

Neutropenia in Infants: A Comprehensive Narrative Review

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Abstract

Neutropenia in infants represents a heterogeneous group of disorders characterized by a reduced absolute neutrophil count (ANC), predisposing affected individuals to recurrent and potentially life-threatening bacterial and fungal infections. This narrative review provides a comprehensive synthesis of the current evidence regarding the epidemiology, etiology, classification, pathophysiology, clinical manifestations, diagnostic approach, differential diagnosis, management, prognosis, and future perspectives of neutropenia in the neonatal and infant population. Neutropenia may arise from transient physiological processes, immune-mediated mechanisms (alloimmune and autoimmune), congenital bone marrow failure syndromes (including severe congenital neutropenia, cyclic neutropenia, and Shwachman-Diamond syndrome), infections, drug-induced causes, or nutritional deficiencies. The diagnostic approach requires systematic evaluation integrating clinical history, serial complete blood counts, peripheral blood smear, antineutrophil antibody testing, bone marrow examination, and increasingly, next-generation sequencing for germline and somatic genetic variants. Management is tailored to the underlying etiology and severity, with recombinant human granulocyte colony-stimulating factor (rhG-CSF) serving as the cornerstone of therapy for severe and symptomatic forms. Prognosis varies markedly by etiology; while autoimmune neutropenia of infancy typically resolves spontaneously within 2–4 years, severe congenital neutropenia

carries a substantial risk of leukemic transformation. Emerging therapies, including targeted gene editing approaches, hold promise for definitive treatment of monogenic forms. This review consolidates contemporary knowledge to guide clinicians in the recognition, evaluation, and evidence-based management of neutropenia in infants.

Keywords: Neutropenia; Infant; Newborn; Severe Congenital Neutropenia; Autoimmune Neutropenia; Alloimmune Neutropenia; G-CSF; ELANE; Bone Marrow Failure

Introduction

Neutropenia, defined as an absolute neutrophil count (ANC) below the age-appropriate reference range, constitutes one of the most commonly encountered hematologic abnormalities in neonates and infants (1). The clinical significance of neutropenia lies in its association with increased susceptibility to bacterial and fungal infections, which can range from mild recurrent skin and mucosal infections to overwhelming sepsis with significant morbidity and mortality (2).

In infants, the interpretation of neutrophil counts is particularly challenging because reference values vary substantially according to gestational age, postnatal age, birth weight, ethnicity, altitude, and the source of the blood sample (capillary versus venous) (3,4).

The etiologic spectrum of infant neutropenia is remarkably broad, encompassing transient physiologic phenomena, immune-mediated destruction of neutrophils, inherited bone marrow failure syndromes, infections, drug-induced marrow suppression, and nutritional deficiencies (5).

Distinguishing among these causes is essential because management strategies, prognosis, and genetic counseling implications differ profoundly. For example, neonatal alloimmune neutropenia, caused by transplacental passage of maternal antineutrophil antibodies, is typically self-limited, whereas severe congenital neutropenia (SCN) due to ELANE mutations requires lifelong therapy and carries a substantial risk of malignant transformation (6,7).

Over the past two decades, advances in molecular genetics have transformed the understanding of inherited neutropenia syndromes.

The identification of causative genes, including ELANE, HAX1, G6PC3, CSF3R, WAS, GFI1, SBDS, and SRP54 has clarified the pathophysiology of these disorders and enabled targeted diagnostic testing (8,9). Simultaneously, the introduction of recombinant human granulocyte colony-stimulating factor (rhG-CSF) in the late 1980s revolutionized the management of severe neutropenia, dramatically reducing infection-related mortality (10). More recently, CRISPR-based gene editing technologies have emerged as potential curative strategies for monogenic neutropenia syndromes, with promising preclinical data published in 2024–2025 (11,12).

This narrative review aims to synthesize the contemporary evidence regarding neutropenia in infants, with particular emphasis on the most recent international guidelines, advances in molecular diagnostics, evidence-based management strategies, and emerging therapeutic frontiers. The review is intended for clinicians, including neonatologists, pediatric hematologists, infectious disease specialists, and general pediatricians, who encounter infants with neutropenia in diverse clinical settings.

Epidemiology

1 General Neonatal Neutropenia

Neutropenia is detected in approximately 1–5% of all newborns when broad ANC thresholds are applied, with substantially higher rates among preterm and low-birth-weight infants (13). In a prospective study of more than 1,000 neonates admitted to a tertiary neonatal intensive care unit, neutropenia ($ANC < 1.5 \times 10^9/L$) was identified in up to 8% of preterm infants compared with less than 1% of term infants (14). The higher prevalence in preterm infants reflects the immaturity of myeloid progenitor cell pools and the greater susceptibility of preterm neonates to perinatal complications that suppress neutrophil production.

2 Alloimmune Neonatal Neutropenia

Alloimmune neonatal neutropenia (ANN), analogous to hemolytic disease of the newborn, occurs when maternal antineutrophil antibodies cross the placenta and destroy fetal neutrophils. The estimated incidence ranges from 0.1% to 0.9% of live births, depending on the population and the diagnostic criteria applied (15,16). A Brazilian cross-sectional study of 10,000 neonates identified an incidence of 0.9%, with maternal-fetal incompatibility for HNA-1 (human neutrophil antigen-1) detected in 44.3% of cases and for HNA-3 in 14.8% (17). The most commonly implicated antigen is HNA-1a, although HNA-1b, HNA-1c, and HNA-3b have also been documented.

3 Autoimmune Neutropenia of Infancy

Primary autoimmune neutropenia of infancy (AIN) is among the most common causes of chronic neutropenia in children under 3 years of age, with an estimated incidence of 1 in 100,000 to 1 in 200,000 per year (18). The median age at diagnosis is 7–12 months, and the condition accounts for the majority of cases of chronic benign neutropenia in early childhood. Unlike ANN, AIN involves autoantibodies directed against the infant's own neutrophils and typically resolves spontaneously within 2–4 years.

4 Severe Congenital Neutropenia

Severe congenital neutropenia (SCN) is a rare disorder with an estimated incidence of 1–2 cases per million live births (19). The most common genetic form, ELANE-related SCN, accounts for approximately 50–60% of cases, followed by HAX1-related (Kostmann disease), G6PC3-related, and other rarer forms (20). Although rare, SCN is clinically significant because of its severe infection risk and the substantial lifetime risk of progression to myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).

5 Ethnic and Geographic Variation

ANC reference ranges vary by ethnicity. Studies have demonstrated that infants of African descent have lower mean neutrophil counts compared with those of European descent, with some authors proposing ethnicity-specific reference ranges to avoid over-diagnosis of neutropenia (21). Geographic factors, including altitude, also influence neutrophil counts, with higher values observed at high altitudes due to chronic hypoxia-induced marrow stimulation (22).

Etiology and Classification

Neutropenia in infants can be classified along several axes: by duration (acute versus chronic), by mechanism (production defect versus increased destruction or sequestration), by inheritance pattern (congenital versus acquired), and by clinical severity. The most clinically useful classification stratifies cases into the following major categories:

1 Transient Neutropenia

Transient neutropenia is the most common form in neonates and typically resolves within days to weeks.

Causes include:

- **Maternal hypertension/preeclampsia:** Infants born to hypertensive mothers frequently develop neutropenia due to impaired placental function and reduced fetal neutrophil production (23).
- **Intrauterine growth restriction (IUGR):** Lineage steal phenomenon redirects hematopoiesis toward erythroid precursors at the expense of myeloid production (24).
- **Perinatal asphyxia and stress:** Severe perinatal stress can cause neutrophil margination and depletion of the circulating pool.
- **Acute bacterial or viral infections:** Sepsis, particularly with gram-negative organisms, and viral infections (including CMV, enteroviruses, and HIV) commonly suppress neutrophil counts (25).

2 Immune-Mediated Neutropenia

This category includes:

- **Alloimmune neonatal neutropenia (ANN):** Caused by maternal IgG antineutrophil antibodies crossing the placenta; analogous to hemolytic disease of the newborn (15).
- **Autoimmune neutropenia of infancy (AIN):** Driven by autoantibodies against neutrophil antigens; typically self-limited (18).
- **Maternal autoimmune neutropenia:** Infants of mothers with autoimmune neutropenia may acquire neutropenia via transplacental antibody transfer.

3 Congenital Bone Marrow Failure Syndromes

- **Severe congenital neutropenia (SCN):** Most commonly due to ELANE mutations; characterized by profound neutropenia from birth, maturation arrest at the promyelocyte/myelocyte stage, and recurrent severe infections (20).
- **Cyclic neutropenia (CyN):** Caused by specific ELANE mutations; characterized by regular 21-day oscillations of the ANC (26).
- **Shwachman-Diamond syndrome (SDS):** Caused by SBDS mutations; features neutropenia, exocrine pancreatic insufficiency, and skeletal abnormalities (27).
- **Other inherited marrow failure syndromes:** Including Fanconi anemia, dyskeratosis congenita, and cartilage-hair hypoplasia, which may present with neutropenia as part of a broader cytopenia profile.

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4 Drug-Induced Neutropenia

Several medications commonly used in neonates can cause neutropenia, including:

- **Antibiotics:** Beta-lactams (particularly piperacillin-tazobactam), vancomycin, linezolid, and chloramphenicol (28).
- **Antifungals:** Flucytosine and high-dose amphotericin B.
- **Antivirals:** Ganciclovir and valganciclovir, particularly in the treatment of congenital CMV infection.
- **Other drugs:** Ibuprofen, indomethacin, and ranitidine have been implicated.

5 Nutritional and Metabolic Causes

- **Folate deficiency:** Particularly in infants fed goat's milk or those with malabsorption.
- **Vitamin B12 deficiency:** In infants of vegan mothers or those with pernicious anemia.
- **Copper deficiency:** Associated with neutropenia and is seen in malnourished infants or those receiving prolonged parenteral nutrition without adequate copper supplementation (29).

6 Severity-Based Classification

The European Hematology Association (EHA) and EuNet-INNOCHRON consensus guidelines classify neutropenia severity based on ANC values (1):

- Mild neutropenia: $\text{ANC } 1.0\text{--}1.5 \times 10^9/\text{L}$
- Moderate neutropenia: $\text{ANC } 0.5\text{--}0.99 \times 10^9/\text{L}$
- Severe neutropenia: $\text{ANC } 0.2\text{--}0.49 \times 10^9/\text{L}$
- Very severe neutropenia: $\text{ANC } < 0.2 \times 10^9/\text{L}$

This severity grading informs the urgency of intervention, with very severe neutropenia requiring immediate hematology consultation and consideration of empirical antimicrobial therapy.

Pathophysiology

The pathophysiology of infant neutropenia can be conceptualized along three principal mechanisms: impaired production, increased destruction, and altered distribution or sequestration.

1 Impaired Production

Impaired neutrophil production is the hallmark of congenital bone marrow failure syndromes. In ELANE-related SCN, mutations in the ELANE gene (encoding neutrophil elastase) cause misfolding of the enzyme, triggering endoplasmic reticulum stress and accelerated apoptosis of myeloid progenitor cells (30). The bone marrow characteristically shows maturation arrest at the promyelocyte or myelocyte stage, with reduced or absent mature neutrophils.

Similarly, HAX1 mutations (the genetic basis of classic Kostmann disease) disrupt mitochondrial homeostasis, leading to enhanced apoptosis of myeloid precursors (31). G6PC3 deficiency impairs glucose-6-phosphatase function, causing accumulation of toxic metabolites and neutrophil apoptosis (32).

In preterm infants, impaired production reflects the developmental immaturity of the myeloid progenitor pool. The bone marrow of preterm neonates contains a smaller proportion of committed myeloid progenitors compared with term neonates, and the storage pool of mature neutrophils is reduced, making these infants particularly vulnerable to neutropenia during periods of increased demand (33).

2 Increased Destruction

Immune-mediated neutropenia results from antibody-mediated destruction of circulating neutrophils. In alloimmune neonatal neutropenia, maternal IgG antibodies directed against fetal neutrophil antigens (most commonly HNA-1a) opsonize fetal neutrophils, leading to their destruction by the reticuloendothelial system (15). In autoimmune neutropenia of infancy, autoantibodies, typically IgG, coat the infant's own neutrophils, with similar downstream consequences. The bone marrow in these conditions typically shows normal or increased myeloid cellularity with appropriate maturation, reflecting a compensatory response to peripheral destruction.

3 Altered Distribution and Sequestration

In certain conditions, neutrophils marginate from the circulating pool into the marginal pool (adhering to vascular endothelium), leading to a reduced ANC without true depletion of total body neutrophils. This mechanism contributes to neutropenia in acute infections, stress states, and after administration of certain drugs (34). The distinction between true neutropenia and pseudoneutropenia due to margination can be challenging but is important for clinical decision-making.

4 Molecular Pathways and Emerging Insights

Recent research has elucidated additional molecular pathways involved in neutrophil homeostasis. The CSF3R gene encodes the G-CSF receptor, and mutations causing receptor truncation lead to impaired response to endogenous G-CSF and severe neutropenia (35). GFI1 acts as a transcriptional repressor that modulates granulopoiesis, with mutations causing both neutropenia and monocytosis (36). The WAS gene, classically associated with Wiskott-Aldrich syndrome, can also cause X-linked neutropenia without the full syndromic features (37).

The recognition that unfolded protein response (UPR) activation plays a central role in ELANE-related SCN has informed the development of novel therapeutic strategies. Gene therapy approaches targeting ELANE expression, using CRISPR-based base editing and prime editing, have demonstrated restoration of neutrophil maturation in preclinical models (11,12).

Clinical Manifestations

The clinical presentation of infant neutropenia is highly variable and depends primarily on the severity and duration of the neutropenia, as well as the underlying etiology.

1 Asymptomatic Presentation

Many infants with mild or moderate neutropenia are asymptomatic, with the abnormality detected incidentally on routine complete blood counts. This is particularly common in cases of transient neutropenia related to maternal hypertension, IUGR, or mild viral infections (38).

2 Infectious Complications

When neutropenia is severe ($ANC < 0.5 \times 10^9/L$) or prolonged, the risk of bacterial and fungal infections increases substantially. Common clinical presentations include:

- **Skin and soft tissue infections:** Cellulitis, abscesses, and impetigo, often with unusual organisms such as *Pseudomonas aeruginosa* or *Serratia marcescens* (39).
- **Omphalitis:** Infection of the umbilical stump, particularly in neonates.
- **Oral and mucosal infections:** Gingivitis, stomatitis, aphthous ulcers, and periodontitis, especially in cyclic neutropenia (26).
- **Pneumonia:** Bacterial pneumonia is a frequent and potentially severe complication.
- **Sepsis:** Gram-negative sepsis is a leading cause of mortality in severe neutropenia, particularly in neonates (40).
- **Fungal infections:** Candidemia and invasive aspergillosis may occur in prolonged severe neutropenia.

3 Characteristic Patterns by Etiology

- **Severe congenital neutropenia:** Presents in early infancy with recurrent, severe bacterial infections including deep-seated abscesses, pneumonia, and sepsis. Omphalitis and delayed umbilical cord separation (>30 days) are classic features (20).
- **Cyclic neutropenia:** Characterized by predictable 21-day cycles of fever, oral ulcers, gingivitis, and pharyngitis, with neutropenic nadirs lasting 3–5 days (26).
- **Autoimmune neutropenia of infancy:** Often presents with mild to moderate infections, including recurrent otitis media, upper respiratory infections, and skin infections. Severe infections are uncommon (18).
- **Alloimmune neonatal neutropenia:** May be asymptomatic or present with mild infections; severe infections occur in approximately 10–20% of cases (15).
- **Shwachman-Diamond syndrome:** Presents with failure to thrive due to pancreatic insufficiency, recurrent infections from neutropenia, and skeletal abnormalities (27).

4 Associated Features Suggesting Specific Diagnoses

- **Delayed umbilical cord separation:** Suggests leukocyte adhesion deficiency but can also occur in severe congenital neutropenia.
- **Congenital anomalies (cardiac, urogenital, vascular):** Suggest G6PC3-related SCN (32).
- **Exocrine pancreatic insufficiency and skeletal dysplasia:** Suggest Shwachman-Diamond syndrome (27).
- **Skin pigmentation anomalies, thumb abnormalities:** Suggest Fanconi anemia.
- **Oral ulcers with cyclic pattern:** Highly suggestive of cyclic neutropenia (26).

Diagnostic approach

The diagnostic evaluation of an infant with neutropenia requires a systematic, stepwise approach that integrates clinical assessment, laboratory testing, and, when indicated, genetic and bone marrow evaluation.

1 Initial Clinical Assessment

A thorough history should include:

- **Perinatal history:** Gestational age, birth weight, maternal health (hypertension, preeclampsia, autoimmune disease), and any maternal medications.
- **Family history:** Consanguinity, recurrent infections in siblings, early childhood deaths, or known inherited marrow failure syndromes.
- **Infection history:** Frequency, severity, and types of infections; pattern of recurrence.
- **Medication exposure:** Recent or current medications, including those administered to the mother during pregnancy or lactation.
- **Nutritional history:** Feeding type, vitamin supplementation, and any signs of malabsorption.

Physical examination should assess for:

- Growth parameters and signs of failure to thrive
- Dysmorphic features or congenital anomalies
- Hepatomegaly, splenomegaly, or lymphadenopathy
- Active infections or their sequelae
- Features of syndromic bone marrow failure (skin pigmentation, nail abnormalities, skeletal anomalies)

2 Laboratory Evaluation

Complete Blood Count (CBC) with Differential Serial CBCs (at least 2–3 measurements over 1–2 weeks) are essential to confirm persistent neutropenia and to assess for cyclic patterns. The differential should include not only the ANC but also the absolute counts of lymphocytes, monocytes, eosinophils, and basophils, as abnormalities in other lineages may suggest broader marrow failure (41).

Peripheral Blood Smear

Morphologic examination can reveal:

- Left-shifted myeloid series suggesting infection
- Giant granules (Chédiak-Higashi syndrome)
- Hypogranular neutrophils (specific granule deficiency)
- Dysplastic features suggesting MDS

Antineutrophil Antibody Testing

Granulocyte agglutination test (GAT) and granulocyte immunofluorescence test (GIFT) can detect antineutrophil antibodies, supporting the diagnosis of immune-mediated neutropenia.

However, these tests have limited sensitivity (approximately 50–60%) and specificity, and a negative result does not exclude immune-mediated neutropenia (42).

Infection Evaluation

Blood cultures, urine cultures, and viral studies (CMV PCR, parvovirus B19, enterovirus) should be obtained based on clinical suspicion. Inflammatory markers (CRP, procalcitonin) may aid in identifying occult infection.

Immunoglobulin Levels

Quantitative immunoglobulins can help exclude combined immunodeficiency syndromes that may present with neutropenia.

3 Bone Marrow Examination

Bone marrow aspiration and biopsy are indicated when:

- Neutropenia is severe ($ANC < 0.5 \times 10^9/L$) and persistent (>2–4 weeks)
- There are additional cytopenias suggesting marrow failure
- Clinical features suggest inherited bone marrow failure syndrome
- Initial workup is inconclusive and the patient is symptomatic
- There is concern for malignant transformation (43)

The bone marrow in SCN characteristically shows maturation arrest at the promyelocyte/myelocyte stage, with reduced or absent mature neutrophils and bands. In immune-mediated neutropenia, the marrow typically shows normal or increased cellularity with appropriate maturation. Cytogenetic analysis and next-generation sequencing (NGS) of the marrow can detect acquired somatic mutations associated with MDS/AML (44).

4 Genetic Testing

Next-generation sequencing (NGS) panels targeting known neutropenia-associated genes (ELANE, HAX1, G6PC3, CSF3R, WAS, GFI1, SBDS, SRP54, DNAJC21, EFL1, VPS45, JAGN1, AK2, and others) have unexplained neutropenia (45). The European Hematology Association guidelines recommend genetic testing for all patients with chronic neutropenia of unknown etiology after initial workup (1).

Whole-exome sequencing (WES) or whole-genome sequencing (WGS) may be considered when targeted panels are non-diagnostic, particularly in syndromic presentations.

5 Diagnostic Algorithm

A practical diagnostic algorithm, adapted from the AIEOP (Italian Association of Pediatric Hematology-Oncology) and EHA guidelines, proceeds as follows:

1. Confirm persistent neutropenia with serial CBCs
2. Review perinatal and family history; perform physical examination
3. Obtain peripheral blood smear and antineutrophil antibody testing
4. Evaluate for infections and drug-induced causes
5. If persistent, severe, or unexplained: proceed to bone marrow examination and genetic testing
6. If genetic testing is non-diagnostic: consider WES/ WGS

Differential Diagnosis

The differential diagnosis of infant neutropenia is broad and requires consideration of multiple categories. A structured approach based on duration, severity, and associated features can help narrow the differential.

1 Transient versus Persistent Neutropenia

Transient neutropenia is suggested by:

- Recent perinatal complication (hypertension, asphyxia, IUGR)
- Concurrent infection
- Recent medication exposure
- Resolution within days to weeks

Persistent neutropenia (≥ 4 weeks) warrants evaluation for:

- Immune-mediated causes (AIN, ANN)
- Congenital bone marrow failure syndromes
- Chronic infections (HIV, CMV)
- Nutritional deficiencies

2 Isolated versus Syndromic Neutropenia

Isolated neutropenia (with normal other cell lines) suggests:

- Immune-mediated neutropenia
- ELANE-related SCN
- Cyclic neutropenia
- Drug-induced neutropenia

Syndromic neutropenia (with other cytopenias or congenital anomalies) suggests:

- Shwachman-Diamond syndrome (pancytopenia, pancreatic insufficiency, skeletal anomalies)
- Fanconi anemia (pancytopenia, thumb anomalies, skin pigmentation)
- Dyskeratosis congenita (pancytopenia, nail dystrophy, mucosal leukoplakia)
- G6PC3-related SCN (cardiac and urogenital anomalies)

3 Severe versus Mild Neutropenia

Severe neutropenia ($ANC < 0.5 \times 10^9/L$) is more commonly associated with:

- Severe congenital neutropenia
- Alloimmune neonatal neutropenia (severe cases)
- Acute severe infections

Mild to moderate neutropenia ($ANC 0.5\text{--}1.5 \times 10^9/L$) is more commonly associated with:

- Autoimmune neutropenia of infancy
- Transient physiologic neutropenia
- Ethnic neutropenia (benign ethnic neutropenia)

4 Cyclic Pattern

A cyclic pattern with regular 21-day oscillations strongly suggests cyclic neutropenia due to ELANE mutations. Serial CBCs (2–3 times weekly for 4–6 weeks) can establish the cyclic pattern before genetic confirmation (26).

Management and Treatment

Management of infant neutropenia is tailored to the underlying etiology, severity, and presence of symptoms. The overarching goals are to prevent and treat infections, restore safe neutrophil counts when possible, and address the underlying cause.

1 General Principles

- **Infection prevention:** Hand hygiene, avoidance of sick contacts, and prompt evaluation of fever.
- **Prophylactic antibiotics:** The role of routine prophylactic antibiotics (e.g., trimethoprim-sulfamethoxazole) is controversial; some centers use them in severe neutropenia, while others reserve them for patients with recurrent infections despite G-CSF therapy (46).
- **Antifungal prophylaxis:** Considered in patients with prolonged severe neutropenia or those receiving high-dose G-CSF.
- **Vaccination:** Routine immunizations are generally safe; live vaccines should be avoided during severe neutropenia or active infection.

2 Management of Transient Neutropenia

Transient neutropenia typically requires no specific therapy beyond monitoring and supportive care. If the infant is well and ANC is $>1.0 \times 10^9/L$, no intervention is needed. For moderate neutropenia ($0.5\text{--}0.99 \times 10^9/L$), serial monitoring and parental education about signs of infection are appropriate. Severe neutropenia ($<0.5 \times 10^9/L$) in a symptomatic infant warrants hospitalization, empirical antibiotics, and hematology consultation (47).

3 Management of Immune-Mediated Neutropenia

Alloimmune Neonatal Neutropenia

- Most cases are self-limited and resolve within weeks as maternal antibodies wane.
- Empirical antibiotics for suspected bacterial infections.
- G-CSF ($5\text{--}10 \mu\text{g/kg/day}$ subcutaneously) is effective in accelerating neutrophil recovery in severe cases (48).
- Recurrence risk in subsequent pregnancies is approximately 25%; antenatal management may be considered in severe cases.

Autoimmune Neutropenia of Infancy

- Most cases are mild and require only observation.
- Antibiotics for documented infections.
- G-CSF reserved for severe or recurrent infections; typically produces rapid ANC response.
- The condition usually resolves spontaneously within 2–4 years (18).

4 Management of Severe Congenital Neutropenia

Granulocyte Colony-Stimulating Factor (G-CSF)

G-CSF is the cornerstone of therapy for SCN. The landmark studies by Bonilla et al. and the Severe Chronic Neutropenia International Registry (SCNIR) demonstrated that daily subcutaneous G-CSF (typically starting at $5 \mu\text{g/kg/day}$ and titrated to maintain ANC $>1.0 \times 10^9/L$) dramatically reduces infection frequency and improves survival (10,49). Approximately 90% of patients respond to G-CSF, with most achieving target ANC values at doses of $5\text{--}10 \mu\text{g/kg/day}$. Higher doses ($>20 \mu\text{g/kg/day}$) are associated with increased risk of MDS/AML and may prompt consideration of hematopoietic stem cell transplantation (HSCT) (50).

Hematopoietic Stem Cell Transplantation (HSCT)

HSCT is the only curative therapy for SCN and is indicated for:

- Patients with poor response to G-CSF (requiring $>20 \mu\text{g/kg/day}$)
- Patients with evidence of clonal evolution or MDS/AML
- Patients with severe infections despite optimal G-CSF therapy (51)

Outcomes of HSCT in SCN have improved substantially in recent years, with overall survival rates exceeding 80% in matched sibling donor transplants (52).

Infection Management

- Prompt empirical antibiotics for fever
- Consideration of antifungal therapy for prolonged fever
- Aggressive evaluation and treatment of focal infections

5 Management of Cyclic Neutropenia

G-CSF is highly effective in cyclic neutropenia, reducing the depth and duration of neutropenic nadirs and preventing symptomatic cycles. Low-dose G-CSF ($1\text{--}3 \mu\text{g/kg/day}$) is often sufficient, and most patients achieve excellent control with minimal side effects (26).

6 Management of Shwachman-Diamond Syndrome

Management of SDS is multifaceted and includes:

- Pancreatic enzyme replacement therapy for exocrine insufficiency
- Fat-soluble vitamin supplementation
- G-CSF for severe neutropenia (with caution due to MDS/AML risk)
- HSCT for progressive marrow failure or leukemic transformation (27)

7 Management of Drug-Induced Neutropenia

- Discontinuation of the offending agent
- Supportive care with monitoring of ANC recovery
- G-CSF in severe or prolonged cases

8 Management of Nutritional Neutropenia

- Folate or vitamin B12 supplementation as appropriate
- Copper supplementation for copper deficiency
- Resolution typically occurs within days to weeks of supplementation

9 Role of Biosimilars

Biosimilar G-CSF products (e.g., filgrastim-sndz) have demonstrated comparable efficacy and safety to reference filgrastim in pediatric populations, including for post-HSCT engraftment and chemotherapy-induced neutropenia prophylaxis (53). The availability of biosimilars has reduced treatment costs and improved access to G-CSF therapy.

Prognosis

The prognosis of infant neutropenia is highly dependent on the underlying etiology.

1 Transient Neutropenia

Prognosis is excellent, with complete resolution typically occurring within days to weeks.

No long-term sequelae are expected.

2 Autoimmune Neutropenia of Infancy

Prognosis is favourable, with spontaneous resolution in approximately 90% of cases within 2–4 years (18).

Long-term follow-up studies have demonstrated low risk of severe late infections after resolution. Some patients may develop other autoimmune conditions, although this association is not firmly established.

3 Alloimmune Neonatal Neutropenia

Prognosis is generally good, with resolution within weeks as maternal antibodies are cleared. However, severe infections (particularly gram-negative sepsis) can be fatal in a minority of cases (15). Recurrence in subsequent pregnancies is a consideration for family counseling.

4 Severe Congenital Neutropenia

Prognosis has improved dramatically with G-CSF therapy. Pre-G-CSF era mortality was approximately 50% within the first year of life; modern series report survival rates exceeding 90% with G-CSF therapy (49). However, the risk of malignant transformation remains a major concern:

- **MDS/AML risk:** Approximately 20–25% of patients with SCN develop MDS or AML, with risk correlated with G-CSF dose and duration (50).
- **High-risk mutations:** Specific ELANE mutations (e.g., G214R, L121H, L121P) and CSF3R truncation mutations confer higher leukemia risk (54).
- **Monitoring:** Regular bone marrow examination (every 1–3 years) with cytogenetic analysis and NGS is recommended to detect early clonal evolution (44).

5 Cyclic Neutropenia

Prognosis is excellent with G-CSF therapy. Unlike SCN, cyclic neutropenia carries minimal risk of malignant transformation, with only rare cases of AML reported (54).

6 Shwachman-Diamond Syndrome

Prognosis is variable and depends on the severity of marrow failure and the risk of leukemic transformation. Approximately 10–20% of patients develop MDS or AML, with the highest risk in those with biallelic SBDS mutations and complex cytogenetic abnormalities (27).

Future Perspectives

The landscape of neutropenia management is evolving rapidly, with several promising developments on the horizon.

1 Gene Therapy and Gene Editing

CRISPR-based gene editing technologies have emerged as potential curative therapies for monogenic neutropenia syndromes. Recent preclinical studies have demonstrated:

- **Base editing and prime editing of ELANE:** Near-universal correction of ELANE mutations in CD34+ hematopoietic stem/progenitor cells, with restoration of neutrophil maturation and function in murine models (11).
- **Adenine base editing to inhibit mutant ELANE expression:** Selective silencing of the mutant allele while preserving wild-type function, offering a potentially safer alternative to nuclease-mediated editing (12).
- **Patient-cell-based gene therapy approaches:** Preclinical models demonstrating long-term disease correction (55).

These approaches hold promise for translation into clinical trials within the next several years, potentially offering curative treatment without the risks of allogeneic HSCT.

2 Improved Diagnostics

- **Expanded NGS panels:** Including newly identified neutropenia-associated genes (e.g., VPS45, JAGN1, AK2, SRP54).
- **Whole-genome sequencing:** Increasingly accessible and may identify novel genetic causes in currently unexplained cases.
- **Functional assays:** Including in vitro neutrophil differentiation assays and UPR activation studies to characterize variant pathogenicity.

3 Refined Risk Stratification

Ongoing research aims to refine leukemia risk prediction in SCN through:

- Integration of genetic data (specific ELANE mutations, CSF3R status)
- Somatic mutation monitoring (e.g., CSF3R, RUNX1, ASXL1)
- Machine learning approaches incorporating clinical and molecular data

4 Novel Therapeutics

- **Small molecule approaches:** Targeting endoplasmic reticulum stress in ELANE-related SCN.
- **Anti-apoptotic agents:** Investigated in preclinical models of HAX1-related neutropenia.
- **Improved G-CSF formulations:** Including longer-acting pegylated forms (pegfilgrastim) and biosimilars.

5 International Collaboration and Registries

International registries, including the Severe Chronic Neutropenia International Registry (SCNIR) and the European Net-INNOCHRON network, continue to play a critical role in advancing understanding of neutropenia through standardized data collection, genotype-phenotype correlation studies, and clinical trial infrastructure (1,49).

Conclusion

Neutropenia in infants encompasses a heterogeneous spectrum of disorders ranging from transient, self-limited conditions to severe, life-threatening congenital syndromes. Accurate diagnosis requires a systematic approach integrating clinical assessment, serial hematologic evaluation, antineutrophil antibody testing, bone marrow examination, and increasingly, comprehensive genetic testing. The advent of molecular diagnostics has transformed the classification and prognostication of inherited neutropenia syndromes, enabling personalized management strategies.

Recombinant human G-CSF remains the cornerstone of therapy for severe and symptomatic neutropenia, dramatically reducing infection-related morbidity and mortality. The recognition of long-term risks, particularly the association between high-dose G-CSF therapy and malignant transformation in SCN, has prompted refined treatment algorithms and careful monitoring protocols. Hematopoietic stem cell transplantation offers curative potential for patients with poor G-CSF response or evidence of clonal evolution.

Emerging gene editing technologies, particularly CRISPR-based base and prime editing approaches targeting ELANE and other neutropenia-associated genes, hold promise for definitive treatment of monogenic neutropenia syndromes. Continued international collaboration through registries and clinical networks will be essential to translate these advances into improved outcomes for affected infants.

Clinicians caring for infants with neutropenia must balance the imperative to prevent and treat infections with the need to avoid unnecessary interventions in self-limited conditions. A nuanced, evidence-based approach, guided by contemporary international guidelines and emerging molecular insights, offers the best path to optimizing outcomes in this vulnerable population.

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