



### May 2010: VOLUME 8, ISSUE 1

### Adverse Association Between Blood Products and Necrotizing Enterocolitis

#### In this Issue...

Over the past several months, the publication of a number of compelling retrospective clinical studies has prompted debate among neonatologists regarding the associations between packed red blood cell and/or intravenous immunoglobulin transfusions and necrotizing enterocolitis. In this issue, we review those findings in order to help clarify these ongoing discussions.



#### Program Information

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#### Length of Activity

1.0 hour Physicians  
1 contact hour Nurses

#### Release Date

May 6, 2010

#### Expiration Date

May 5, 2012

## LEARNING OBJECTIVES

At the conclusion of this activity, participants should be better able to:

- Evaluate the evidence regarding the relationship between blood product transfusions and necrotizing enterocolitis.
- Discuss the synergism among diverse risk factors for necrotizing enterocolitis and identify opportunities for risk reduction when acute risk factors do arise.
- Reassess the definition of necrotizing enterocolitis and determine when a new disease entity should be included under this diagnostic category.

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- **Christoph U. Lehmann, MD**, has indicated a financial relationship of honoraria from Mead Johnson and PediatrIX. Dr. Lehmann is also the Editor-In-Chief of *Applied Clinical Informatics Journal*. He serves on the Board of Directors for the American Medical Informatics Association.
- **Anthony Bilenki, MA, RRT, Edward E. Lawson, MD, Lawrence M. Nogee, MD and Mary Terhaar, DNSc, RN** indicated they have no relevant financial relationships with any commercial supporters.

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### Guest Faculty Disclosure

Philip V. Gordon, MD, PhD,  
indicated he has no relevant  
relationships to disclose.

### Unlabeled/Unapproved Uses

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## COMMENTARY

Bob Christensen and colleagues at Intermountain Healthcare, headquartered in Salt Lake City, Utah, are fearless in the types of questions they pose. Last month, they asked, "Is transfusion-associated necrotizing enterocolitis (NEC) an authentic pathogenic entity?"<sup>1</sup>

It begins with having a high granularity regional database. Christensen has proven this concept time and again with his very high publication rate and precise focus on such topics as NEC, hematology, and growth. Although our national neonatal databases, including Vermont Oxford, the National Institute of Child Health and Human Development (NICHD), and Pediatrix, all have prodigious power, they sometimes lack sufficient data granularity to address these more subtle associations that may reflect disease mechanism. Moreover, Christensen has a team of clinical researchers who, when necessary, can return to the original charts to minimize data dropout and retrieve essential data elements in select patient subsets.

Over a 7-year period, 112 patients within Christensen and coworkers' health care system developed surgical NEC (i.e. severe NEC). Of these patients, 40 developed NEC within 48 hours of receiving a packed red blood cell (PRBC) transfusion, whereas the other 72 cases were unrelated temporally to any transfusions. The investigators conducted a more detailed analysis of 38 in-house patients who acquired NEC following transfusion vs. 38 matched controls, and found that age of the transfused blood, number of transfusions, and the preservatives used all had no association with the development of NEC. In contrast, feeding volumes and failure to receive breast milk were both associated with the development of NEC following transfusion. In fact, the latter 2 features have been found to be common risk factors associated with all forms of NEC.

Clear differences existed in the demographic characteristics of patients who acquired NEC following transfusions vs. those who did not. The mean gestational age and mean birth weight of patients with transfusion-associated NEC were 27 weeks and 981 grams, respectively, compared with 30 weeks and 1371 grams, respectively, for those who developed NEC without undergoing transfusion. The time of diagnosis was 1 week later in life for the NEC-with-transfusion group, with 40% of these patients dying vs. only 28% dying in the NEC-without-transfusion group. We need to examine these findings more carefully. Although the mortality difference was not significant ( $P = .11$ ), it was close enough to be called a trend (particularly since the cohort was too small to discriminate a real difference in mortality).

Christensen and associates found that NEC with transfusion affected a more premature group of neonates than did NEC without transfusion. One might reasonably ask whether anybody else has reported similar results. The answer is yes, because in the only other 2 published, retrospective studies to demonstrate an association between PRBCs and NEC

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in the postsurfactant era, the neonates in the NEC-with-transfusion cohorts also had mean birth weights of <1000 grams (766 grams and 855 grams, respectively).<sup>2,3</sup> Christensen seems to have discovered a new risk factor - one that is relatively specific for preterm NEC and is associated with substantial morbidity.

Perhaps the reader might recall a disease called spontaneous intestinal perforation (SIP). For years, SIP was thought to be NEC, and it was only because of the ability to demonstrate that patients with SIP had separate demographic characteristics, distinct clinical outcomes, and novel risk factors that the neonatal and surgical worlds gradually came to accept SIP as a distinct clinical entity.<sup>4</sup> So here, too, Christensen and collaborators are establishing a unique disease entity. Although it is a type of NEC, transfusion-associated NEC is also distinct in its risk factors, its demographic characteristics, and potentially in its outcomes (a larger cohort study will be needed to demonstrate a true difference in mortality). Certainly, this type of successful NEC reductionism highlights the inadequacies of Bell's criteria, based on all the reasons that have been argued.<sup>5</sup> Specifically, Christensen's data indicate that transfusion-associated NEC and the entity described as preterm NEC greatly overlap, and may be part of the same smaller NEC spectrum.

This exciting new finding is controversial. The next questions most people are going to ask are: "Why are PRBC transfusions associated with NEC?" "What is the biology behind this association?" "What about other blood products and NEC?" These and other, similar questions are likely to be the source of much consternation among neonatologists. Some of the answers are there for us to ponder if only we look for them in the right places.

A reductionist's approach to the NEC literature results in a rather optimistic view: the more risk factors we identify and the more diverse populations we correctly demonstrate to be at risk, the better able we will be to limit acquired neonatal intestinal diseases in the future. Recent evidence for a decline in SIP has been encouraging. Now we have to hold that ground and move on to the next front. Christensen and colleagues have masterfully drawn attention to transfusion-associated NEC. It took about a decade to reverse the trends with SIP. Hopefully, we can do better this time as we focus on transfusion-associated NEC.

In addition, intravenous immunoglobulin (IVIG)-associated pneumatosis in near-term infants with antibody-mediated hemolysis seems to be a thromboembolic entity that mimics acute NEC in its presentation. It is likely there are important adjunct risk factors that have yet to be elucidated, since comparable IVIG preparations have good safety profiles in preterm infants. A Web-based adverse outcomes registry would be a good methodology for capturing additional data on this emerging disease entity. Manufacturers of IVIG should be eager to help support such a site, since doing so will help to identify the adjunct risk factors and improve the safety of their product.

## Commentary References

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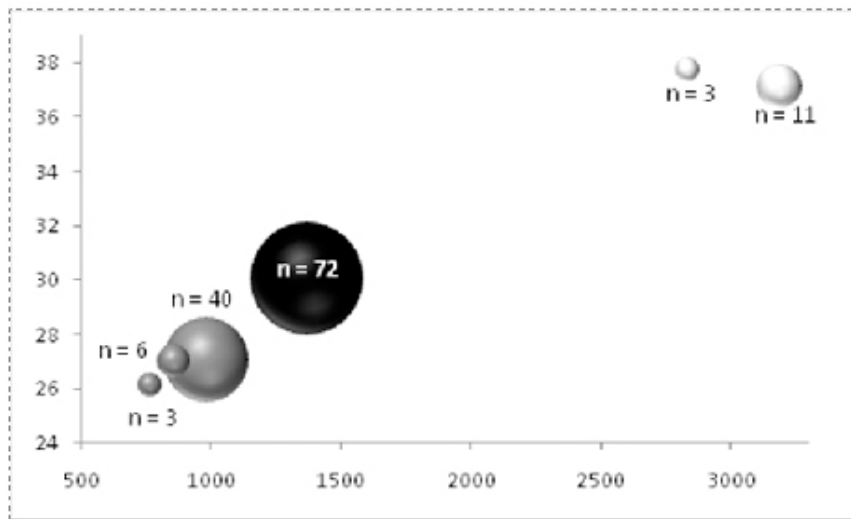
### Who is at risk for developing NEC after PRBC transfusion?

Part of the answer to this question depends on the length of time involved in defining the term "after." The Commentary section described 3 retrospective studies of PRBC-associated NEC. In the Christensen and Mally studies, "after" transfusion was defined as 48 hours, whereas the Seattle group defined "after" transfusion as 1 week (with a mean presentation of 4.8 days following transfusion). The definition of NEC is critical to the answer as well. Christensen defined NEC as surgical NEC (excluding SIP). In contrast, Mally's definition of NEC largely included medical NEC, surgical NEC, and SIP (of particular concern was the fact that one-third to two-fifths of the nontransfused NEC group presented with free air, did not have pneumatosis, were not fed substantially, received indomethacin early in life, weighed <1000 grams, and perforated in the first 10 days of life-patterns that are all highly suspicious for SIP). Although the Seattle group used Bell's criteria unmodified and thus would have potentially captured medical NEC, surgical NEC, and SIP - their cohort comprised medical cases only and thus consisted of just medical NEC. Thus, we have described 3 relatively different cohorts. In the Christensen study, we have only the most severe NEC cases--that is, those exposed to PRBC transfusion within 48 hours of diagnosis vs those who were not. In the Mally study, on the other hand, we seem to have NEC primarily in the transfused cohort, but most likely NEC plus SIP in the nontransfused cohort. In the Seattle cohort, we have medical NEC within a relatively long window following PRBC transfusion. We have apples, lemons, and prunes, to wit, and cannot answer the question without delineating the data further.

### *Can we characterize the at-risk population using a simple subset analysis?*

Technically, the Christensen study is the best. The only thing it really lacks is a denominator. The Seattle study is the least compelling for a direct association with the transfusion event (with only 3 cases that actually qualify using the definitions of the other 2 studies). We know that the Christensen group pulled 121 cases of surgical NEC from 7 years of a regional database. It would have been ideal if they had included the number of admissions by gestational age and birth weight during that time period, so we could have calculated regional prevalence. The Seattle and Mally studies are weaker because they are smaller and use broader definitions of NEC. The real value in combining data from these 3 studies comes from capturing 49 cases with a standardized definition of transfusion association (<48 hours). However, because all the NEC definitions differ, the data cannot be pooled. The best we can do is to use subset group analyses to confirm that transfusion-associated NEC cohorts all cluster into a common low gestation, low birth weight group (see the figure below). This demonstrates that low birth weight, very preterm infants are the patient group at risk.





**Figure Legend:** Bubble plot comparing birth weight (grams, depicted on the x-axis) vs gestational age (weeks, depicted on the y-axis) in 5 cohorts of patients with NEC. The 3 gray bubbles represent PRBC transfusion-associated NEC subcohorts derived from Christensen et al, 2009 (n = 40); Valieva et al, 2009 (n = 3); and Mally et al, 2006 (n = 6). The black bubble represents an NEC subcohort not associated with transfusion (Christensen et al, 2009, n = 72). The white bubbles represent cohorts of patients with NEC associated with IVIG administration for hyperbilirubinemia from Figueras-Aloy et al, 2010 (n = 11)<sup>1</sup> and Navarro et al, 2009 (n = 3).<sup>2</sup>

#### *What is the etiology of transfusion-associated NEC?*

Christensen suggested one possibility, based on the work of Krimmel and coworkers,<sup>3</sup> whereby transfusion is associated with transient loss of splanchnic bed responsiveness to feeding bolus, resulting in relative intestinal ischemia in infants who are challenged with feeding advances or formula fortification. Christensen used a matched control analysis to verify that paucity of breast milk and excess feeding volumes were related to transfusion-associated NEC, consistent with this hypothesis. A second, perhaps more ominous, possibility is the hypersensitivity theory.

In this less well-substantiated hypothesis, initial transfusions contain an unknown antigen, infectious agent, or inflammatory agent that conveys sensitization, followed by subsequent transfusions (from the same or a different donor), thereby triggering a hypersensitivity reaction. Because the gut is highly sensitive to inflammation in the neonate and responds with innate-immune, self-destruct programming, it is hypothesized to be especially sensitive to systemic inflammation. Similar mechanisms have been postulated for transfusion-related acute lung injury (TRALI) in older patient populations. It has been suggested at national meetings that perhaps transfusion-associated NEC should be called TRAGI (transfusion-related acute gut injury). Christensen and collaborators found that transfusion-associated NEC correlated with earlier and more frequent PRBC exposure compared with matched controls who received transfusions but did not develop NEC. In a separate analysis,<sup>4</sup> infants who developed transfusion-associated surgical NEC had later onset of diagnosis than did those who developed non-transfusion-associated surgical NEC, potentially consistent with the plausibility of a "2-hit hypothesis."

These 2 explanations are not exclusive, nor are they the only possible explanations. They are, however, the 2 most widely discussed explanations among individuals with an interest in transfusion-associated NEC. One potential caveat of the second hypothesis is the possibility that there might be cross effects between various blood products. Investigations appear to be lacking, however, about the potential of harmful synergy with combinations of blood products or donors.

#### *What can we do to prevent or reduce the incidence of transfusion-associated NEC now that we have established its existence?*

Anyone who has seen one of these truly virulent cases of NEC following a transfusion knows that there is precious little that can be done once the cat is out of the bag. However, Christensen and colleagues have given us hope that should be taken seriously.

If most of these cases involve infants who are on formula or fortifier, who are being advanced during or shortly before the time of transfusion, then we have control of the situation. First and foremost, we should always advocate for breast milk for every mother at every feeding, unless she is taking a medication that is contraindicated with breastfeeding or is unable to do so for societal reasons (eg, the mother is incarcerated). The more infants we have who are receiving breast milk, the fewer cases of NEC that will develop. Second, we have to be judicious with our transfusions and cognizant of their timing. If a child is advancing up to full feeds, it might be a good idea to hold the advance until the next day; which is the same advice when it comes to advancing the fortifier. If a child is showing signs of feeding intolerance even before the transfusion, then it might be sensible to cut back on the feeding by half for a day or so while administering the transfusion. Although weight gain is important, it is equally important to avoid events that result in gut loss.

Some may advocate the use of erythropoietin. Others may want to follow a strict regimen with respect to the manner in which transfusions are administered. The best action may be to simply accept the relationship—that is, to understand that there is a temporal link between administration of PRBCs in the latter half of the first month of life and NEC. If we recognize that this association exists, just as it does with early postnatal steroids, indomethacin, and SIP, then we will avoid these deleterious combinations in the future simply because we now know better.

One final point: National databases should actively begin to track transfusion-associated NEC so that we can study it within better powered datasets. Likewise, the non-transfusion-associated NEC that Christensen identified still must be considered. This entity occurs earlier in life within a somewhat older gestational age patient population and has yet to be elucidated. Is this one entity? Is it multiple entities? Breaking NEC into large subsets is just the beginning. The more success we have, the easier it gets to chase down the next one. Then we uncover a key risk factor for that one, and the next one, and so on, until suddenly there is no NEC subentity for which we do not have some preventive or therapeutic strategy that we did not have before. It is likely that we will never cure all forms of NEC with a magic bullet, but perhaps one day there will be no version of NEC that we do not understand.

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## NEC AND IVIG TRANSFUSIONS

Figueras-Aloy J, Rodríguez-Miguélez JM, Iriondo-Sanz M, Salvia-Roiges MD, Botet-Mussons F, Carbonell-Estrany X. **Intravenous immunoglobulin and necrotizing enterocolitis in newborns with hemolytic disease**. *Pediatrics*. 2010; 125(1):139-144.



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Shah PS, Kaufman DA. **Antistaphylococcal immunoglobulins to prevent staphylococcal infection in very low birth weight infants.** *Cochrane Database Syst Rev.* 2009; (2):CD006449.



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#### *Are intravenous immunoglobulin transfusions a risk factor for NEC?*

A recently published article by Figueras-Aloy and coworkers suggests an association between IVIG transfusion and NEC in near-term, predominantly female infants being treated primarily for hyperbilirubinemia (7 with ABO incompatibility, 4 with Rh disease). Of the total cohort of 492 patients, half were male, 11 developed NEC, with 9 of these infants being female). In addition to gender, other significant differences indicated a highly skewed cohort, including younger gestational age, smaller birth weight, need for resuscitation, and poorer 1-minute Apgar score. There were also strong trends approaching significance for small-for-gestational-age (SGA) status and 5-minute Apgar score, which proved to be significant, along with IVIG, in a multivariate analysis. The only risk factor for NEC that these girls did not exhibit was having received an excess of formula. It appears that in a number of cases, only a couple of hours of feeds were given prior to the development of symptoms (and at least 1 patient did not receive any feeding), which would indicate that the infants did not have NEC but more likely had ileus from thrombosis. Since the authors did not define what they considered to be NEC (specifically, they did not invoke the editorial “get-out-of-jail-free pass” known as Bell’s staging criteria, nor did they mention whether pneumatosis was a required finding), it is impossible to determine if the patients actually had NEC (generally defined as the presence of pneumatosis following successful, sustained feeding).

Fortunately, there is an excellent case series from Spain by Navarro and colleagues, in which the authors not only describe the rapid onset of pneumatosis in 3 infants within hours of receiving IVIG, but also describe “disseminated thrombi obstructing multiple minor vessels of the mesenteric circulation” from a pathologic specimen. In short, they are not describing NEC; rather they are describing an acute mesenteric thromboembolic event occurring shortly after high-dose IVIG administration. This latter explanation appears more palatable, as it accounts for why these patients do not die very often (in the 2 studies, although 14 infants developed acute symptoms, only 1 died in the acute period). Presumably, this is because they do not yet have enough substrate in their intestines to drive bacterial overgrowth. Thus, the initial plume of pneumatosis is self-limited. As an aside, of the 14 pooled infants with IVIG-associated disease, 11 were female, suggesting once again that there might be a true sex predilection. We need larger numbers of patients to test this hypothesis.

#### *What about IVIG in preterm infants?*

There are, in fact, fairly good safety data on IVIG preparations in preterm infants. The largest dataset is to be found with antistaphylococcal-enriched IVIG preparations, which have now been investigated in 2 large, multicenter, randomized trials (reviewed in a Cochrane analysis by Shah and Kaufman). No association with NEC was demonstrated in either trial. Associations were examined separately by each of Bell’s 3 staging criteria. With the polyclonal immune globulin Veronate® (Inhibitex, Inc.; Alpharetta, GA), the authors also delineated NEC vs. SIP and found no association with either entity. Based on these findings, there is no evidence to support an association between IVIG and NEC in cohorts of patients who are predominantly preterm.

#### *What is the mechanism by which IVIG causes pneumatosis in term infants?*

Term vs. preterm is an important distinction. Clearly, IVIG-associated NEC differs from PRBC-associated NEC in that it affects near-term infants (see the figure in Review 1). Several years ago, Lambert and associates from the Intermountain Healthcare group

conducted the definitive study on risk factors for term NEC. The authors demonstrated that SGA, slightly less mature, term infants with perinatal hypoxic events and rapid formula advances were at highest risk for term NEC. Although the Figueras-Aloy study contains many patients who were designated NEC and had many of those same risk factors, the study does not appear compelling for IVIG and NEC. However, in combination with the Navarro study, it appears likely that the viscosity effects of IVIG, which are thought to be quite profound when IVIG is administered too quickly, could induce sudden thrombosis and yield NEC-like symptoms. Therefore, it can be argued that this disease entity is not NEC, as we have conceptualized it for the last 50 years, but is rather a form of diffuse mesenteric thromboembolism. In term infants who are barely fed, morbidity and mortality should be better with this disease entity than in term infants with NEC (which is actually not as bad as we used to think). There may be confounders, such as high-intensity phototherapy, biliblankets, cephalosporins, and central lines, which all need to be investigated as possible adjunct thrombosis risks. One of the things that neither the Figueras-Aloy study nor the Navarro study examined was the route of IVIG administration (one might imagine that administration of IVIG via an umbilical artery catheter would be an unfortunate correlate). Future research will require capturing more patients with better data granularity. This would perhaps be an ideal disease entity for an adverse outcomes registry Web site, so that we could gather cases worldwide.

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## ADDRESSING CONCERNS ABOUT OTHER BLOOD PRODUCTS ASSOCIATED WITH NEC RISK IN PREMATURE NEONATES

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Baer VL, Lambert DK, Henry E, Snow GL, Sola-Visner MC, Christensen RD. **Do platelet transfusions in the NICU adversely affect survival? Analysis of 1600 thrombocytopenic neonates in a multihospital healthcare system.** *J Perinatol.* 2007;27(12):790-796.



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*Is there any evidence that other blood products are associated with the development of NEC?*

Currently, there is no evidence that receiving either fresh frozen plasma (FFP) or platelets is associated with the development of NEC. Randomized trials have compared the use of FFP vs crystalloid or gelatin as initial volume expanders in very low birth weight infants, with no difference in NEC rates reported with FFP vs gelatin but an improvement in NEC rates with FFP vs crystalloid. Thus, it seems clear that FFP is not associated with NEC and, in appropriate situations, actually may be protective. The evidence for the association of platelet transfusion with NEC is more difficult to assess.

Because thrombocytopenia is a common, albeit late, clinical presentation for NEC, the need for platelet transfusion is a challenging procedure to study as a risk factor. Perhaps the best study to explore this situation was a randomized, controlled trial by Andrew and coworkers of prophylactic platelet transfusion for the prevention of intracranial hemorrhage (ICH) in infants with platelet counts <150,000/ $\mu$ L. There was no reduction in ICH with transfusion and no difference in NEC between the 2 treatment groups (78 treated infants vs 74 controls; 3 cases of NEC in the platelet-transfused group vs 1 in the control group). Based on these findings, it is probably safe to assume that platelet transfusions are not associated with the development of NEC.



However, it is probably not correct to assume that platelet transfusions are safe in general. Once again, the Intermountain Healthcare group (Baer and colleagues) has conducted an important study worthy of consideration. The investigators posed another fearless question. They posited that platelet transfusions are often given to sick infants who die, but they then asked whether cumulative platelet transfusions added to the risk for death. The simple answer is that even after factoring out severity of illness and such intrinsic risks as early gestational age, platelet transfusions are associated with a cumulative risk for mortality. The authors suggest that one reason for this situation is that each platelet transfusion is derived from a different single donor, and thus cumulative transfusions equate almost one to one as multiple donor exposures. In this study, for infants receiving =20 platelet transfusions, the predicted mortality rate was 50%, compared with 35% in those receiving >10 platelet transfusions.

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## TO COMPLETE A POST-TEST

### Step 1.

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