

Hematological Abnormalities in Neonatal Necrotizing Enterocolitis

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ABSTRACT:

Objective: Necrotizing enterocolitis (NEC) is a leading cause of morbidity and mortality in preterm infants born prior to 32 weeks gestation or with a birth weight less than 1500 grams. In this article, we review hematological abnormalities associated with NEC.

Methods: A literature search was performed using the databases PubMed, EMBASE, and Scopus, and the electronic archive of abstracts presented at the annual meetings of the Pediatric Academic Societies.

Results: Thrombocytopenia, disseminated intravascular coagulation, increased or decreased neutrophil counts, and hemolytic anemia are frequent events in NEC.

Conclusions: NEC is associated with several hematological abnormalities, which may play a direct or indirect role in the pathogenesis of gut mucosal injury. Some of these abnormalities carry important prognostic information.

Key words: NEC, thrombocytopenia, neutropenia, anemia, nucleated RBC, DIC

Introduction: Necrotizing enterocolitis (NEC), an inflammatory bowel necrosis of premature infants, is a leading cause of morbidity and mortality in infants born prior to 32 weeks' gestation and with a birth weight less than 1500 grams (1, 2). Although the etiology of NEC is unclear, current evidence associates NEC with diverse pre- and postnatal factors such as placental insufficiency, prolonged/ premature rupture of membranes, chorioamnionitis, gut ischemia, altered bacterial colonization, viral infections of the gastrointestinal tract, bacterial overgrowth, and blood transfusions (1, 2). These conditions presumably alter/disrupt the epithelial barrier and promote the translocation of luminal bacteria into the sub-epithelial *lamina propria*, thereby triggering an inflammatory reaction in the immature gastrointestinal tract (1, 3). Severe cases of NEC may be associated with massive spillage of bacterial products into the bloodstream or even frank bacteremia, resulting in a systemic inflammatory response and multi-organ dysfunction (4).

Hematological abnormalities were first reported in NEC by Hutter *et al.* (5), who noted that thrombocytopenia, disseminated intravascular coagulation, increased or decreased neutrophil counts, and hemolytic anemia occur frequently in these patients. Although these abnormalities remain mild and require no intervention in many infants with NEC, others with severe disease require blood product transfusions and careful vigilance for complications such as hemorrhage, infections, anemia, and even death (4, 6). In this article, we review the clinical presentation, pathophysiology, and treatment of hematological abnormalities associated with NEC.

Platelet counts: Thrombocytopenia, defined as a platelet count $<150 \times 10^9/L$, is seen at clinical presentation in 50-95% of all infants with NEC, and many have platelet counts in the range of 30

$\times 10^9/L$ to $60 \times 10^9/L$ (5, 7, 8). Ververidis *et al.* (9) reviewed the clinical course of 58 consecutive neonates with advanced NEC (Bell's stages II or III, gestational age 23-41 weeks, birth weight 550-4,270 grams) and noted platelet counts $< 150 \times 10^9/L$ in 54 (93%) infants and counts $< 100 \times 10^9/L$ in 51 (88%). These data are similar to previous reports by Hutter *et al.* (5), Patel *et al.* (8), O'Neill *et al.* (7), and Kenton *et al.* (10). More recently, Baer *et al.* (11) reviewed the clinical course of 11281 neonates admitted to level III neonatal intensive care units to determine the causes of severe thrombocytopenia (platelet counts $< 50 \times 10^9/L$) in this population. They identified severe thrombocytopenia in 273/11281 (2.4%) infants, and NEC was used to explain the low platelet counts in 52 (14%) of these neonates.

Most neonates with advanced NEC develop thrombocytopenia within 24-72 hours of onset of disease (5, 8, 10). The severity of thrombocytopenia correlates with Bell's clinical stage of NEC, and a rapid drop in platelet counts to $< 100 \times 10^9/L$ is a sensitive (although not specific) predictor of bowel gangrene (full-thickness bowel necrosis) or the need for surgical intervention (7, 9). Ververidis *et al.* (9) noted most of their patients who showed a rapid drop in platelet counts to $< 100 \times 10^9/L$ were bacteremic. In patients without intestinal necrosis, platelet counts recovered to normal levels within 24 hours (9). Overall, in survivors, the median time to recovery to a platelet count greater than $150 \times 10^9/L$ is about 7 to 10 days (5, 8).

Infants who die of NEC may have lower nadir platelet counts than survivors. In the cohort described by Ververidis *et al.* (9), 42/58 (72%) patients survived the acute episode of NEC. Patients who died of NEC had a lower nadir in platelet counts than the survivors. All patients with a platelet count greater than $100 \times 10^9/L$ during the course of the disease survived. Ragazzi

et al. (12) recorded platelet counts $<150 \times 10^9/L$ in 86% of non-survivors vs. 43.3% of the survivors ($p<0.0001$). Severe thrombocytopenia ($<100 \times 10^9/L$) was noted more frequently in non-survivors (70%) than in survivors (33%; $p<0.0001$). In another study, Kenton *et al.* reported higher median platelet counts in survivors than in non-survivors ($203 \times 10^9/L$ vs. $33 \times 10^9/L$; $p<0.001$). Severe thrombocytopenia was a predictor of mortality (adjusted OR 6.39; $p=0.002$) and NEC-related gastrointestinal complications such as cholestatic liver disease and short bowel syndrome (adjusted OR 5.47; $p=0.006$).

Although most patients with NEC do not show signs of disseminated intravascular coagulation, the primary mechanism for thrombocytopenia is widely believed to be increased platelet destruction. Indirect evidence for platelet consumption is seen in the rapid drop in platelet counts in many patients, and also in the short-lived rise in platelet concentrations following transfusions that last less than 24-48 hours (13). The mechanism(s) of thrombocytopenia in NEC has not been investigated in clinical studies, but existing information from animal models indicates a likely role of platelet-activating factor and increased circulating concentration of bacterial products such as lipopolysaccharide (14). These mediators stimulate endothelial cells and macrophages to release inflammatory cytokines and nitric oxide, which, along with thromboplastin released from gangrenous bowel, can increase platelet activation and aggregation in the microvasculature (7).

Several studies have evaluated thrombopoietin (Tpo) concentrations in neonates with NEC/bacterial sepsis, and have consistently shown higher plasma thrombopoietin (Tpo) concentrations in these infants than their healthy counterparts (15, 16). However, it was unclear whether these elevated Tpo levels were the result of increased Tpo production or rather reflected

decreased megakaryocytes and therefore sepsis-mediated suppression of megakaryocytopoiesis. To answer this question, Brown *et al.* (17) measured plasma Tpo concentrations, circulating megakaryocyte progenitors, reticulated platelet counts, and the percentage of reticulated platelets in the circulating platelet pool (RP%) in 20 neonates with sepsis and/or NEC. They showed elevated concentrations of Tpo, circulating megakaryocyte progenitors, and RP% in thrombocytopenic neonates, indicating increased Tpo-mediated thrombopoiesis, although the degree of up-regulation was relatively modest. The authors hypothesized that this dampening of thrombopoietic response may be due to increased levels of platelet factor 4, which is released from activated platelets and is a potent inhibitor of megakaryocytopoiesis.

Most infants with NEC and severe thrombocytopenia ($<50 \times 10^9/L$) receive one or more platelet transfusions. In the absence of a consensus for transfusion thresholds, practices vary considerably between Centers, and there is some information that transfusion thresholds may be higher in the United States than other countries (18). Important concerns remain about potential adverse effects of platelet transfusions, which, in combination with data showing a lack of correlation between low platelet counts and risk of bleeding, have been the subject of much debate (18). To investigate the effects of platelet transfusions, Kenton *et al.* (19) reviewed the hospital course of 46 infants with NEC (gestational age 28 ± 4 weeks, birth weight 1166 ± 756 g, mean $\pm$ SD). A total of 406 platelet transfusions were administered, where 151 (37.2%) were given in the presence of active bleeding. Other listed indications for platelet transfusions were hypovolemia and severe thrombocytopenia. There was no improvement in either mortality or morbidity with greater number and/or volume of platelet transfusions. Furthermore, infants who developed short bowel syndrome and/or cholestasis had received a significantly higher number

and volume of platelet transfusions than those who did not have these adverse outcomes [median (minimum - maximum) - number of transfusions : 9 (0 to 33) vs. 1.5 (0 to 20), $p=0.010$; volume of transfusions (mL/kg): 121.5 (0 to 476.6) vs. 33.2 (0 to 224.3), $p=0.013$].

Further study is needed in patients with NEC-related thrombocytopenia to optimize the use of platelet transfusion, which is the only intervention with immediate efficacy in patients with active bleeding. Recombinant cytokines and growth factors such as interleukin-11, Tpo, and Tpo-mimetic agents, which take about 5-7 days to increase platelet counts, may not be useful in most patients with NEC but could find use in selected cases with persistent thrombocytopenia secondary to short bowel syndrome and cholestasis (13). Melatonin has also been used in a small number of term infants with sepsis and may find use in a selected group of patients (20).

Coagulopathy: Severe NEC is frequently associated with coagulation disturbances. Hutter *et al.* (5) noted signs of disseminated intravascular coagulation (DIC) in 14 of their 40 infants. Many of these infants showed decreased plasma fibrinogen levels, tested positive for fibrin split products, and had elevated partial thromboplastin times. These data are similar to Patel *et al.* (8) and Sonntag *et al.* (21), who described a similar frequency of DIC in their respective cohorts. The treatment of DIC in these infants is largely supportive, including the administration of fresh frozen plasma and/or cryoprecipitate.

Neutrophil counts: Increased neutrophil counts comprise an appropriate inflammatory response in patients with mild-moderately severe disease. In contrast, neutropenia, defined as an absolute neutrophil count less than $1500/\mu\text{L}$, can be seen in severe NEC and is associated with adverse

outcome (5, 8, 9, 12). Patel *et al.* (8) noted that 14 of their 23 patients who died of NEC were neutropenic, compared to 6/24 of the survivors. In another study, Ragazzi *et al.* (12) noted that the detection of neutropenia in the initial blood counts at the time of onset of NEC was associated with adverse outcome; there was a trend for a higher frequency of neutropenia in non-survivors (37%) than in survivors (25%; $p=0.136$), and thrombocytopenia and neutropenia occurred together more frequently in non-survivors (39%) than in survivors (14%; $p=0.0007$). In infants greater than 34 weeks gestation, lower total neutrophil counts, higher immature neutrophil number, and greater immature: total neutrophil ratio at first presentation of NEC were associated with the need for surgical intervention (22). Although the pathophysiology of neutropenia in NEC is not well-understood, depletion of the circulating neutrophil pool due to emigration into the intestines and peritoneum, and increased margination in the microvasculature are some of the possible causes (5, 9, 12). Consistent with this hypothesis, the bone marrow is usually normocellular in these infants (5, 8).

Recombinant granulocyte-colony stimulating factor (rG-CSF) and recombinant granulocyte-macrophage colony stimulating factor (rGM-CSF) can be used to treat neutropenia in patients with NEC. Overall, rG-CSF may be more efficacious in raising neutrophil counts than GM-CSF (23). The use of these myelopoietic growth factors in NEC is extrapolated from studies on neonatal sepsis and neutropenia. Recombinant G-CSF may reduce mortality in patients with neonatal sepsis, although the benefit was not evident when non-randomized studies were excluded (24). Carr *et al.* (25) showed that rG-CSF/rGM-CSF therapy reduced mortality in neonates with sepsis and neutropenia [relative risk 0.34 (95% CI 0.12, 0.92); risk difference - 0.18 (95% CI -0.33, -0.03); number needed to treat 6 (95% CI 3-33)].

Anemia: Patients with NEC may develop anemia due to multiple pathogenetic mechanisms. In the presence of mucosal injury, thrombocytopenia, and coagulation disturbances, occult and obvious blood loss is common. Sites of bleeding may include bloody stools, peritoneal hemorrhage, pulmonary hemorrhage, hemopericardium, myocardial hemorrhage, and intracranial hemorrhage (6). Iatrogenic anemia due to phlebotomy losses is an added problem. In some patients, hemolysis can cause further worsening of anemia. Thrombotic microangiopathy can cause red cell damage, which can often be seen on blood smears as tear drop cells, schistocytes, spherocytes, and acanthocytes. Hutter *et al.* (5) reported red cell fragmentation in 25 of their 40 patients. Another possible cause is activation of the Thomsen-Friedenreich (T) cryptantigen on the RBC surface, a naturally-occurring antigen that is normally concealed by a layer of N-acetylneuraminic acid but can be exposed in NEC by bacterial or other neuraminidases. T-activation can cause hemolysis and anemia in multi-transfused patients who have previously received adult blood containing anti-T antibodies (26, 27). Studies show considerable variation in the frequency of T-activation in NEC, ranging from rare occurrences to up to a third of all patients (6, 28). T-activation is associated with increased morbidity and mortality in NEC. Finally, infants with NEC may be at enhanced risk of inflammatory suppression of erythropoiesis. NEC tends to occur most frequently in extremely premature infants, who show an impaired erythropoietin response for a given level of anemia and are prone to develop severe anemia of prematurity (6). The presence of inflammation following onset of NEC in these infants can cause further suppression of erythropoietin and red cell production.

Red cell transfusions form the mainstay of treatment of anemia in patients with NEC and associated multi-organ dysfunction. In patients with hemolysis, transfusions may need to be

administered cautiously after meticulous cross-matching. The value of washing or packing erythrocytes, washing platelets, or using low T cryptantigen titer plasma in patients with NEC remains unproven. Although recombinant erythropoietin is not useful in reducing the immediate need for transfusion in these patients, longer-acting synthetic erythropoietin-mimetics such as darbepoietin may still prove useful by preventing repeated transfusions in patients with a complicated course and ongoing inflammation.

Eosinophilia: Eosinophilia is diagnosed when the blood eosinophil counts exceed the 95th percentile upper reference limit, which ranges from 1180/ μ L during the 1st postnatal week to 1560/ μ L after 3 weeks (29). Christensen *et al.* (30) noted eosinophilia in 54 of 275 infants (19.6%) who were evaluated for bloody stools. They hypothesized that premature infants with bloody stools and eosinophilia were likely to have atopic enteropathy and not develop the classical signs of NEC, and were therefore, more likely to have a benign course of disease. However, the rate of *pneumatosis*, bowel resection, and death in infants with bloody stools and eosinophilia was similar to those with normal blood eosinophil counts. Interestingly, infants with eosinophilia were more likely to have received a RBC transfusion in a 48 hour period prior to passing a bloody stool. These infants with a preceding history of a blood transfusion showed a progressive rise in eosinophil counts. In contrast, infants who developed bloody stools and eosinophilia but did not have a history of a prior transfusion showed reduction in eosinophil counts once the feedings were discontinued and had a relatively benign course of disease. Although the mechanism for transfusion-associated eosinophilia is unclear, exposure to foreign antigens on donor RBCs or to medications administered during the transfusion may play a role.

Macrophages and Monocytes: We have shown recently that the cellular inflammatory response in NEC is characterized by the presence of a macrophage-rich infiltrate (31). We counted 128.6 ± 9.4 cells/high-power field (HPF) in tissue specimens of NEC, compared to 12.8 ± 1.1 cells/HPF ($p < 0.001$) in tissues resected for reasons other than NEC (such as atresia). Because intestinal macrophages are terminally-differentiated and incapable of clonal expansion, these macrophage infiltrates likely develop via recruitment of blood monocytes to sites of injury. Further study is needed to characterize circulating monocyte populations in infants with NEC.

Lymphocyte counts: In a recent study, Lambert *et al.* (32) noted that infants who died of fulminant NEC within 48 hours of onset may have low blood lymphocyte counts. They reviewed the medical records of 523 infants with a diagnosis of NEC, of which 35 (6.7%) had a fulminant course. These infants were more likely to have a blood lymphocyte count $< 4000/\mu\text{L}$ ($p = 0.018$), besides having portal venous air, severe anemia, recent increase in feeding volume or introduction of human milk fortifier, and increased immature to total neutrophil ratio.

Nucleated red blood cells: Infants who develop NEC may have a higher number of nucleated RBCs at birth than their gestation-matched controls. Mandel *et al.* (33) compared 23 preterm infants diagnosed with NEC with pair-matched controls who were admitted immediately after a case, had the same gestational age (± 1 week), 1- and 5- minute Apgar scores (± 1), and who did not develop NEC. Exclusion criteria included factors that may influence the ANRBC at birth, such as maternal diabetes, pregnancy-induced hypertension, major congenital malformations, chromosomal abnormalities, hemolysis and perinatal blood loss. Infants who developed NEC

had higher absolute nucleated RBC counts than controls, suggesting that these neonates may have experienced intrauterine hypoxemia, which may increase the risk of NEC. These data are consistent with observations by Baschat *et al.* (34), who showed that nucleated RBC counts >30/100 white blood cells beyond 3 days were associated with later risk of NEC.

Conclusions: NEC is associated with several hematological abnormalities, which may play a direct or indirect role in the pathogenesis of gut mucosal injury. Some of these abnormalities carry important prognostic information.

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