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Transfusion-associated Necrotizing Enterocolitis (TANEC): Evidence and Uncertainty

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Abstract

Transfusion-associated Necrotizing Enterocolitis (TANEC) has been described as necrotizing enterocolitis (NEC) that arises within 48 hours of a blood transfusion. [1, 2] TANEC is concerning to clinicians and has been shown to be associated with 25–35% of NEC in recent studies. Evidence related to TANEC is limited to observational, retrospective studies. Infants who develop TANEC tend to be smaller, born at earlier gestation, more severely ill and develop NEC after 30 days of age. Evidence in two studies support holding feedings during transfusion to protect the preterm gut from the cascade of events that lead to NEC but higher quality research, including prospective randomized controlled trials, is needed to evaluate the effect of feeding on TANEC.

Background

NEC is a devastating gastrointestinal disease that all clinicians within the neonatal intensive care unit (NICU) maintain vigilance to detect and treat. In recent years, researchers have conducted retrospective observational studies to examine the occurrence of NEC within 48 hours of transfusion. Most of the published studies on TANEC have been published in the last three years although the association between NEC and transfusion was described as early as 1987.[3] The incidence of TANEC varies from 20–35% of NEC cases and reports suggest that infants with TANEC are more likely to develop more surgical NEC.[1, 2]

Neonates are among the most transfused patients in the hospital but adherence to transfusion guidelines and adoption of unit-specific guidelines vary significantly.[4] Differences exist in the criteria for transfusion both within units between providers and across units. Dangers from multiple transfusions include exposure to multiple donors, viruses, preservatives used in blood products, iron and volume overload, and a potential for increased risk of retinopathy of prematurity and necrotizing enterocolitis.[5]

In a study of 6 units' transfusion practices, Bednarek and colleagues discovered great variability among units in the quantity of blood transfused over an infant's stay. They found that high and low transfusing units can vary by about 70 ml/kg over an infant's NICU stay.

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Competing interests

The author has no competing interests to disclose.

Authors' contributions

Dr. Gephart conceptualized, searched the literature and wrote the article. A research librarian, Ms. Sandy Kramer assisted her in the literature search.

[5] High transfusing units gave infants a median of 2 transfusion and an average of 56 ml/kg (range of 56–203 ml/kg) over the NICU stay. Medium transfusing units delivered a median of 1 transfusion (range 0–7) and a total volume of 42 ml/kg (range 0–103 ml/kg) over the NICU stay. Low transfusing units gave a median of 1 transfusion (range 0–3) and a total volume of 38 ml/kg (range 0–96) over the NICU stay.[5]

Even when transfusion guidelines are in place, adherence is inconsistent. In one multi-center study, 30% of transfusions given were delivered outside of the guideline. [4] Adherence was drastically improved and the number of transfusions provided decreased when the guideline was integrated into a clinical decision-support system and a reason for violating the guideline was required. For example, when ordering the transfusion within the computerized provider order entry (CPOE) system, the provider was cued with the transfusion guideline to guide the ordering of the transfusion. The CPOE system issued an alert to the provider if the order was made outside of the guideline and the provider had to enter a reason for violating the guideline.

At least one group of researchers has hypothesized that transfusion-related acute gut injury (TRAGI) is a type of adverse reaction to a blood transfusion similar to the adult reaction, transfusion related acute lung injury (TRALI).[6] Most often, infants are transfused because of underlying anemia, bleeding, or respiratory symptoms with anemia. The mechanism of injury in TANEC/TRAGI has been hypothesized as a reaction to the blood transfusion,[6] the result of an abnormal response of the mesenteric blood flow velocity (MBFV) in the post-transfusion state such that low perfusion interacts with the mechanisms of feeding and contributes to intestinal injury, [7] or the effect of banked red blood cells (RBCs) that may be less competent to increase oxygen delivery to the tissue, leading to ischemia and vasoconstriction in the gut. Further, it may be possible that multiple pathways exist for TRAGI that leads to NEC development and that the mechanisms of injury are not mutually exclusive. [8]

In one survey of attending neonatologists and Neonatal Intensive Care Unit (NICU) directors, 56% claim to have experienced TRAGI (or TANEC as defined in other literature). [9] Of 59 respondents, the majority said they transfuse if the infant is experiencing respiratory illness including infants:

- Without symptoms but have a Hematocrit (Hct) = 20–25%
- Are symptomatic (i.e. $\text{FiO}_2 > 40\%$ per nasal cannula) with Hct 25–30%
- Who require ventilator assistance with $\text{FiO}_2 > 40\%$ and have a Hct 30–35%

Yet, of those surveyed, most NICU directors and attending neonatologist (83–86%) do not withhold enteral feedings before, during, or after transfusion. The authors surmised that clinicians surveyed do not relate TRAGI to feeding practices during transfusion. In contrast, Christensen and colleagues report that infants with TANEC accounted for 35% of their surgical NEC cases and were significantly more likely to have been fed large volumes of milk in the 24 hours prior to and during the transfusion ($p=.04$) especially if it was formula ($p=.004$) as compared to those who developed NEC not associated with transfusion. The purpose of this brief is to review the evidence on TANEC and evaluate the impact of enteral feeding on TANEC.

Search Strategy

Literature was searched in several databases including: Medline, CINAHL, the archive of abstracts for the Pediatric Academic Societies meetings (2007–2012), and the Cochrane Database of Systematic Reviews. Key words used included “Necrotizing enterocolitis” AND

“Transfusion.” In Medline, this search yielded 176 articles, most of which were irrelevant (reviews, editorials, articles where NEC was mentioned but not a main subject, etc). A search using “Transfusion-associated NEC,” yielded 10 articles and “Transfusion-related acute gut injury” one article with 4 editorial comments. No new reports were identified in CINAHL or the Cochrane database. Article bibliographies were searched to identify additional relevant articles.

Summary of Evidence

One systematic review with a meta-analysis of observational studies was retrieved, contributing the highest level of evidence to this review. No randomized controlled trials (RCTs) were identified. All of the reported research was observational and retrospective and every study used a case-control design. Studies varied in how they matched TANEC cases. The highest quality studies matched TANEC cases to other NEC cases not associated with a transfusion.

The meta-analysis included 10 studies with 2 studies reporting the impact of changing their practice to hold feedings during transfusions on the development of NEC. In addition, 2 studies met the systematic review criteria but were not included in the meta-analysis because they did not report the rate of NEC in non-transfused infants. Studies varied in their level of bias with most demonstrating moderate to low risk because of the manner in which they selected the controls and evaluated the presence of confounders on the outcome of NEC.[2]

Overall, Mohamed and Shah found within their meta-analysis that infants who had recently been transfused (defined as within 48 hours or two days) were more likely to develop NEC than those who developed NEC not associated with transfusion. In studies that did not adjust for confounders (such as gender, patent ductus arteriosus, gestational age, and birthweight), infants were nearly four times more likely to develop NEC after transfusion (5 studies, pooled OR: 3.91, 95% CI: 2.97–5.14; $I^2 = 58\%$). The odds of developing NEC after transfusion was found to be less when these confounders were considered (4 studies, OR: 2.01, 95% CI: 1.61–2.50, $I^2 = 91\%$). When confounders were considered, one study demonstrated a *reduced* risk associated with transfusion and contributed to significant variability to the pooled estimates of odds (i.e. $I^2 = 91\%$).[10] This study by Harsono and colleagues did not match cases 1:1 but looked at overall odds when comparing the two groups: TANEC (n=26) and NEC not associated with a transfusion (n=17). When this study was removed from the analysis, the pooled odds of developing TANEC were found to be higher and the homogeneity of the studies improved (pooled OR: 2.48, 95% CI: 1.97–3.12, $I^2 = 0\%$).[2]

Secondly, Mohamed and Shah looked for predictors of TANEC. They found that infants who developed TANEC were of lower gestational age by 1.5 weeks on average, smaller birthweight by 528 grams and nearly three times more likely to have a patent ductus arteriosus (pooled OR: 2.68, 95% CI: 1.81–3.97) and three times more likely to be mechanically ventilated (pooled OR: 3.16, 95% CI: 1.60–6.22) when diagnosed with NEC. Infants who developed TANEC were significantly more likely to develop it at later postnatal ages than those who developed NEC not associated with a transfusion in six studies. [1, 6, 11–14] One study did report an earlier onset in TANEC cases compared to NEC not associated with transfusion.[15]

Although few studies evaluated multiple morbidities associated with TANEC, Stritzke and colleagues found that TANEC cases were more like to experience severe intraventricular hemorrhage as well (38% TANEC compared to 17% non-TANEC, $P < .0001$). [16] Males were not more likely to develop TANEC than females. Of note, the authors did not evaluate the impact of feeding, specifically the proportion of human milk fed to infants in either

group (TANEC or NEC not associated with a transfusion). Infants with TANEC were nearly twice as likely to die than those who developed NEC not associated with transfusion (pooled OR: 1.88, 95% CI: 1.35–2.61).

In two reports the effect of withholding feeding during transfusion are described. The details of those two studies are described in Table 1. [14, 15] Both studies report a drastic reduction in the unit's NEC rate after the practice change and a near-eradication of TANEC.

Unfortunately, some may consider the quality of these studies to be inferior but it is difficult to argue with the impact of the practice change on NEC rates.

Recommendations for Practice

Balancing the infant's hemodynamic stability and nutritional needs are an important challenge for clinicians in the context of NEC risk. The evidence is not conclusive about the best approach to feeding during transfusion but preliminary evidence suggests a protective effect of holding feedings before and during transfusion. Several years ago when less evidence was available about TANEC, Agwu and colleagues concluded that their clinical bottom line led them to withhold feeding during a transfusion.[17] On the basis of the El-Dib and colleagues' significant reduction in NEC incidence after changing practice [15], Christensen et al's finding of the significantly higher association of formula feeding during transfusion with TANEC [1] and Perciaccante's eradication of TANEC in their unit when feedings were held [14] holding feedings during transfusion may be prudent especially if it is not human milk. General recommendations for practice to prevent NEC and evaluate TANEC are included in Table 2.

Holding feeding during transfusion appears to be a small change to potentially make a significant impact on TANEC rates but more prospective randomized controlled trials are needed to validate this practice. At any rate, limiting feeding during transfusion to human milk alone may be a possible first step if a clinician is not willing to hold feeding altogether. This practice change is supported by one study that found infants with TANEC were significantly more likely to have received formula than human milk ($p=.004$). [1]

Recommendations for Research

TANEC continues to be a hot topic for research and opportunities to fill research gaps are many. Mohamed and Shah recommend prospective study of all transfusion episodes associated with NEC. Adjusting for confounders (i.e. other NEC risk factors) in TANEC studies needs to be standardized to allow for comparison of TANEC across studies [2] Based on the meta-analysis, confounders to consider include the presence of patent ductus arteriosus, gestational age, birth weight, and illness severity. A comprehensive discussion of NEC risk factors are included in Gephart et al's recent review on NEC risk. [18] More research is needed to evaluate the relationship of risk reduction strategies for NEC to TANEC including the feeding of human milk and the adoption of standardized feeding guidelines by evaluating the quantity and substance of feeding (i.e. mother's milk, donor milk, formula with calorie content, or fortified human milk) with TANEC.

Volunteer reporting of TRAGI (or TANEC) may allow for an in-depth understanding of TANEC and is underway at.[19] It is possible that bias in reporting will be an issue in this registry due to the need for clinicians to voluntarily participate. For neonatal nurse practitioners and neonatologists, it may be useful to consider entering TANEC episodes into this registry and consider participating in multi-center prospective trials evaluating the impact of feeding on TANEC. If unit-specific efforts are underway, the results of feeding changes on TANEC should be published.

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Table 1**Impact of Feeding Changes on TANEC**

Study Authors	Indications for Transfusion	Blood Handling (PRBCs)	Feeding practices used	Result
El-Dib et al [15]	Hct < 35% if symptomatic Hct < 30% and Birth weight < 1200 grams in the first 14 days of life and provider judgement indicated	One unit dedicated to patient to limit donors. Each RBC unit was 2–11 days old with first aliquot 15 ml/kg given over 4 hours O Rh negative blood stored in citrate-phosphate-dextrose-adnine-1, hemoglobin S negative, leukoreduced, irradiated and cytomegalovirus seronegative	Changed practice to hold feeding immediately before and during the transfusion Feeding resumed immediately after the transfusion was completed No specification of type of feeding (i.e. human milk or formula)	Unit NEC rate of 5.3% decreased to 1.3% after the change in feeding practice during transfusion
Perciaccante et al [14]	Not specified It appears that transfusion indications did not change between the pre- and post- change in transfusion feeding practices	Unclear from the report. Appears that handling of PRBCs did not differ between the pre- and post-change in transfusion feeding practices	Feeding held 4 hours before and during transfusion Feeding resumed 4 hours after transfusion No specification of type of feeding (i.e. human milk or formula)	Epoch 1: TANEC= 7/17 (39%) of NEC cases. Overall incidence of NEC was 18/289= 6.2% Epoch 2 (after change in feeding practices): No TANEC and incidence of NEC decreased to 11/306 (3.6%)

Hct= Hematocrit

RBC= Red Blood Cells

PRBCs= Packed Red Blood Cells

Table 1**Practice Change to Potentially Reduce TANEC**

1.	Evaluate unit-specific NEC rate and benchmark unit performance against other unit NEC rates because the rate may be reducible.
2.	Communicate the unit-specific NEC rate with every physician, neonatal nurse practitioner, bedside nurse, dietitian and lactation consultant.
2.	Encourage mothers to provide human milk as soon as possible by initiating early pumping.[17]
3.	Consider feeding pasteurized donor milk if mother's milk is not available.[17]
4.	Evaluate unit-specific transfusion practices <ul style="list-style-type: none"> • Are they standardized? [4,5] • How are feedings handled before, during and after transfusion? • Do most infants < 1500 grams receive > 1 transfusion? [5] • Consider developing and implementing a standardized transfusion guideline
5.	Consider changing practice to exclusive human milk or nothing by mouth during transfusion and measure the impact on unit-specific NEC rate [14,15]