

# Neutropenia in neonate – an overview

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## Introduction

Neutrophils are the first line of innate immune defense against bacterial infectious diseases. Therefore in presence of neutropenia, neonates are extremely vulnerable to develop infection. On the other hand acquired immune response requires time to develop and is dependent on previous interaction with specific microbes. In neonatal age the ability of neutrophils to kill microorganisms is immediate, non-specific, and not dependent on previous exposure to microorganisms.

Neutrophils are pivotal to antibacterial host defense. People who are lack of neutrophils, whether by a congenital or an acquired defect, will experience a natural history that includes repeated local and systemic infections and early death. In neonate neutrophil function and neutrophil kinetics during infection differ considerably from those of adults. Infected adults neutrophilia occurs due to accelerate the release of neutrophils from their marrow reserve into the circulation, and simultaneously recruit quiescent neutrophil progenitors into cycle, on the other hand in neonate specially in infected preterm neonates neutropenia occurs due to depleting their relatively small marrow neutrophil reserves before it can be replaced by granulocytopoietic acceleration. Neutrophil function of neonates, particularly preterm neonates, is less vigorous than that of adults and might also contribute to the increase in propensity to infection. A postnatal improvement of chemotaxis, phagocytosis, and respiratory burst activity begins at about two to three weeks of age and thereafter improves slowly

Definition: The definition of neutropenia, the lower limit of normal for blood neutrophil concentrations, has been reported variously as 1,500/mcL,<sup>1</sup> 1,800/mcL,<sup>2</sup> and 1,100/mcL.<sup>3</sup> Several investigators have provided normal

expected ranges for blood neutrophil concentrations among neonates. The relationship between blood neutrophil concentration and the risk of developing an infection has not been established for neonates. Extrapolating from the Chronic Severe Neutropenia Registry and chemotherapy studies in children, neonates who have neutrophil counts higher than 1,000/mcL are not likely to be at an increased risk. Those whose blood neutrophil concentrations are less than 500/mcL probably are at increased risk for infection, particularly if the severe neutropenia persists for days or weeks<sup>4,5</sup>. Neonates whose blood neutrophil counts are between 500 and 1,000/mcL may be at some intermediate risk.

The diagnosis of neutropenia is based on a low blood neutrophil concentration. The blood neutrophil count can be calculated readily from a routine complete blood count as follows:

Blood neutrophil count = White cells X % neutrophil on the differential count

## Causes of neutropenia

Neutropenia can be due to decreased production of neutrophils, excessive neutrophil margination, increased neutrophil destruction or combinations of these three mechanisms

### 1. Decreased Neutrophil Production

- Infants of hypertensive women
- Donors of twin-twin transfusions
- Neonates who have Rh hemolytic disease
- Chronic neutropenia in bone marrow failure syndromes as for example: Kostmann syndrome, Reticular dysgenesis, Barth syndrome, Schwachman-Diamond syndrome, Cartilage-hair hypoplasia, Cyclic neutropenia
- Inherited errors of metabolism
  - Glycogen storage disease type 1b
  - Organic acidemias

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- Viral infections  
Rubella, Cytomegalovirus (Intrauterine infections)
- Copper deficiency
- Alloimmune neutropenia associated with anti-NB1 antibodies

## 2. Increased Neutrophil Destruction

- Bacterial or fungal sepsis
- Necrotizing enterocolitis
- Alloimmune neonatal neutropenia
- Neonatal autoimmune neutropenia

## 3. Excessive neutrophil margination

## 4. Drug-induced Neutropenia

## 5. Others

- Idiopathic Neutropenia of Prematurity

## 1. Decreased Neutrophil Production

Neonatal Neutropenia Not Categorized as Severe Chronic Neutropenia :

### ● Pregnancy Induced Hypertension (PIH)/Infants of hypertensive women

Neutropenia due to PIH is the most common variety of neutropenia seen in the neonatal intensive care unit. 50% of neonates born to mothers with PIH have this variety of neutropenia. The ANC can be very low, frequently less than 500/ $\mu$ L, but the count generally rises spontaneously within the first days and is almost always greater than 1000/ $\mu$ L by day 2 or 3.<sup>6</sup> Usually no leukocyte "left shift" is seen, and no toxic granulation, Döhle bodies, or vacuolization is present in the neutrophils.<sup>7</sup> It is not clear whether this variety of neutropenia predisposes neonates to acquire bacterial infection. Usually the condition is so transient that such a predisposition is unlikely. The condition probably is caused by an inhibitor of neutrophil production of placental origin that might function mechanistically by depressing natural G-CSF production.

### Neutropenia Associated With Severe Intrauterine Growth Restriction:

This variety of neonatal neutropenia seems to be mechanistically identical to that associated with PIH.<sup>8</sup> No difference in onset, duration, or severity of neutropenia in small for gestational age (SGA) neonates versus neonates born after PIH. Obviously, some neonates born after PIH are also SGA, and it might be true that the most severe neutropenias in this category occur among those with both PIH and SGA. The neutropenias of PIH and SGA are similar, and both are transient with few clinical consequences.<sup>9</sup>

### ● Neutropenia in donor twins

Neutropenia generally occurs in the "donor" (anemic) twin affected with the twin-twin transfusion syndrome. As in the variety of neonatal neutropenia associated with PIH, this neutropenia is the

kinetic result of diminished neutrophil production.<sup>10</sup> Thus, no left shift is present, no morphologic abnormalities and it is transient, persisting generally about 72 hours.

### ● Neutropenia in neonates who have Rh hemolytic disease

It has been speculated that the marked increase in erythropoiesis results in a downmodulation of neutrophil and platelet production.<sup>11</sup>

### ● Varieties of neutropenia among neonates who generally are considered to have severe chronic neutropenia

#### Kostmann syndrome (severe congenital neutropenia)

Severe congenital neutropenia (SCN) occurs due to "maturation arrest" of marrow myeloid precursors at the step where promyelocytes mature to become myelocytes. This disorder of granulopoiesis is characterized by severe neutropenia (absolute neutrophil count [ANC] <500/mcL, generally <200/mcL) and a<sup>n</sup>. Patients who have SCN experience frequent episodes of severe bacterial infection, usually starting in the first month after birth.<sup>12</sup> The original Kostmann family appears to have an autosomal recessive inheritance, the genetic patterns of most patients described in other parts of the world are more consistent with sporadic mutations, resulting in an autosomal dominant condition.<sup>13</sup>

#### Shwachman-diamond syndrome

Shwachman-Diamond syndrome is an autosomal recessive disorder characterized by exocrine pancreatic insufficiency with steatorrhea and neutropenia. The initial symptoms typically are diarrhea and failure to thrive beginning in early infancy, although neonatal presentations have been reported. Neutropenia is common, and the ANC periodically falls below 1,000/mcL. Some children also have a defect in neutrophil chemotaxis. The illness may progress to bone marrow hypoplasia, leading to moderate thrombocytopenia and anemia.<sup>14</sup>

#### Cyclic neutropenia

Cyclic neutropenia also is known, perhaps more appropriately, as "cyclic hematopoiesis" because all of the formed elements of the blood cycle fluctuate in recurrent oscillations in this disorder. Blood neutrophil concentrations of infants who have this variety of neutropenia can fall to as low as 0/mcL, then increase to normal with a 21-day periodicity. The condition is congenital, but it is not diagnosed commonly in the neonatal period. Usually it is diagnosed later in infancy because it generally takes several cycles of neutropenia before the condition is suspected.

### ● Inherited errors of metabolism

#### Glycogen storage disease type Ib (GSD-Ib)

Glycogen-storage disease type 1b is a rare metabolic disorder, which affects the glucose-6-phosphate metabolism. The liver, spleen, and other tissues accumulate glycogen. Patients

with an enlarged liver and spleen, failure to thrive, kidney problems, hypoglycaemia (low blood sugar) and recurrent infections. The presence of an enlarged spleen can be associated with low red blood cells causing anaemia and thrombocytopenia whereas neutropenia is always present. Chronic neutropenia in these patients is accompanied by a defective function of the cells that are responsible for the killing of bacteria. Patients respond to treatment with G-CSF not only with an increase in ANC but also with improvement of the activity of their neutrophils.

### Intrauterine infections

Intrauterine cytomegalovirus and rubella infections can be associated with neutropenia or pancytopenia.<sup>16</sup> These hematologic abnormalities are considered to be due to hypersplenism, but likely they involve an element of reduced production, perhaps from direct infection of progenitor cells.

## 2. Increased Neutrophil Destruction

### ● Sepsis-induced neutropenia

Overwhelming bacterial infection is a relatively common cause of neutropenia. For many septic neonates, neutropenia is present at the time of diagnosis, but the neutropenia usually persists for fewer than 24 hours. It has been reported that sepsis-related mortality was threefold higher among neonates who developed neutropenia.<sup>17</sup>

This variety of neutropenia is the kinetic consequence of accelerated neutrophil utilization and is accompanied by a leukocyte "left shift" and neutrophil morphologic characteristics such as toxic granulation, vacuolization, and Döhle bodies.<sup>18</sup> The development of severe neutropenia can reflect exhaustion of the marrow neutrophil storage pool.<sup>19</sup>

### ● Neutropenia in necrotizing enterocolitis

Neutropenia commonly occurs in neonates who have necrotizing enterocolitis. Implicated mechanisms include increased use/destruction in tissues, margination due to endotoxemia, and increased mobilization of neutrophils into the peritoneum.<sup>20</sup>

### ● Alloimmune neonatal neutropenia (ANN)

In ANN the mother develops antibodies to a paternal antigen present on fetal neutrophils, and transplacental passage of these antibodies results in fetal neutropenia. Antineutrophil antibodies have been found in as many as 20% of randomly surveyed pregnant and postpartum women, although ANN is reported to occur in 0.2% to 2% of consecutively sampled newborns.<sup>21</sup>

### ● Neonatal autoimmune neutropenia

This disorder is seen in mothers who have autoimmune disease, when their neutrophil autoantibodies are transferred passively to the fetus. The neonates show transient neutropenia, with the duration depending on the time taken to clear the maternal immunoglobulin (Ig)G antibody. Frequently, both the mother and neonate are neutropenic. As in ANN, the recovery process

occurs over a few weeks to a few months.<sup>22</sup> Most affected neonates remain asymptomatic. Clinical features similar to those described previously, depending on the severity of neutropenia and its duration, have been noted.

### 3. Excessive neutrophil margination

A phenomenon that occurs in the early phases on inflammation as a result of dilatation of the capillaries, slowing of the blood stream. Leucytes occupy the periphery of the cross sectional lumen and adhere to the endothelial cells of the blood vessels. Endotoxaemia, Pseudoneutropenia.

### 4. Drug-induced neutropenia

Neutropenia has been reported as an adverse effect of several drugs used commonly in the NICU, including beta-lactam antibiotics, thiazide diuretics, and ranitidine.<sup>23</sup> With certain drugs, such as ganciclovir, neutropenia is a significant problem and sometimes necessitates cessation of therapy.<sup>24</sup>

## 6. Others

### ● Idiopathic neutropenia of prematurity

In some studies, late-onset neutropenia has been observed in 7.5% to 26% of stable, growing preterm infants.<sup>25</sup> The condition generally resolves spontaneously.

### Investigations :

Once neutropenia is suspected, the first step is aimed at identifying whether there is isolated neutropenia or associated signs of bone marrow failure, such as thrombocytopenia and anemia. Preliminary steps therefore include-

- **CBC with differential count and smear**, to assess neutrophil morphology.
- **Normal or low I/T ratio:** in the presence of severe neutropenia suggests that the neutropenia is from decreased production, as would be inferred for erythrocytes in a patient who has anemia and a low reticulocyte count.
- **Neutropenia and a very high I/T ratio:** suggest increased neutrophil production, thus implying increased peripheral destruction/tissue recruitment of neutrophils.

The immature-to-total (I/T) neutrophil ratio can be calculated as:

$$\frac{(\text{Bands} + \text{metamyelocytes} + \text{myelocytes})}{(\text{segmented neutrophils} + \text{bands} + \text{metamyelocytes} + \text{myelocytes})}$$

- **A bone marrow biopsy :** can be useful in cases with prolonged (>2 wk), unusual, or refractory neutropenia.
- **Other investigations:** according to cause, eg.

Coombs (direct antiglobulin test) for associated hemolytic anemia IgA, IgG, IgM/antineutrophil antibodies/viral serologies etc.

### Management of Neutropenia in neonate :

Various treatments have been proposed as means of enhancing neutrophil production and function in preterm infants

## 1. Intravenous immunoglobulin

IVIG has been tested as a means of preventing or treating neonatal sepsis among neonates with neutropenia. In theory IVIG should improve the preterm neonate's capacity to defend against infections. A systematic review suggests that IVIG therapy in infants with sepsis may improve outcome, however, its prophylactic use has produced inadequate clinical benefits.<sup>26</sup>

## 2. Corticosteroids

Corticosteroids have also been tried in the management of immune-mediated neonatal neutropenia and in the congenital bone marrow failure syndromes. The inconsistent response does not encourage a larger use in neutropenic neonates.

## 3. Granulocyte transfusions

Current evidence does not show a clear beneficial role for granulocyte transfusions in septic neutropenic neonates. A recent meta-analysis concluded that evidence from randomized controlled trials is insufficient to confirm or refute the use of granulocyte transfusions in neutropenic, septic neonates.<sup>27</sup>

## 4. Gamma interferon

Gamma interferon has been claimed to have potential for correcting abnormalities of cell movement and bacterial killing in vitro, raising the possibility that increasing IFN- levels might be beneficial. No studies have focused on using IFN- among neutropenic neonates.

## 5. Recombinant granulocyte colony-stimulating factor (rG-CSF) and recombinant granulocyte macrophage-colony-stimulating factor (rGM-CSF)

rG-CSF increases the number of circulating neutrophils by stimulating the release of neutrophils from bone marrow, inducing myeloid proliferation, expanding the marrow reserves, and reducing neutrophil apoptosis. rGM-CSF has been evaluated in neonates and the results are similar to those obtained with rG-CSF. One study showed that 5 day period of G-CSF therapy in premature infants with neutropenia that presented with clinical sepsis is safe and can reduce the length of hospital stay.<sup>28</sup>

## Conclusion

Neonatal neutropenia occurs in neonate for many reasons. So, neutrophil counts should be carefully evaluated in premature and critically ill neonates. Among them neonatal sepsis is one of the important cause. Neutropenia in neonates can occur due to many non infective causes and are usually benign and self limiting in most of the cases. Sometimes it can be prolonged, and constitutes a serious deficiency in antimicrobial defense in some infants.

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