storage lesions in combination with other risk factors may contribute to the development of TRAGI. Increased oxygen demand (enteral feeding) in the setting of extreme anemia and PRBC transfusion may result in injury to the mucosal barrier, enabling bacterial invasion and NEC **(Figure 2)**.

Table 1. Factors associated with RBC storage lesion.[8]

1) RBC Physical & Structural – increased propensity to obstruct flow or cause vasoconstriction - Stacking (eg, roll of coins); microaggregates (flow obstruction) - Increased adhesiveness (stickiness) - Stiffer, less deformable (difficulty in passing through capillaries) - Increased viscosity due to higher Hct - RBC fragmentation creating microparticles w/ Hgb and free Hg (NO scavenging) - Free membrane lipids (vasoactive)	**3) Nitric Oxide – increased propensity to cause vasoconstriction due to NO depletion** - Reduced RBC NO, S-NO-Hgb during storage - Lower pH + derivative left shift in P50 of RBC - P50 shift depletes nitrite substrate via oxy-Hgb converting it to nitrate - Free Hgb has 100-1,000 fold higher affinity for NO than RBC Hgb
2) RBC Metabolic – altered O_2 carrying capacity; vascular effects - Low pO_2 plus low 2,3 DPG (higher affinity for O_2 – less O_2 available) - Increased lactate, low pH, large base deficit, higher K+ (altered vascular resistance) - Lower ATP (RBC energy crisis) - Donor-specific reduced survivability (cysteine, caffeine, etc) - Free iron (oxidant injury)	**4) Humoral Factors – host versus graft reactions; inflammatory mediators released** - Haplotype antibodies (anti-HLA in 2nd pregnancy) - Cytokines released from WBC during filtering to remove CMV/WBC - Reactive increase PAF from infused humoral factors - Activation of endothelial receptors by humoral factors - T-antigen exposure

Hgb, hemoglobin; NO, nitric oxide; pO_2; oxygen partial pressure; DPG, diphosphoglycerate; ATP, adenosine triphosphate; S-NO-Hgb, S-nitrosylated hemoglobin; P50, partial pressure of a gas required to achieve 50% hemoglobin saturation; HLA, human leukocyte antigen; WBC, white blood cells; CMV, cytomegalovirus; PAF, platelet activating factor.

Figure 2. Proposed mechanism for TRAGI.[8]



Hgb, hemoglobin; NO, nitric oxide.

Inhaled nitric oxide has been shown to improve systemic microcirculation in infants and children with hypoxemic respiratory failure.[11] It is possible that inhaled nitric oxide could be used to prevent nitric oxide scavenging by free hemoglobin when giving PRBC transfusions for extreme anemia. A clinical trial (iNO-TRAGI) is currently underway to assess whether providing inhaled nitric oxide during and after a PRBC transfusion for anemia can improve oxygen delivery and prevent TRAGI in preterm infants.

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