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Neutropenia in the Newborn

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Abstract

PURPOSE OF REVIEW—Review normal blood neutrophil concentrations and the clinical approach to neutropenia in the neonatal period. A literature search on neonatal neutropenia 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.

RECENT FINDINGS—This review summarizes current knowledge on the causes of neutropenia in premature and critically-ill neonates, focusing on common causes such as maternal hypertension, neonatal sepsis, twin-twin transfusion, alloimmunization, and hemolytic disease. The article provides a rational approach to diagnosis and treatment of neonatal neutropenia, including current evidence on the role of recombinant hematopoietic growth factors.

SUMMARY—Neutrophil counts should be carefully evaluated in premature and critically-ill neonates. Although neutropenia is usually benign and runs a self-limited course in most neonates, it can be prolonged and constitute a serious deficiency in antimicrobial defense in some infants.

Keywords

neonate; neutropenia; ANC; reference ranges; leukemoid

Introduction

Neutropenia is a frequently identified abnormality in neonatal intensive care units (NICUs). Blood neutrophil counts $<1000/\mu\text{L}$ are seen in about 8% of all NICU admissions (1–4), and depending on the definition of neutropenia, 6–58% of preterm infants are identified as having had low blood neutrophil counts on at least one occasion (5, 6). In this article, we review normal blood neutrophil concentrations and outline the clinical and laboratory evaluation of neutropenia in the neonatal period.

Normal blood neutrophil concentrations in neonates

The absolute neutrophil count (ANC) can be calculated from a routine complete blood count (CBC) by multiplying the white cell count ($/\mu\text{L}$) with the sum of segmented and band neutrophil percentages on the differential count. The ANC value can then be interpreted by comparison with one of several available reference ranges (7–9).

The first reference ranges for blood neutrophil concentrations were published by Manroe *et al.* (10), who compiled blood counts from 434 neonates born at 38.9 ± 2.4 weeks gestation.

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They showed that neutrophil counts peaked at 12–24 hours with 95% confidence limits of 7,800–14,500/ μ L and then stabilized at a lower value of 1,750 by 72 hours of life. These reference ranges were useful for term infants but were somewhat limited for preterm infants (11–14). The same group (Mouzinho *et al.*) then compiled a new set of ANC values using CBCs drawn from 63 neonates born at 29.9 ± 2.3 weeks gestation (9). This newer data set was compared to the Manroe charts but showed greater variation at the lower end of the reference ranges.

Schmutz *et al.* (7) recently compiled reference ranges for ANC using a large data set of 30,354 CBCs from neonates born at 23–42 weeks' gestation. In the interval between 72 and 240 hours after birth, the ANC ranged between 2700–13,000/ μ L (5th–95th percentile) for infants >36 weeks gestation, between 1000–12,500/ μ L at 28–36 weeks, and 1300–15,300/ μ L at <28 weeks gestation. The upper limits of ANC in this study were higher than those in the ranges reported in the Manroe and Mouzinho studies, possibly an effect of the high altitude at which the participating centers were located (15–17).

Definition of neutropenia

Statistically, neutropenia is defined as an ANC less than 2 standard deviations below the mean value or below the 5th percentile for postnatal age (8, 9, 18). Mouzinho *et al.* defined neutropenia as an ANC <1100/ μ L, a more stringent cutoff than the 1800/ μ L limit proposed by Manroe *et al.* (8, 9).

In neutropenic neonates, the relationship between low ANC and risk of infection remains speculative and has been extrapolated from older children with neutropenia secondary to Kostmann's syndrome or cancer chemotherapy. Whereas ANCs >1,000/ μ L are unlikely to increase the risk of nosocomial infection, ANC <500/ μ L may be more likely to increase the risk, particularly if neutropenia persists for more than a few days (19–21). Besides the severity of neutropenia, the risk of infection in a neutropenic neonate is also affected by the overall severity of illness and the presence of co-morbidities that may require invasive monitoring. In very low birth weight infants, the risk of infection secondary to neutropenia and the mortality attributable to infection in the setting of neutropenia are significantly higher than in term newborns (22).

Clinical evaluation of neutropenia in neonates

Neutropenia can be secondary to decreased production of neutrophils, increased neutrophil destruction, or a combination of these mechanisms (Table 1 [23–28]). Neonatal neutropenia occurs most frequently in association with maternal hypertension, sepsis, twin-twin transfusion, alloimmunization, and hemolytic disease (29, 30).

In many infants, maternal history of hypertension or pre-eclampsia with fetal growth restriction, multiple gestation with disparity between twins, or an infectious illness during pregnancy can be diagnostic. The incidence of neutropenia is reported as high as 49% in infants born to mothers with pregnancy-induced hypertension (31). The severity of neutropenia has been correlated with the severity of growth restriction (6). Kinetic investigations have suggested that neutropenia in infants born to mothers with preeclampsia is secondary to decreased production of WBCs (31). Kush *et al.* (32) showed that hematological abnormalities in growth-restricted fetuses correlated with the degree of placental dysfunction, estimated by fetal Doppler measurements of umbilical artery end-diastolic velocity. However, Zook *et al.* (33) did not find an association between decreased ANC in the newborn infant and histopathological changes in the placenta such as infarction or vasculopathy.

A history of prolonged rupture of membranes or chorioamnionitis in a newborn infant with neutropenia can indicate increased risk of early-onset sepsis. Sepsis-induced neutropenia is usually transient and resolves with recovery from sepsis, but in a critically-ill infant with multi-system dysfunction, neutropenia could be a sign of overwhelming sepsis and bone marrow depression (22).

In a well-appearing infant with persistent neutropenia, an immune-mediated etiology involving anti-neutrophil antibodies should be considered (34–39). Alloimmune neonatal neutropenia occurs due to maternal sensitization to a paternal antigen present on the neutrophils of her fetus, and produces specific antibodies that are transported across the placenta and cause neutropenia in fetus (35). Neonatal autoimmune neutropenia results from the transmission of pre-existing maternal anti-neutrophil autoantibodies into the fetus (35, 36). Unlike these two disorders caused by maternal antibodies, autoimmune neutropenia of infancy is a transient autoimmune phenomenon where the infant's own immune system produces the anti-neutrophil antibodies (38).

Laboratory evaluation of neutropenia in neonates

In a neutropenic infant, concomitant presence of anemia and/or thrombocytopenia may indicate the presence of a generalized bone marrow failure syndrome. Differential leukocyte counts can be used for kinetic evaluation of the neutrophil lineage by calculating the 'immature to total neutrophil (I:T) ratio' $[(\text{bands} + \text{metamyelocytes} + \text{myelocytes}) / (\text{segmented neutrophils} + \text{bands} + \text{metamyelocytes} + \text{myelocytes})]$. Schelonka *et al.* (40) reported that normal I:T ratios in term neonates have a mean value of 0.16 (SD 0.10), with a 10–90th percentile range extending from 0.05 to 0.27. In the presence of neutropenia, an elevated I:T ratio (> 0.3) reflects depletion of the neutrophil storage pool in the bone marrow due to increased peripheral destruction or recruitment of neutrophils into inflamed tissues. A normal/low I:T ratio in a neutropenic infant may indicate decreased neutrophil production. The I:T ratio retains its discriminatory value for sepsis in premature infants and can be employed in conjunction with other screening tests such as C-reactive protein concentrations (41–43).

A bone marrow biopsy (44) should be considered in infants with prolonged (> 2 wks), unusual, or severe neutropenia refractory to treatment with recombinant granulocyte-colony stimulating factor (G-CSF). Marrow evaluation can provide useful kinetic information, including the size of the proliferative and the post-mitotic storage pools of neutrophils. Reduction in both cellular populations suggests decreased marrow production, while increased numbers of proliferative precursors with a depleted storage pool is consistent with increased peripheral destruction of neutrophils. A combination of an expanded proliferative pool with a normal storage pool can be seen during marrow recovery and is relatively non-specific (45, 46).

Clinical Management of a Neonate with Neutropenia

Sepsis should be considered a possibility in unwell neonates with neutropenia and a presumptive course of antibiotics should be started pending the maturation of cultures over 48 hours (30). Routine antibiotic prophylaxis is not recommended in neonates as most cases have a benign, self-limited course. Infants with severe and prolonged neutropenia may be candidates for reverse isolation.

Recombinant G-CSF and Granulocyte-Macrophage-Colony stimulating factor (GM-CSF) are frequently used to treat neonatal neutropenia. G-CSF stimulates neutrophil production and release from the bone marrow, and reduces neutrophil apoptosis (47). GM-CSF can generate both granulocyte and macrophage colonies from precursor cells (48). Unlike G-

CSF, which is the primary systemic regulator of the circulating concentrations of neutrophils (47), GM-CSF may not play a major role in steady state conditions but can be induced in inflamed tissues to promote neutrophil and macrophage maturation (49). In the clinical setting, both G-CSF and GM-CSF increase neutrophil counts, although G-CSF may be more efficacious in raising neutrophil counts than GM-CSF (50).

The efficacy of G-CSF in neonatal sepsis has also been examined by several investigators with conflicting results (51–56). In meta-analysis, Bernstein *et al.* (57) reported that 73 G-CSF recipients had a lower mortality than 82 infants in the control arms [odds ratio, 0.17; 95% confidence interval (CI) 0.03–0.70; $p < 0.05$]. However, when non-randomized studies were excluded, the effect did not remain statistically adequate. The role of GM-CSF in prevention or treatment of neonatal sepsis remains similarly unclear (58–60). Carr *et al.* (61) reviewed the quality of evidence for the use of G-CSF/GM-CSF in neonatal sepsis. In preterm infants with suspected systemic infection, G-CSF or GM-CSF did not improve survival [typical relative risk of death 0.71 (95% CI 0.38, 1.33)]. However, in a subgroup of 97 infants with systemic sepsis and clinically-significant neutropenia at trial entry ($< 1.7 \times 10^9/l$), there was a significant reduction in mortality by day 14 [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)]. In prophylactic studies, recombinant GM-CSF did not reduce mortality [relative risk 0.59 (95% CI 0.24, 1.44); risk difference -0.03 (95% CI -0.08 , 0.02)].

G-CSF is highly effective in correcting immune-mediated neutropenias. Besides its effects on neutrophil production and delaying apoptosis, G-CSF may also downregulate antigen expression and render the neutrophils less vulnerable to circulating antibodies (62), increase additional antibody mopping sites such as soluble FcR γ III (63), and correct some of the functional impairments in neutrophils induced by anti-neutrophil antibodies (64).

G-CSF is effective in many patients with congenital neutropenias (65, 66). Kostmann syndrome presents in early infancy with ANC's often $< 200/\mu L$ and recurrent bacterial infections. These patients have mutations in the neutrophil elastase gene *ELA2* (67). G-CSF is highly effective in most patients with Kostmann syndrome (66, 68) and has reduced the need for antibiotics and hospitalization (69), and improved survival of these patients (70).

Cyclic neutropenia is a rare hematological disorder characterized by regular drops in ANC's to levels as low as $250/\mu L$ at 3-week intervals (71). Bone marrow may appear normal during periods of higher ANC's but may show a 'maturation arrest' of myeloid cells during or just before onset of severe neutropenia. G-CSF may be used to raise neutrophil counts during periods of severe neutropenia. Although the characteristic cycles are not eliminated by G-CSF, the number of days with neutropenia can be reduced (72). In contrast to G-CSF, these patients respond poorly to GM-CSF (73).

Neutropenia related to maternal preeclampsia is usually self-limited and the risk of infection in these neonates is unclear (74, 75). If needed, G-CSF can be used to correct neutropenia in these patients (76–78). In patients with 'idiopathic neutropenia of prematurity', neutropenia can be severe and prolonged but resolves spontaneously (79). These infants were neutropenic at or shortly following delivery, and remained neutropenic (generally $< 500/\mu L$) for 1–9 weeks. Blood and bone marrow studies indicated that the neutropenia was caused by decreased neutrophil production, although the cause was unclear. G-CSF treatment resulted in immediate and marked rise in ANC, indicating the presence of a substantial marrow neutrophil reserve (80). Treatment decisions may have to be individualized on the basis of the duration and severity of neutropenia.

The usual dose of G-CSF is 5–10 µg/kg/day, administered by intravenous or subcutaneous injection. In most situations, the ANC rises within 24–48 hours. In an occasional patient, G-CSF therapy will not raise blood neutrophil counts. G-CSF doses may be increased in increments of 10 µg/kg at 7–14-day intervals if the ANC remains below 1000/µL (37, 69). Doses can be reduced or withheld once ANCs reach >5000/µL. G-CSF treatment is usually tolerated in neonates without adverse effects. Long-term G-CSF therapy in congenital neutropenias has been associated with splenomegaly, thrombocytopenia, osteoporosis, myelodysplastic syndrome/leukemia, and development of anti-G-CSF antibodies (65, 81, 82).

Besides recombinant hematopoietic growth factors, several other modalities such as intravenous immunoglobulin (IVIG) have also been tried in neonatal neutropenia. IVIG is effective in about half of all infants with alloimmune and autoimmune neutropenia (19, 38, 83–85). IVIG can mobilize neutrophils from the marrow storage pool into the circulation and raise blood ANC, although repeated doses may be needed to obtain a sustained effect (38, 86, 87). Steroids are generally not effective in alloimmune neutropenia (88, 89). The response has been slightly better in autoimmune neutropenia of infancy. Steroids have been used in conjunction with G-CSF in a patient with Kostmann syndrome who was refractory to treatment with G-CSF alone (90). Granulocyte transfusions can be helpful to tide over acute crises, although current evidence does not show a clear benefit of granulocyte transfusions in neonatal sepsis (91). Exchange transfusions have not been successful in treating immune-mediated neutropenia (92).

Conclusions

Neutropenia is a commonly diagnosed condition in premature and critically-ill neonates. The most frequent causes are maternal hypertension, sepsis, twin-twin transfusion, alloimmunization, and hemolytic disease. Detailed evaluation is indicated in infants with severe (ANC <500/µL) or persistent (>5–7 days) neutropenia. Initial testing may include examination of the peripheral blood film, a complete blood count on the mother, and, if her blood neutrophil concentration is normal, maternal neutrophil antigen typing and an anti-neutrophil antibody screen. A bone marrow biopsy can be useful in cases with prolonged, unusual, or refractory neutropenia. In infants with severe or persistent neutropenia, treatment with recombinant G-CSF or GM-CSF should be considered.

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Key points

- Neutropenia is seen in 6–8% of all neonates admitted to NICUs
- Maternal pre-eclampsia, sepsis, twin-twin transfusion, alloimmunization, and hemolytic disease are the most common causes of neonatal neutropenia
- Severe or persistent neutropenia should trigger evaluation
- Severe congenital neutropenia and other bone marrow failure syndromes can be caused by diverse genetic mutations and may need specific testing
- Recombinant G-CSF or GM-CSF can be used to correct ANC in most infants

Table 1**Causes of neutropenia in newborn infants****Decreased neutrophil production**

Infants of hypertensive mothers (unknown; possible causes include presence of a placenta-derived inhibitor of neutrophil production)

Donors of twin-twin transfusions

Neonates with Rh hemolytic disease (precursors diverted towards erythroid differentiation to increase RBC production)

Congenital Neutropenias

Bone Marrow Failure Syndromes

Kostmann syndrome (promyelocytic maturation arrest and increased apoptosis of precursors; mutations in neutrophil elastase gene ELA1. Other gene mutations may involve antiapoptotic gene HAX1, and enzyme glucose-6-phosphatase, G6PC3; rarely, mutations in the gene encoding the transcription factor GFI1, activating mutations in the Wiskott-Aldrich syndrome (WAS) gene, or the vacuolar protein sorting-associated protein 45 (VPS45). Frequent acquisition of somatic mutations in the gene CSF3R (cognate receptor for G-CSF). (23, 24)

Reticular dysgenesis (severe combined immunodeficiency with impairment of both myeloid and lymphoid production; caused by homozygous or compound heterozygous mutation in the mitochondrial adenylate kinase-2 gene) (25)

Barth syndrome (organic aciduria, dilated cardiomyopathy, and neutropenia; also known as 3-methylglutaconic aciduria type II; caused by mutation in the tafazzin gene) (26)

Shwachman-Diamond syndrome (exocrine pancreatic insufficiency, failure to thrive, skeletal abnormalities, and neutropenia; defect in SBDS protein, which may be involved in ribosomal biogenesis)

Cartilage-hair hypoplasia (short-limbed dwarfism; impairment of proliferation in neutrophil precursors; caused by mutations in the mitochondrial RNA-processing endoribonuclease RMRP)

Cyclic Neutropenia (cyclic hematopoiesis with nadirs at 3-week intervals; associated with heterozygous neutrophil elastase mutations that prevent membrane localization of the enzyme) (27)

Inborn Errors of Metabolism

Organic acidemias (loss of neutrophil precursors)

Glycogen storage disease type 1b (increased neutrophil apoptosis; caused by mutations in the glucose-6-phosphate transporter gene)

Viral infections (infection of neutrophil progenitors, hypersplenism)

Cytomegalovirus

Rubella

Copper deficiency

Alloimmune neutropenia associated with anti-HNA-1b antibodies (antigen present on neutrophil precursors)

Increased neutrophil destruction

Bacterial or fungal sepsis (increased tissue migration; marrow suppression in severe cases)

Necrotizing enterocolitis (egress into intestines and peritoneum)

Anti-neutrophil antibody-mediated disorders (alloimmune neonatal neutropenia, neonatal autoimmune neutropenia, and autoimmune neutropenia of infancy)

Idiopathic neutropenia of prematurity (precursors diverted towards erythroid differentiation to compensate for anemia of prematurity)

Drug-induced neutropenia (β -lactam antibiotics, thiazides, ranitidine, acyclovir)

Pseudoneutropenia (benign condition; circulating neutrophil pool is smaller than the vascular marginated pool)

Artifactual Neutropenia (benign condition; neutrophils agglutinate upon exposure to ethylenediaminetetraacetic acid, an anticoagulant used in blood collection tubes)

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