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## Red Blood Cell Transfusion-Related Necrotizing Enterocolitis in Very Low Birth Weight Infants: A Near-Infrared Spectroscopy Investigation

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### Abstract

**Background**—Recent evidence suggests that antecedent packed red blood cell (PRBC) transfusions increase the risk for necrotizing enterocolitis (NEC), the most common gastrointestinal emergency encountered by very low birth weight (VLBW) infants. The underlying mechanism for this association is unknown. Altered oxygenation of the mesenteric vasculature during PRBC transfusion has been hypothesized to contribute to NEC development and was investigated in this study.

**Study design and methods**—Oxygenation patterns among four VLBW infants who developed transfusion-related NEC (TR-NEC) were compared to four VLBW infants with similar gestational age who were transfused but did not develop NEC (non-NEC). Cerebral and mesenteric patterns were recorded before, during and 48 hours subsequent to PRBC transfusion using near-infrared spectroscopy technology (NIRS). Percentage change from mean baseline regional saturation (rSO<sub>2</sub>) values and cerebro- splanchnic oxygenation ratio (CSOR) were analyzed.

**Results**—All TR-NEC infants (24–29 weeks gestation; 705–1080 grams) demonstrated greater variation in mesenteric oxygenation patterns surrounding transfusions than non-NEC infants (27.6–30 weeks gestation; 980–1210 grams). TR-NEC infants received larger mean volumes of total blood (27.75 ml/kg ± 8.77) than non-NEC infants (15.25ml/kg ± 0.5).

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**Conclusion**—Wide fluctuation and decreases in mesenteric oxygenation patterns are more pronounced in TR-NEC infants, especially prior to TR-NEC onset, as compared to non-NEC infants. Greater total volume of infused blood was associated with TR-NEC in preterm infants. Using NIRS, larger prospective studies are needed to further evaluate potential risk factors for NEC in this high risk population.

### Keywords

Transfusion-related NEC; necrotizing enterocolitis; near-infrared spectroscopy

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### Introduction

Necrotizing enterocolitis (NEC) is a major cause of neonatal morbidity and mortality; especially in very low birth weight (VLBW) infants weighing < 1500 grams.<sup>1</sup> The pathogenesis of NEC is unclear. A leading hypothesis proposes that the development of NEC is characterized by mesenteric ischemia which results in an inflammatory cascade and eventual bowel necrosis.<sup>2</sup> However, other hypotheses suggest a multi-factorial pathophysiology with specific causal factors yet to be identified. Current prevention strategies for NEC are ineffective, and consequently the incidence has remained unchanged over the last several decades.<sup>2,3</sup>

Several recent studies suggest that packed red blood cell (PRBC) transfusions are temporally related with NEC onset, which tends to occur immediately and up to 48 hours post-transfusion (TR-NEC).<sup>4-12</sup> The underlying mechanism of this relationship is unknown. Our prospective study endeavors to quantify mesenteric tissue oxygenation patterns, using Near Infrared Spectroscopy (NIRS) technology, of very low birth weight (VLBW) premature infants receiving PRBC transfusions. Prior studies have utilized NIRS technology to observe mesenteric oxygenation changes during and for the 12-hour period following PRBC transfusion; however, no occurrences of TR-NEC were analyzed. Transient improvement was seen during and immediately after PRBC infusion; however, levels began to decline 12 hours post transfusion.<sup>13</sup> Therefore, we evaluated cerebral and mesenteric tissue oxygenation during and for 48 hours following PRBC transfusion to further examine tissue oxygenation trends at a time when VLBW infants are most likely to develop TR-NEC. This case series compares mesenteric tissue oxygenation patterns exhibited by a subset of VLBW infants, due to the development of TR-NEC, to tissue oxygenation patterns of four VLBW infants of similar gestational age in the same study who did not develop NEC subsequent to PRBC transfusion.

### Materials and Methods

#### Study population

Premature infants were recruited into the Emory institutional review board approved study from November 30, 2010 to December 31, 2011. Recruited infants were preterm gestational age (GA) < 37 weeks, admitted to Emory level IIIB neonatal intensive care unit (NICU), who were to receive a PRBC transfusion. Infants with congenital anomalies, intraventricular hemorrhage Grade III or greater, hemodynamically significant patent ductus arteriosus, requiring vasopressor support and current or previous NEC were excluded. All routine care was recorded from nursing flow sheets. Transfusion administration (volume and duration) and enteral feeding continuation or cessation during the transfusion event was determined by the attending physician. All infants were followed until discharge, death or transfer for the development of NEC. NEC diagnosis was based on Bell's Staging criteria.<sup>14</sup> TR-NEC was defined as infants diagnosed with NEC within 48 hours post- PRBC transfusion. The timing of TR-NEC onset was determined based on medical record documentation of actual disease

onset. Medical TR-NEC was defined as infants who were medically managed (antimicrobial therapy, bowel rest and decompression) and did not require surgical intervention due to complications associated with NEC progression. Surgical TR-NEC was defined as infants who required surgical intervention for complications directly resulting from TR-NEC onset and/or progression of disease.

As part of a larger ongoing study examining oxygenation patterns during and subsequent to PRBC transfusion using NIRS, this case series describes four VLBW infants who developed TR-NEC and were compared to four VLBW infants who received a transfusion that did not develop this complication. The non-NEC infants were selected from other VLBW infants on study with the closest corrected GA at the time of transfusion. Only 4 of the 19 infants enrolled in the larger study met this criterion.<sup>15</sup>

### **Packed Red Blood Cell Data and Characteristics**

All PRBC units transfused to infants were stored in a citrate-phosphate-dextrose-adenine (CPDA-1) solution. In this case series, all infants received cytomegalovirus negative, irradiated, leukoreduced, group O Rh-negative PRBC units, except one infant who received group O Rh-positive PRBCs. Irradiation storage time and age of PRBCs were recorded. Infant hemoglobin values were recorded prior to each PRBC transfusion per routine NICU care prior to transfusion.

For each infant, the number of PRBC transfusion events received before, during and after the study transfusion event were recorded, as were the volume and duration of the study PRBC transfusion. Enteral feeding events were recorded during and after transfusion events including type, volume, duration, route, frequency, tolerance and timing related to the transfusion event.

**Near-Infrared Spectroscopy Monitoring**—Cerebral and mesenteric regional oxygen saturation ( $rSO_2$ ) values were measured using an INVOS 5100C Cerebral/Somatic Oximeter (Covidien, Boulder, CO), an FDA approved NIRS device. NIRS measures total oxygen bound to hemoglobin, which at the tissue level is a result of oxygen delivered, minus oxygen consumed by the tissue and is reported as the  $rSO_2$ . This measure reflects overall tissue perfusion status.<sup>16</sup> The range of  $rSO_2$  measurements of this NIRS device is 15–95%. Data were recorded every 30 seconds in real-time prior to, during and 48 hours subsequent to receiving a PRBC transfusion. NIRS sensor probes were placed on the forehead and lower abdomen to obtain cerebral and mesenteric measurements. Upon completion of the monitoring period, data were downloaded from the NIRS device and transferred to a research computer for data analysis.

### **Data Analysis**

SAS statistical software (SAS/STAT Software, version 9.2 Cary, NC: Institute; 2000–2008) was used to calculate mean mesenteric and cerebral  $rSO_2$  values in 30-minute intervals for all infants. Baseline means were calculated from every 30 second  $rSO_2$  readings for the first 30-minute period for each initial transfusion event. All  $rSO_2$  values for the remainder of the monitoring period were averaged in 30-minute intervals for comparison as percentage change from baseline values. We chose this empiric approach to quantify fluctuations from mesenteric baseline means for pattern comparison. Cerebro-splanchnic ratios (CSOR) were calculated from raw  $rSO_2$  cerebral and mesenteric values by dividing mesenteric  $rSO_2$  by cerebral  $rSO_2$ , and then 30-minute interval means were calculated. Cut-off values for CSOR raw and mean scores were set at 0.75 to depict altered perfusion.<sup>17</sup> Mesenteric and CSOR mean  $rSO_2$  patterns were descriptively interpreted as they related to concurrent events during transfusions and over time subsequent to each transfusion event.

## Results

### Infant Characteristics

Characteristics of TR-NEC (n=4) and non-NEC (n=4) infants are listed in Table 1. Due to small sample size, p values were not computed to statistically evaluate the differences between TR-NEC and non-NEC groups. During the study period, five infants received 2 PRBC transfusions in a short period of time. Two infants received divided aliquots of equal volume separated by 12 hours, and 3 received 2 full volume PRBC transfusions (15–20ml/kg) in 67 hours. TR-NEC infants received larger volumes of PRBCs ( $27.75 \text{ ml/kg} \pm 8.77$ ) compared to the non-NEC infants ( $15.25 \text{ ml/kg} \pm 0.5$ ). Hemoglobin levels were collected per routine NICU policy prior to the first transfusion event for all infants. All PRBC transfusion in this case series were administered for anemia of prematurity. All infants were receiving enteral feedings prior to the transfusion event. The decision to continue or hold feedings during transfusion events was made by attending physician independent of this study.

### TR-NEC Onset

The onset of Bell's Stage IA or greater as diagnosed and documented in the medical record by attending physician occurred within 48 hours of the second (or split volume) transfusion for all TR-NEC group infants (see Table 1). TR-NEC infants 1 and 2 were medically managed and infants 3 and 4 required surgical intervention. Infant 1 acutely developed medical TR-NEC within 30 minutes following the second split-volume transfusion, and infant 2 developed acute medical TR-NEC within 11.5 hours subsequent to the second full-volume transfusion event. Following mechanical ventilation for respiratory distress, antimicrobial therapy, nothing by mouth status and gastric decompression, both infants recovered without further problems. Infant 3 developed gastrointestinal perforation 38.5 hours subsequent to receiving a second full volume transfusion (15ml/kg). Peritoneal drains were placed with transient improvement in clinical status over the next 14 days; however, bowel resection and ileostomy were required for bowel necrosis two weeks subsequent to this event. Infant 4 developed symptoms of TR-NEC during the second full-volume transfusion event including abdominal distention, green gastric residuals, and dilated loops of bowel on abdominal radiograph without pneumatosis. Enteral feedings were held for 12 hours. Feeding intolerance re-developed and this infant was again placed on NEC precautions four days subsequent to the second transfusion event. Eight days later, pneumatosis was evident on abdominal radiograph confirming Bell's Stage IIB NEC. Bowel resection related to stricture development was required five weeks after this event.

### Near-Infrared Spectroscopy Data

Mean mesenteric baseline values calculated for the 30 minute period for every first or single transfusion received are listed in Table 1. TR-NEC group  $r\text{SO}_2$  mesenteric baselines were  $41.5 \pm 19.4$  compared to  $32.9 \pm 15.6$  for the non-NEC group.

**$r\text{SO}_2$  Pattern Comparison**—Figures 1 and 2 demonstrate  $r\text{SO}_2$  mean percent changes from baseline (increased or decreased) for TR-NEC infants; figure 3 demonstrates  $r\text{SO}_2$  patterns for all non-NEC infants. Mesenteric means for TR-NEC infants overall exhibited greater fluctuation above and below baselines than did the non-NEC infants. Medical TR-NEC infants (Figure 1)  $r\text{SO}_2$  means fell during enteral feedings following the first transfusion event, and remained below baseline prior to initiation of the second transfusion event. Increases in mean  $r\text{SO}_2$  values were not as great during the second transfusion event; however, means dramatically rose at the end of the second transfusion for both infants. This dramatic rise for infant 1 coincided with TR-NEC onset, which was clinically diagnosed 30 minutes post-transfusion. Mean  $r\text{SO}_2$  for infant 2 remained 17% above baseline and rose to

54% above baseline at the time of TR-NEC onset 12 hours following the end of the second transfusion.

Changes in  $rSO_2$  patterns for TR-NEC infants are shown in Figure 2. Infant 3 means fell to 69% below baseline immediately following initiation of the first full volume transfusion (15ml/kg) and persisted at this low level between transfusions and throughout the second full volume (15ml/kg) PRBC transfusion until gastrointestinal perforation developed 38.5 hours later. Following peritoneal drain placement,  $rSO_2$  means rose (data not shown) to 40% above baseline levels. Infant 4 demonstrated increased oxygenation change from baseline, yet highly variable with a large range in oxygenation (-7% to 178%) throughout the study. TR-NEC development (Bell's stage IA) occurred during the second transfusion with slow progression until Stage IIB NEC was confirmed four days later. Surgical stricture repair and ileal resection was required five weeks following our study. Prior to TR-NEC onset and during periods of  $rSO_2$  fluctuations, all 4 infants remained normotensive with  $SpO_2$  readings > 92%.

Mean  $rSO_2$  patterns for the non-NEC group are shown in Figure 3. Overall, there was much less variability above and below baseline measurements in these patterns as compared to the TR-NEC infants. In general,  $rSO_2$  means remained higher than baseline values for non-NEC infants following each transfusion event. One large drop from baseline was seen 6 hours post-transfusion in infant 6 which coincided with enteral feeding intolerance, but no symptoms of NEC.

### Cerebro-splanchnic Oxygenation Ratio (CSOR) Pattern Comparison

CSOR values (data not shown) among the TR-NEC group revealed greater fluctuation than non-NEC infants. However, infants from both groups demonstrated CSOR values below and above our assigned cutoff value of 0.75. During medical TR-NEC onset, CSOR values for were > 0.75 and ranged from 0.25 to 1.09 for surgical TR-NEC infants.

CSORs for non-NEC infants were less variable over time ranging from 0.25 to 1.15. During episodes of profound apnea, bradycardia and desaturation, raw CSOR values for non-NEC infant 7 rose (from 0.36 to 1.00) and mesenteric  $rSO_2$  signal drop out was frequently recorded with associated sharply decreased cerebral values (data not shown). This elevation in CSOR means was related to sharp decreases in both cerebral and mesenteric values. Once this infant was placed on mechanical ventilation, cerebral values returned to baseline, but mesenteric means remained low generating overall low CSOR values (0.19–0.24).

## Discussion

This study demonstrated mesenteric tissue oxygenation pattern changes using NIRS technology during TR-NEC onset in VLBW infants. Although previous studies have used NIRS to prospectively examine tissue oxygenation patterns during and following PRBC transfusions, the occurrence of TR-NEC was not observed.<sup>13,18</sup> Further, these previous studies did not observe or include the combined effect of enteral feedings and transfusions on mesenteric oxygenation pattern changes.

NIRS technology simultaneously measures real-time regional tissue oxygenation producing  $rSO_2$  values which reflect differential organ oxygenation. The actual  $rSO_2$  reading measures changes in tissue concentration of oxyhemoglobin and deoxyhemoglobin, or the balance of oxygen that is delivered minus the amount extracted at the tissue level.<sup>16</sup> There are several reasons for decreased  $rSO_2$  values: increased consumption of oxygen at the tissue level, diminished or absent blood flow, or altered and/or decreased oxygen carrying capacity.<sup>16</sup> A

combination of any or all of these factors may also be present. Therefore, it is vital that infant factors be closely monitored for reasons contributing to low rSO<sub>2</sub> measurements.

The results of this study demonstrate unique tissue oxygenation pattern variations between infants experiencing TR-NEC to those who did not. Oxygenation changes in TR-NEC infants showed greater variability between time points than non-NEC counterparts. Gastrointestinal immaturity may have played a substantial role in this pattern variation.<sup>3</sup> In the presence of impaired immune response and ineffective circulatory regulation, VLBW infants are vulnerable to the effects of impaired mesenteric blood flow.<sup>19,20</sup> Studies have shown that sustained decreased blood flow in the superior mesenteric artery followed by reperfusion may disrupt mesenteric circulatory regulation mechanisms and increase susceptibility to intestinal barrier injury.<sup>21</sup> The decreased rSO<sub>2</sub> means with subsequent increases at the time of TR-NEC onset in the medical TR-NEC infants may have been related to perfusion-reperfusion injury.<sup>21,22</sup> It is also possible that the increase in rSO<sub>2</sub> following TR-NEC onset in these infants was the result of volume resuscitation.<sup>23</sup> These findings are consistent with previous studies in which rSO<sub>2</sub> pattern variability was associated with low to high rSO<sub>2</sub> readings preceding NEC development.<sup>24</sup> Moreover, these abrupt changes in rSO<sub>2</sub> values were not reflected in routine physiologic monitoring, as SpO<sub>2</sub> values in all TR-NEC infants remained > 92% until actual disease onset.

The sharp decline in mesenteric oxygenation in TR-NEC infant 3 who developed pneumoperitoneum may have resulted from distortion of infrared light path length, ischemic bowel or absence of mesenteric perfusion. The highly fluctuant patterns exhibited in infant 4 may have been related to perfusion-reperfusion injury,<sup>21,25,26</sup> the consequence of enteral feedings immediately post-transfusion,<sup>27</sup> or combined effect. However, non-NEC infant 8 also demonstrated wide swings in the immediate post-transfusion period, but subsequently stabilized with increased oxygenation levels. Larger studies are needed for further evaluation of tissue oxygenation pattern changes relative to PRBC transfusion and NEC development and should include the effects of enteral feeding continuation during and post-transfusion.

Tissue oxygenation patterns of the non-NEC infants in this case series demonstrate overall improvement in tissue oxygenation during and following PRBC transfusions. Although point-to-point mesenteric variability from baseline measurements was fairly wide, 30-minute rSO<sub>2</sub> means were fairly stable throughout our study period.

Studies have also evaluated rSO<sub>2</sub> values in CSOR format which is calculated as mesenteric rSO<sub>2</sub>/cerebral rSO<sub>2</sub>.<sup>17,18,28</sup> Fortune et al found NEC occurred in preterm infants when CSOR values were < 0.75.<sup>17</sup> Furthermore, Bailey et al reported recently that infants with pre-transfusion CSOR values < 0.73 are more likely to demonstrate clinical improvement following a PRBC transfusion than those infants with beginning CSOR values > 0.73.<sup>18</sup> Our study findings related to CSOR values were not in agreement with these previous studies. We support the concept that CSOR values are beneficial when cerebral autoregulation is intact as the change in value directly reflects mesenteric changes. However, we postulate that if cerebral autoregulation is lost or impaired which is common in critically ill VLBW infants,<sup>29,30</sup> an improvement in the CSOR value may be reflective of decreased cerebral tissue oxygenation with little or no change in mesenteric values. We posit that it is necessary to evaluate absolute cerebral and mesenteric rSO<sub>2</sub> values to ensure an improved CSOR value reflects mesenteric, not cerebral changes. For these reasons, we chose to evaluate absolute mesenteric measurements as a percentage of increased or decreased fluctuations from baseline mean to describe the effects of related PRBC transfusion. We then analyzed CSOR means within the context of absolute rSO<sub>2</sub> pattern changes. Our study demonstrates that CSOR values < 0.75 are not always associated with ischemic bowel and NEC development.

We further illustrate that infants who develop TR-NEC may exhibit CSOR values  $> 0.75$ . To increase the generalizability of our study findings, we did not exclude infants with confirmed or suspected sepsis as did the Bailey study.<sup>18</sup>

Previous retrospective studies suggest that PRBC transfusions are an independent risk factor for TR-NEC,<sup>12</sup> with a 25–35% incidence in VLBW preterm infants.<sup>4,7–9,12,31</sup> Furthermore, TR-NEC occurs immediately and up to 48 hours post PRBC transfusion in VLBW infants.<sup>4–6,8,11,12</sup> Compared to previous studies, 21% (4/19) of the VLBW infants in our larger study developed Bell's Stage IA NEC or greater following a PRBC transfusion, with all cases occurring in  $< 48$  hours subsequent to a transfusion event.<sup>15</sup>

There were several limitations to this study, the first major limitation being a small sample size. We recognize our comparison group differed maturationally as compared to the TR-NEC group, and these differences may have influenced the risk factor for disease development, feeding intolerance and mesenteric tissue oxygenation changes. Additionally, pre-transfusion baseline means for all infants in this case series were not obtained which limited direct comparison of post-transfusion oxygenation changes. NIRS technology can be associated with probe displacement which interferes with continuous trend monitoring, and ability to calculate CSOR values if cerebral and/or mesenteric values are missing. Continuous mesenteric monitoring is challenging, given the large surface area of the intestine, peristalsis, and increased infrared path length in the presence of pneumoperitoneum, abdominal distention or increased fluid/gas surfaces. These limitations may lead to “signal drop out” which was observed on our infant with pneumoperitoneum. However, it is more likely that persistent low  $rSO_2$  readings coupled with frequent signal drop is associated with a substantial decrease in tissue oxygenation.<sup>24</sup> Finally, this study was limited by the inability to quantify decreased percentage changes from baseline values when beginning measurements are extremely low. Because the lowest measurement capable of NIRS technology is 15%, infants with baseline values at or near this level exhibited a “floor” effect. Therefore, in these cases, it is crucial to evaluate if oxygenation improves or remains persistently low signifying potential perfusion impairment.

In conclusion, this prospective observational case series demonstrates actual changes in mesenteric tissue oxygenation patterns in infants who developed TR-NEC. Further distinct differences in these patterns were demonstrated in the TR-NEC infants as compared to similar infants that did not develop NEC. The major differences between our groups were greater fluctuations above and below beginning baseline values demonstrated by our TR-NEC infants than infants who did not develop NEC. We demonstrate that analyzing percent changes from baseline quantifies the magnitude of baseline changes, and may be more beneficial when used in conjunction with CSOR values, rather than CSOR values alone.

We recognize that establishing  $rSO_2$  patterns during enteral feedings prior to the transfusion event would strengthen our understanding of pattern changes during and subsequent to transfusions, illustrating the need for further research. This study demonstrates that severe and sudden decreases in mesenteric tissue oxygenation patterns may increase the risk for TR-NEC onset, especially if low readings persist. Enteral feedings may have a compounded impact on mesenteric oxygenation and perfusion during and following PRBC transfusions; however, further analysis of this possibility are needed. NIRS is a useful diagnostic tool to directly observe tissue bed oxygenation in real-time without interrupting routine bedside care and may elucidate compromised mesenteric perfusion before changes in routine physiologic monitoring are evident, primarily  $SpO_2$  measurements. Future studies utilizing this technology to analyze mesenteric oxygenation pattern changes relating to risk factors for TR-NEC development seems promising and feasible with the capability to improve prediction and prevention strategies especially when modifiable risk factors are present.

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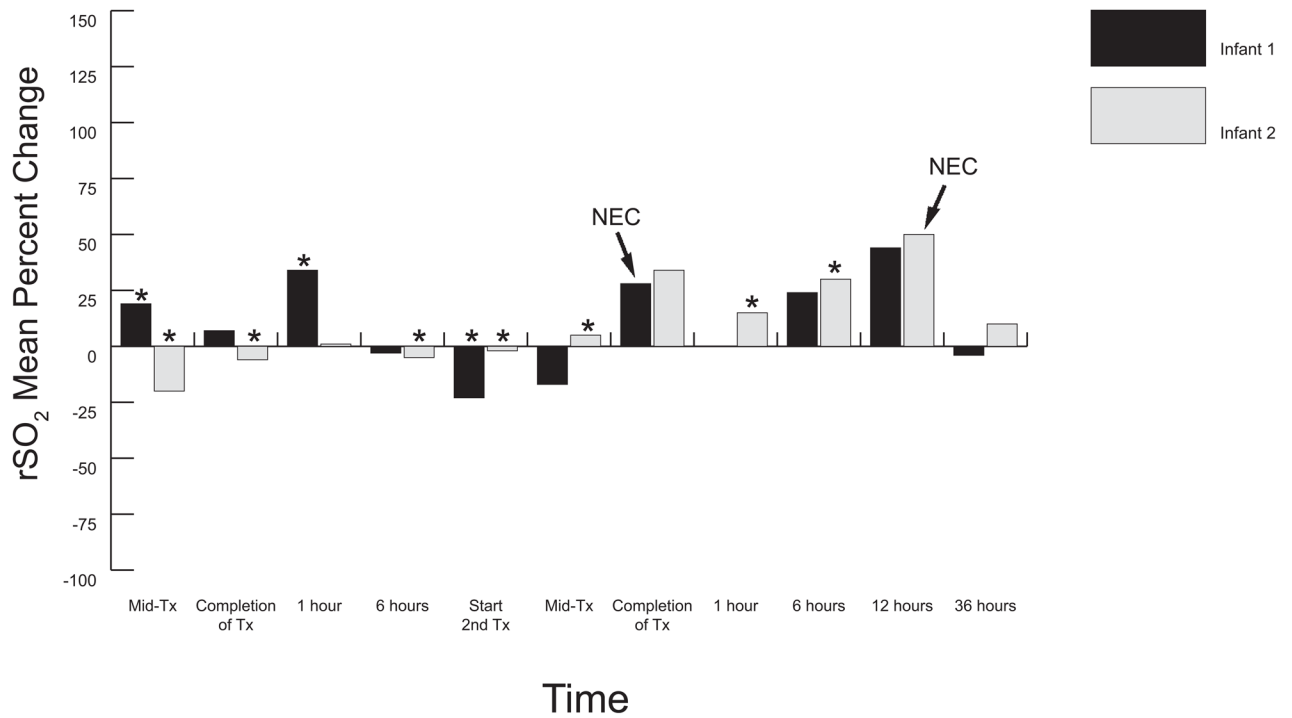
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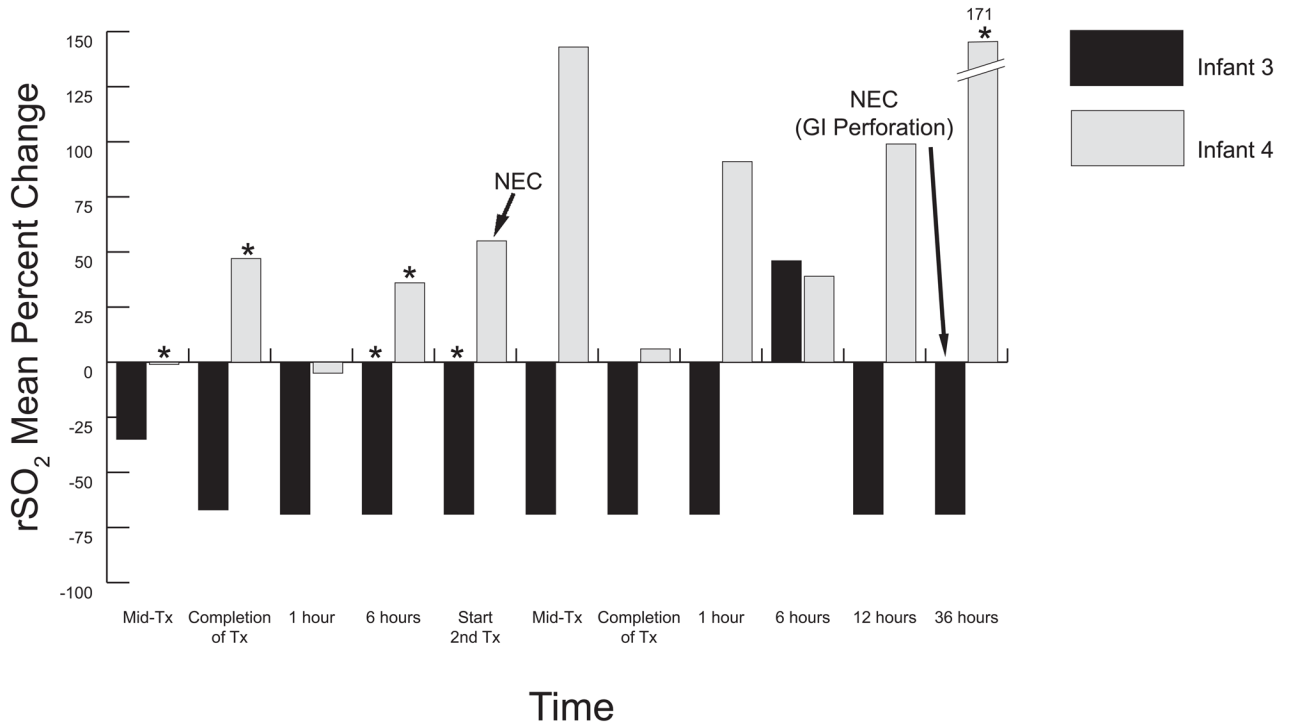


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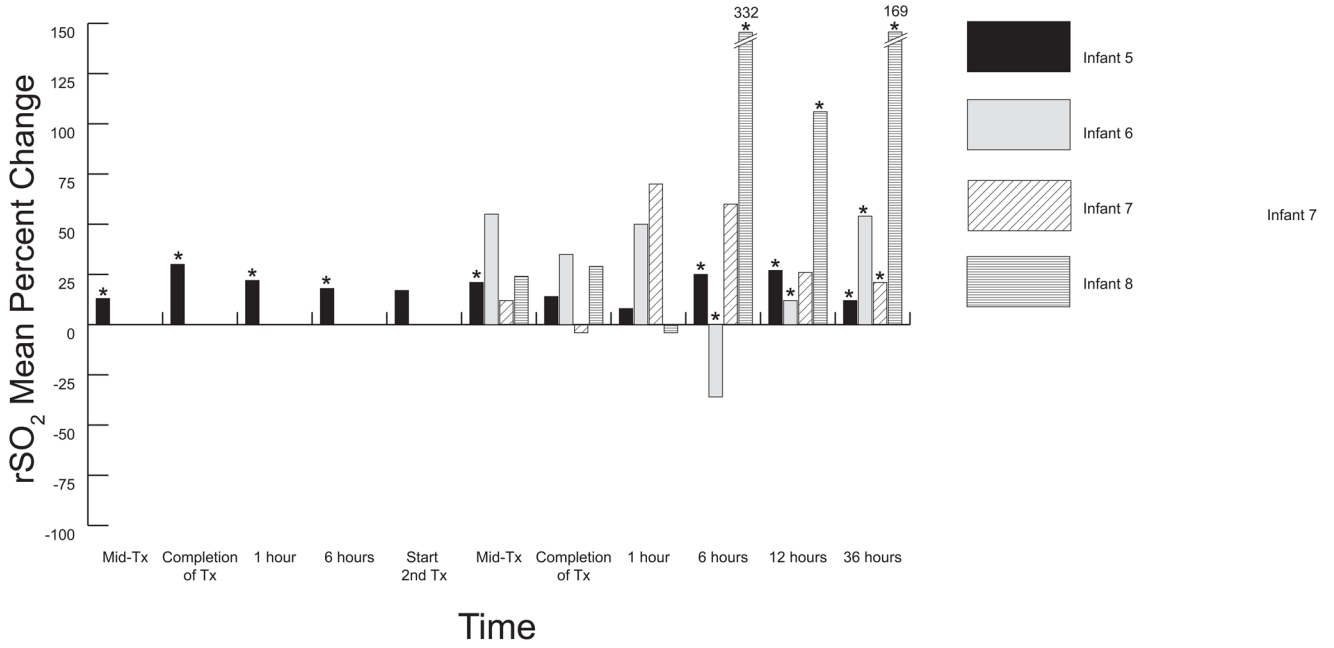


**Figure 1.**

Mesenteric Mean Percentage Change from Baseline: Medical TR-NEC Infants. This graph illustrates the wide mesenteric oxygenation fluctuations above and below baseline measurements during and subsequent to each transfusion event and further reveals decreased oxygenation immediately prior to TR-NEC onset and subsequent increased patterns at the time of TR-NEC onset. Infant 1 received two half-volume PRBC transfusions (7.5ml/kg each) separated by 12 hours. Infant 2 received two full volume (15ml/kg) PRBC transfusions separated by 21 hours. Infant 1 had NIRS monitor removed during resuscitation and transfer to NICU (time point 1 hour after 2<sup>nd</sup> transfusion). Tx, transfusion; TR-NEC, transfusion-related necrotizing enterocolitis; Mid-Tx, time at which 50% of total volume had infused; \* enteral feeding given during specified time frame; 0 = baseline; NEC, onset of TR-NEC.



**Figure 2.** Surgical TR-NEC Infants Percent Change from Baseline Means. This graph illustrates mesenteric oxygenation patterns of infants that developed surgical TR-NEC. Both infants received two full volume PRBC transfusions; infant 3 transfusions separated by 67 hours, and infant 4 separated by 24 hours. Infant 3 demonstrated an immediate large and persistent decline in oxygenation (-69%) immediately following the initiation of the 1<sup>st</sup> full volume transfusion (20ml/kg) which persisted until gastrointestinal perforation developed 38.5 hours after the conclusion of the second full volume (20ml/kg) PRBC transfusion. Wide fluctuations in mesenteric oxygenation were observed in infant 4 prior to and following the development of Bell’s Stage IA TR-NEC symptoms at the beginning of the 2<sup>nd</sup> full volume transfusion (15ml/kg). Enteral feedings were held for 18 hours and then resumed. Tx, transfusion; TR-NEC, transfusion-related necrotizing enterocolitis; Mid-Tx, time at which 50% of total volume had infused; \*enteral feeding given during specified time frame; 0 = baseline.



**Figure 3.** Mesenteric percent change from baseline mean for Non-NEC Infants. Infant 5 received two half-volume PRBC transfusions (7.5ml. kg each) separated by 12 hours; all other infants received one full volume PRBC transfusion. Overall increased oxygenation in mesenteric oxygenation was prevalent among the non-NEC infants, although wide mean fluctuation was apparent in infant 6, 7 and 8 (closely resembling surgical TR-NEC infant 4). Six hours post-transfusion, infant 6 demonstrated a dramatic decline in oxygenation that coincided with severe bradycardic and apneic episodes, which improved following elective intubation. Tx, transfusion; Mid-Tx, time at which 50% of total volume had infused; \*enteral feeding given during specified time frame; 0 = baseline.

Table 1

Infant Demographics and Clinical Data.

	TR-NEC group								Non-NEC group							
	1	2	3	4	5	6	7	8	Mean±SD	5	6	7	8	Mean±SD		
Infant Number	29	27	24	26	26.5 ± 2.1	29	30	27.6	28	28.6 ± 1.07						
GA Birth (weeks)	1080	1000	705	803	897.0 ± 173	1210	1160	980	1060	1102.5 ± 102.6						
Birth weight (g)	31	22	11	8	18 ± 10.6	31	24	8	14	19.3 ± 10.2						
PNA (days)	40.8	47	48.1	16.1	38 ± 14.9	43.4	42.8	18.9	15.7	30.2 ± 15.0						
Mean mesenteric baseline (rSO <sub>2</sub> )	0	1	7	0	0	0	1	1	1							
# transfusions received prior to study	7.5	15	20	15	14.4 ± 5.2	7.5	15	15	16	13.4 ± 3.9						
Volume of 1 <sup>st</sup> transfusion (ml/kg)	7.5	15	15	16	13.4 ± 3.9	7.5	-	-	-	-						
Volume of 2 <sup>nd</sup> transfusion (ml/kg)	12	21	67	24	12	-	-	-	-	-						
Time between transfusions (hours)	0.5	11.5	38.5	0	12.6 ± 18	-	-	-	-	-						
Time to TR-NEC Onset (hours)																

TR-NEC, Transfusion-related necrotizing enterocolitis; GA, gestational age at birth; PNA, postnatal age; rSO<sub>2</sub>, regional oxygenation saturation.