Neutropenia in preterms: to treat or to ignore?

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Neutrophils and Host Defense
Neutropenia in a Neonate
Severe Chronic Neutropenia in the Neonate
Neonatal Neutropenia Not Categorized as Severe Chronic Neutropenia
Treatment of Neutropenia
Outline

- Treatment of Neutropenia
- Neutrophils and Host Defense
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- A Consistent Approach to the Use of rG-CSF in the NICU
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Treatment of Neutropenia

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

- Intravenous immunoglobulin
- Corticosteroids
- Granulocyte transfusions
- Gamma interferon
- Recombinant granulocyte colony-stimulating factor (rG-CSF) and recombinant granulocyte macrophage-colony-stimulating factor (rGM-CSF)
**Treatment of Neutropenia**

- Intravenous immunoglobulin (IVIG)

- 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.

Jenson HB, Pollock BH. Pediatrics 1997

Ohlsson A, Lacy J., Cochrane Database Syst Rev, 2010
Treatment of Neutropenia

- 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.
Treatment of Neutropenia

- 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

Mohan P, Brocklehurst P. Cochrane Database Syst Rev 2003
Pammi M, Brocklehurst P. Cochrane Database Syst Rev 2011
Treatment of Neutropenia

- Gamma interferon (IFN-\(\gamma\))

- Gamma interferon has been claimed to have potential for correcting abnormalities of cell movement and bacterial killing \textit{in vitro}, raising the possibility that increasing IFN-\(\gamma\) levels might be beneficial.

- No studies have focused on using IFN-\(\gamma\) among neutropenic neonates

Treatment of Neutropenia

- 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.

References:
- Kocherlakota P, La Gamma EF. Pediatrics 1997
Neutrophils and Host Defense

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Neutrophils and Host Defense

- Neutrophils are the **first line of innate immune defense** against infectious diseases.

- Compared with the acquired immune response, which requires time to develop and is dependent on previous interaction with specific microbes, the ability of neutrophils to kill microorganisms is immediate, non-specific, and **not dependent on previous exposure to microorganisms**.

- Recent studies revealed their importance in the regulation of immune response and the emerging role of neutrophils in the regulation of both **innate** and **adaptive** immunity during acute infectious or inflammatory conditions.

Kumar V, Sharma A. Int Immunopharmacol, 2010
This **multifunctional cell** is also a necessary actor of the acquired immune response. Neutrophils have the capacity to *degrade and process antigens* as well as efficiently *present antigenic peptides to lymphocytes*.

Neutrophil interactions with immune cells, in particular **dendritic cells**, lead to the formation of **IL-12** and **TNF-alpha** deviating the immune response towards a **Th1 phenotype**. Thus, the neutrophil exhibits a **cellular plasticity** that explains its capacity to transdifferentiate depending on the local requirements of the immune response.

The neutrophil is probably the most **underappreciated immune cell** among hematopoietic leukocytes, and many neutrophil functions remain to be unraveled.

Neutrophils and Host Defense

- Neutrophils are pivotal to antibacterial host defense

- People who lack neutrophils, whether by a congenital or an acquired defect, will experience a natural history that includes repeated local and systemic infections and early death

- Neutrophil function and neutrophil kinetics during infection differ considerably from those of adults

Christensen RD, Calhoun DA. Clin Perinatol, 2004
Borregaard N. Immunity, 2010
Neutrophils and Host Defense

Infected adults → neutrophilia

- They accelerate the release of neutrophils from their marrow reserve into the circulation, and as they simultaneously recruit quiescent neutrophil progenitors into cycle.

Infected preterm neonates → neutropenia

- The result of depleting their relatively small marrow neutrophil reserves before it can be replaced by granulocytotoxic acceleration.

References:
- Christensen RD, Calhoun DA. Clin Perinatol, 2004
- Borregaard N. Immunity, 2010
Neutrophils and Host Defense

- **Neutrophil function** of neonates, particularly preterm neonates, is **less robust 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**.
Neutrophils and Host Defense

Neutrophil Maturation in the Marrow

Myeloblast       Promyelocyte        Myelocyte    Metamyelocyte     Band             Seg

--- PROLIFERATIVE POOL ---       ------- STORAGE POOL ------

Studies on neonatal rats revealed that the neonate’s neutrophil proliferative and storage pools are only approximately 25% of adult values, when measured on a cell per gram body weight basis.

POST-MITOTIC NEUTROPHILS

TOTAL BLOOD NEUTROPHIL POOL
1. CIRCULATING $0.3 \times 10^9$/kg (0.1 - 0.4)
2. MARGINATED $0.3 \times 10^9$/kg (0.1 - 1.1)

NEUTROPHIL STORAGE POOL
$6 \times 10^9$/kg (4.5 - 7.5)
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Neutropenia in a Neonate

Accelerated Usage/Destruction

Neutrophils

**Normal**

**Band**
Called into service in times of need

**"Toxic" granulation/vacuolization**
Think "sepsis"!

**Alder-Reilly**
Mucopolysaccharidosis

**Hyper-segmented**
Slowed DNA synthesis

**Döhle Bodies**
May-Hegglin; bad infections

**Sepsis**

- Left shift, toxic granulation, neutrophil vacuolization, Döhle bodies, falling platelet count, acidosis and hypotension

- Neutropenia can be severe but is not prolonged
Neutropenia in a Neonate

Neutropenia is a relatively frequent finding in the neonatal intensive care unit, with an overall incidence reported at about 8% of all patients at sometime during their NICU stay.

Neutropenia is more common in VLBW, affecting up to 50% in the first week of life.

The presence of neutropenia itself might place VLBW neonates at higher risk for sepsis and mortality, especially if the neutropenia is severe and prolonged.
Neutropenia in a Neonate

What is a “normal” neutrophil count for a neonate?

Normal Range
Established by testing normal, healthy volunteers

Reference Range
Established by compiling clinically-ordered tests performed on patients with “minimal relevant pathology”
Neutropenia in a Neonate

Reference Range

Example: Collect CBC’s drawn on thousands of neonates who did not have: Infection, SGA, PIH, Down Syndrome

Express the 5th % value as the “lower reference range” and the 95th % value as the “upper reference range”

Neutropenia in a Neonate

What is the “Reference Range” for blood neutrophils in neonates?

In 1979 Manroe et al. the range of neutrophils during the first 60 h. Data from 108 neonates 1974 to 1976.

In 1992 Mouzinho et al. neutrophil concentrations from VLBW neonates. The range of counts differed from that of higher gestation neonates, with lower counts and a wider range. Counts formed the basis of the chart.

Reference range for blood neutrophil concentrations during the first 72 hours after birth of term and late-preterm neonates. A total of 12,149 values were used in this analysis. The 5th percentile, mean, and 95th percentile values are shown.

For neonates, this definition is complicated because the reference range varies according to several situations, including gestational age, postnatal age, gender, type of delivery (vaginal delivery vs. cesarean section), and altitude (meters above sea level).
Reference range for blood neutrophil concentrations, with superimposition of the Manroe (Dallas, Tex) and Schmutz (Intermountain Healthcare) curves. The dots represent neonates in Utah who would have been regarded as having an elevated neutrophil count using the sea level (Dallas) curve, but who fell within the high-altitude (Intermountain) Schmutz curve.

The definition of neutropenia is very similar in the sea level and high-altitude reference ranges.
Neutropenia - Definition

• Sea-level. Neonates >1500 gm, use the Manroe chart (J Pediatr 1979)

• Sea-level. Neonates ≤1500 gm, use the Mouzinho chart, (Pediatr 1992)

• Centers ≥1200 m, use the Schmutz chart (J Perinatol 2008)
Neutropenia in a Neonate

A much simpler approach to define neutropenia in a neonate is:

- to use a neutrophil concentration **less than 1000/μL**
- to define **severe neutropenia** by a count **less than 500/μL**

Although **this approach lacks the accuracy of data-derived reference range approaches**, it offers the advantages that it is **easy to remember**, and it is in keeping with the standard definitions for neutropenia used in pediatric and adult medicine.


It is not clear whether blood neutrophil counts labeled as low by the reference range approach actually convey a **host-defense deficiency**, unless they are less than 1000/μL.

Al-Mulla ZS, Christensen RD. Clin Perinatol, 1995
Carr R. Br J Haematol, 2000
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Severe Chronic Neutropenia in the Neonate

Severe chronic neutropenia (SCN) consists of a cluster of diagnoses that bear the common feature of very low circulating neutrophil concentrations from birth.

### VARIETIES OF NEUTROPENIA AMONG NEONATES WHO GENERALLY ARE CONSIDERED TO HAVE SEVERE CHRONIC NEUTROPENIA

- Kostmann syndrome, autosomal recessive type
- Severe congenital neutropenia, autosomal dominant type
- Shwachman-Diamond syndrome
- Barth syndrome
- Cartilage-hair hypoplasia
- Cyclic neutropenia
- Glycogen storage disease type 1b
- Severe neonatal immune-mediated neutropenias

Christensen RD, Calhoun DA. Clin Perinatol, 2004
Severe Chronic Neutropenia in the Neonate

SCN International Registry, established in 1994 at the University of Washington

Enrollment in the SCN International Registry can be accomplished at the website [http://depts.washington.edu/registry/](http://depts.washington.edu/registry/) using the entry criteria and exclusion criteria.

**Inclusion Questions**
1. Has a blood neutrophil count less than 500/µL been documented on at least three occasions over the past 3 months?
2. Is there a history of recurrent infection? *(specify)*
3. Is the bone marrow evaluation consistent with severe chronic neutropenia? *(date performed)*
4. Has a cytogenetic evaluation been completed?
5. Is the patient now receiving Neupogen (rG-CSF)?

**Exclusion Criteria**
1. Neutropenia is known to be drug induced.
2. Thrombocytopenia is present (<50,000/µL), except in the case of Shwachman-Diamond syndrome or glycogen storage disease type 1b.
3. Anemia is present (Hgb <8 g/dL), except in the case of Shwachman-Diamond syndrome or glycogen storage disease type 1b.
4. The patient has a myelodysplastic syndrome or aplastic anemia, is HIV positive, has some other hematologic disease or rheumatoid arthritis, or has received previous chemotherapy for cancer.
Rarely, patients with SCN are diagnosed as neonates, or even as patients in neonatal intensive care units. Most patients with SCN are not diagnosed until several months of age, after infectious episodes have prompted an investigation into immunologic deficiencies.

The advent of rG-CSF dramatically improved the lives of patients with SCN, in most cases elevating their circulating neutrophil concentrations, reducing infectious illnesses, and extending their life expectancy.

When SCN is diagnosed in a neonate, that patient should receive the benefit of rG-CSF treatment.
Is there biologic plausibility to propose the use of rG-CSF in neonates with varieties of neutropenia distinct from SCN?
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Neonatal Neutropenia Not Categorized as Severe Chronic Neutropenia

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Neonatal Neutropenia Not Categorized as Severe Chronic Neutropenia

1. Neutropenia due to PIH is the most common variety of neutropenia seen in the neonatal intensive care unit.

2. 50\% of neonates born to mothers with PIH have this variety of neutropenia.

3. The ANC can be very low, frequently less than 500/μL, but the count generally rises spontaneously within the first days and is almost always greater than 1000/μL by day 2 or 3.

4. Usually no leukocyte “left shift” is seen, and no toxic granulation, Döhle bodies, or vacuolization is present in the neutrophils.
5. It is not clear whether this variety of neutropenia **predisposes neonates to acquire bacterial infection**

6. Usually the condition is so **transient** that such a predisposition is unlikely

7. The condition probably is caused by an **inhibitor of neutrophil production of placental origin** that might function mechanistically by **depressing natural G-CSF production**

Koenig JM, Christensen RD. N Engl J Med, 1989
Several clinical trials have investigated prophylactic administration of rG-CSF to neonates with neutropenia, most of whom have neutropenia associated with PIH.

1. Kocherlakota found a protective effect of rG-CSF administration toward early infection.
2. Miura reported a protective effect toward late-onset infection.
3. Kuhn, in a large, multicenter, randomized, placebo-controlled trial in France (n = 200), found that rG-CSF recipients had only a transient (2-week) period of fewer infections, but did not have an overall significant improvement in infection-free survival.
A Multicenter, Randomized, Placebo-Controlled Trial of Prophylactic Recombinant Granulocyte-Colony Stimulating Factor in Preterm Neonates with Neutropenia

Pierre Kuhn, MD, Jean Messer, MD, Alain Paupe, MD, Sandrine Espagne, MD, Nadine Kacet, MD, Genevieve Mouchnino, MD, Serge Klosowski, MD, Gérard Krim, MD, Sandra Lescure, MD, Stephane Le Bouedec, MD, Pierre Meyer, MD, and Dominique Astruc, MD

Conclusions

In this population, prophylactic rG-CSF did not significantly increase survival free of infection at 4 weeks after treatment. The transient effect observed at 2 weeks in the most immature infants should be evaluated further.

(J Pediatr 2009;155:324-30)
Neutropenia Associated with Severe Intrauterine Growth Restriction

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:

- 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.

Neonatal Neutropenia Not Categorized as Severe Chronic Neutropenia

- The donor in a twin-twin transfusion is generally neutropenic.
- The recipient can also have neutropenia, although it is usually not as severe.
- As with the varieties of neutropenia accompanying PIH and SGA, no leukocyte "left shift" is usually noted, nor are neutrophil morphologic abnormalities reported.
- This condition is transient, with the ANC generally spontaneously rising to greater than 1000/μL by 2 or 3 days.

Neonatal Neutropenia Not Categorized as Severe Chronic Neutropenia

- Neonates with anemia from Rh hemolytic disease are almost always **neutropenic on the first day of life**
- This type of neutropenia is **similar to that of PIH/SGA** and of donors in a twin-twin transfusion
- It is likely due to **reduced neutrophil production**
- Neutropenia is **transient**, generally resolving in a day or two

Evidence is currently insufficient to support the introduction of rG-CSF or rGM-CSF into neonatal practice, either as treatment for established systemic infection to reduce resulting mortality, or as prophylaxis to prevent systemic infection in high-risk neonates.


In ill VLBW infants, the occurrence of neutropenia during a course of sepsis can suggest a Gram-negative bacterial infection.

In VLBW infants, common organisms causing infection have different effects on neutrophil responses. Occurrence of neutropenia during evaluation of sepsis in sick VLBW infants is more common with Gram-negative bacterial infection.
Neonatal Neutropenia Not Categorized as Severe Chronic Neutropenia

- Thrombocytopenia is known to accompany fungal infection in the NICU, but neutropenia can also accompany such infections.
- Early-onset neutropenia is a risk factor for Candida colonization in very low birth weight neonates.
- No studies have specifically focused on the use of rG-CSF among neutropenic neonates with fungal infection.

Neutropenia is relatively common among severe cases of NEC.

Some cases are transient and resemble the neutropenia that follows endotoxin.

No studies have focused on using rG-CSF among neutropenic neonates with NEC.

There is no clear benefit of rG-CSF administration.

Chronic Idiopathic Neutropenia of Prematurity

- Certain preterm neonates develop neutropenia when 4 to 10 weeks old.
- This variety of neutropenia is often associated with a patient’s spontaneous recovery from anemia of prematurity.
- Neutrophil counts are generally less than 1000/μL but rarely less than 500/μL.
- The condition is transient, lasting a few weeks to perhaps a month or longer.
- It appears to be a hyporegenerative neutropenia because it is not accompanied by a leukocyte “left shift” nor by morphologic abnormalities of the neutrophils.

Juul SE, Christensen RD. J Perinatol., 2003
Patients with this condition have an “rG-CSF mobilizable neutrophil reserve” meaning that if rG-CSF is given, neutrophil count increases within hours.

This fact has been taken as evidence that patients do not have a significant host-defense deficiency, because in theory they can supply neutrophils to tissues when needed.

Thus, although patients are neutropenic, this condition is likely benign and requires no treatment.

Chronic Idiopathic Neutropenia of Prematurity

Juul SE, Christensen RD. J Perinatol., 2003
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A Consistent Approach to the Use of rG-CSF in the NICU

Does the neonate have a variety of severe congenital neutropenia?

- Yes
  - Initiate treatment with rGCSF

- No
  - No rG-CSF

- Uncertain
  - Initiate treatment with rGCSF only if:
    1. ANC < 500/μL for 2 days or more
    2. ANC 500–999/μL for 5 days or more
# Neutropenia - Kinetic Classification

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Consider rG-CSF when the neonatal neutropenia is severe (<500/µL) and prolonged (> 5 - 7 days)
rG-CSF is not recommended for varieties of neonatal neutropenia likely to be transient (or mild): Sepsis, PIH/SGA, Twin-Twin, Rh hemolytic, chronic-idiopathic of preterm
Conclusions

1. We propose beginning treatment with a dose of 10 μg/kg subcutaneously, once per day for 3 consecutive days.
2. Doses are given as needed to titrate the ANC to around 1000/μL.
3. We propose that if a neonatal patient has neutropenia, and the variety of neutropenia is NOT one of the varieties of SCN, rG-CSF treatment should not be used.
4. We propose that if a neonatal patient has neutropenia, and the variety of neutropenia is NOT known (and therefore might be a SCN variety), while the type of neutropenia is evaluated, rG-CSF treatment can be instituted if the ANC was less than 500/μL for 2 or more days, or less than 1000/μL for 5 to 7 days or longer.
Conclusions

5. There is insufficient evidence for rGM-CSF use in the NICU
6. If one follows this schema, rG-CSF will be used very little in any given NICU
7. The schema should focus rG-CSF usage on those patients with the most to gain and the least to lose by its application
8. As additional pertinent investigative work is published, these guidelines should be modified accordingly
A Consistent Approach to the Use of rG-CSF in the NICU

**Varieties of Neutropenia Among Neonates Who Generally Are Considered to Have Severe Chronic Neutropenia**

- Kostmann syndrome, autosomal recessive type
- Severe congenital neutropenia, autosomal dominant type
- Shwachman-Diamond syndrome
- Barth syndrome
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- Severe neonatal immune-mediated neutropenias

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