Received: 3 November 2024 | Accepted: 27 February 2025

DOI: 10.1002/hem3.70113

GUIDELINES - CONSENSUS-BASED

HemaSphere eha

European guidelines on treatment and supportive measures in chronic neutropenias: A consensus between the European Hematology Association and the EuNet-INNOCHRON COST Action based on a systematic evidence review

Francesca Fioredda[1] | Michail Spanoudakis[2] | Julia Skokowa[3] | Hannah Tamary[4] | Piero Farruggia[5] | Antonio Almeida[6,7] | Daniela Guardo[1] | Jan Palmblad[8,9] | Petter Höglund[8,9,10] | Ivo P. Touw[11] | Cornelia Zeidler[12] | Alan J. Warren[13,14,15] | Mario Csenar[16] | Nicole Skoetz[16] | Elio Castagnola[17] | Erica Ricci[17] | David C. Dale[18] | Peter E. Newburger[19] | Karl Welte[20] | Helen A. Papadaki[21,22,*] | Carlo Dufour[1,*]

Correspondence: Francesca Fioredda (francescafioredda@gaslini.org)

Abstract

The treatment of chronic neutropenias and control of neutropenia-related infections remain challenging topics for pediatric and adult hematologists. This article aims to fill the gap in the treatment of neutropenias and, in combination with the previously published European guidelines on diagnosis of neutropenias, gives complete and comprehensive guidance on the whole management of patients with neutropenia. In terms of methodology, an Evidence-Based Medicine team produced an evidence synthesis of the literature on the treatment of neutropenias. Then, according to the robustness of the evidence, consensus recommendations were elaborated and voted by an expert's panel from the Cooperation in Science and Technology European Network for the Innovative Diagnosis and Treatment of Chronic Neutropenias (https://eunet-innochron.eu/) and the Specialized Working Group on Granulocytes and Constitutional Bone Marrow Failure Syndromes of the European Hematology Association. Whenever evidence was not available, recommendations were based on the expert's panel opinion. Consensus-based recommendations are related to granulocyte colony-stimulating factor indications and schedule of administration, indications for hematopoietic stem cell transplantation, supportive treatments and measures, and new treatments that have been evolving over the recent years. These guidelines, rather than a numerical correction of the absolute neutrophil count, suggest a holistic, patient-centered approach aiming at optimizing the management of chronic neutropenic patients and offering valuable and practical guidance to the hematologists for their daily clinical practice.

[1]Unit of Hematology-IRCCS Istituto Giannina Gaslini, Genova, Italy
[2]Department of Haematology, Warrington and Halton Teaching Hospitals, NHS Foundation Trust, Warrington, UK
[3]Department of Oncology, Hematology, Immunology, Rheumatology, and Clinical Immunology, University Hospital Tübingen, Germany
[4]Hematology/Oncology Division, Safra Children Hospital Sheba Medical Center, Ramat-Gan, Israel
[5]Unit of Pediatrics, S.Cimino Hospital, Termini Imerese, Palermo, Italy
[6]Department of Hematology, Hospitalda Luz Lisboa, Portugal
[7]Faculdadede Medicina, Universidade Católica Portuguesa, Lisbon, Portugal
[8]Center for Hematology and Regenerative Medicine (HERM), Department of Medicine Huddinge, Karolinska Institutet, Stockholm, Sweden
[9]Department of Hematology, Karolinska University Hospital, Stockholm, Sweden
[10]Clinical Immunology and Transfusion Medicine Clinic, Karolinska University Hospital, Stockholm, Sweden
[11]Department of Hematology and Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, Netherlands
[12]Department of Oncology, Hematology, Immunology and Bone Marrow Transplantation, Hannover Medical School, Hannover, Germany
[13]Department of Hematology, University of Cambridge, UK

INTRODUCTION

Chronic neutropenias are a group of heterogeneous disorders with the common feature of decreased absolute neutrophils count (ANC), ranging from mild to severe, for a period of more than 3 months.[1–3] According to our previous published work on the definition and diagnosis of chronic neutropenias, the condition is defined as congenital (CN; isolated or associated with extra-hematological features) or acquired, which can be further characterized as primary/idiopathic (associated with the presence of antineutrophil antibodies or other unknown mechanisms) and secondary (associated to underlying conditions/diseases).[3] A new provisional category has been recognized as "likely acquired neutropenia," which is usually diagnosed from childhood to young adulthood and is probably associated with underlying immune dysregulation, thus requiring extensive work-up to exclude potential genetic causes.[3,4]

The two most common complications associated with neutropenia are predisposition to infections and transformation to myelodysplastic neoplasms (MDS)/acute leukemia (AL).[1,2,5] Infections are mainly bacterial, rather than fungal or viral, and in CN are related to the depth of neutropenia, whereas this is not generally the case in acquired forms.[1,2,5–7] Evolution to MDS/AL is mostly observed in CN and in the acquired forms with clonal hematopoiesis.[1,2,5,8]

Protection against infections can be obtained by increasing ANCs through stimulation of neutrophil production. Since the early 1990s recombinant human granulocyte colony-stimulating factor (rh G-CSF, from now on, G-CSF) has been introduced in clinical practice, dramatically improving the prognosis and life expectancy of patients with severe chronic neutropenia (severe CN).[9–11]

To date, recommendations for the treatment of patients with neutropenia are mostly related to G-CSF indications, dosages, and treatment schedules across different types of CN. In this field, the quality and level of evidence are relatively weak due to the absence of randomized clinical trials.[1,10] Other treatments such as steroids or granulocyte transfusions are not established or investigational approaches while the indications for the hematopoietic stem cell transplantation (HSCT), the only current curative procedure for specific CN patients, are still a matter of debate. Interestingly, novel therapeutic strategies that can effectively treat the genetic cause of CN are under development.

This article on the treatment of chronic neutropenias aims to cover a gap in the field by providing recommendations based on existing literature and expert opinion. Specifically, this article is based on a systematic review of the literature on the treatment of neutropenia, which was revised, discussed, and voted on by a panel of experts from the Cooperation in Science and Technology (COST) European Network for the Innovative Diagnosis and Treatment of Chronic Neutropenias (EuNet-INNOCHRON; https://eunet-innochron.eu/) in collaboration with the Specialized Working Group on Granulocytes and Constitutional Bone Marrow Failures of the European Hematology Association (EHA). The same group of experts have produced the recently published guidelines on the diagnosis and management of chronic neutropenias.[3]

METHODS

As mentioned earlier, this article is the second part of a collaborative project between the COST Action EuNet-INNOCHRON and EHA for the establishment of European Guidelines on chronic neutropenias. The first part was focused on the definition, classification, diagnosis, and special situations, while this second part addressed treatment and supportive approaches of patients with chronic neutropenias.[3]

Like the first part of the guidelines, the treatment EuNet-INNOCHRON–EHA panel consists of two chairs: a steering committee and an expert panel including the chairs of the European and North American Branches of the Severe Chronic Neutropenia International Registry. Given that more robust evidence exists on the treatment compared to the diagnosis and management areas of chronic neutropenias, a methodological support team from Evidence-Based Medicine/Department I of Internal Medicine, now Institute of Public Health, at the University of Cologne, was asked to contribute in establishing evidence-based guidelines.

The first step of evidence synthesis entailed a scoping of literature aimed at providing an overview of the most broadly applied interventions in the treatment of chronic neutropenia patients, including severe CN, cyclic neutropenia (CyN), autoimmune neutropenia (AIN), and chronic idiopathic neutropenia (CIN). The evidence synthesis team identified three key interventions: G-CSF, corticosteroids, and granulocyte transfusions. In the second step, the robustness of the evidence was addressed, taking an outcome-centric approach. The pre-defined outcomes assessed were related to treatment efficacy (overall survival and infection-free survival), health-related quality of life, malignant transformation, infectious complications (e.g., incidence and duration of infection-related events), neutrophil response, and treatment-related adverse events (excluding malignant transformation) (Figure 1). Any study or trial report identified through systematic searches was eligible for inclusion, irrespective of its design or publication type. The sample cut-off for study eligibility was set at a minimum of five participants, given the rarity of the disorders. Database searches were conducted by an experienced information specialist in MEDLINE via OvidSP, covering publications since the database's inception.

The search identified 705 records and six additional records through citation and manual searches. Participant samples across studies and reports ranged from five in small case series to larger registry analyses, including up to 1752 registrees. Ultimately, 35 reports were considered eligible for analysis: three were randomized controlled trials (RCTs), 13 were registry analyses, and 19 were observational studies. Figure 1 depicts an evidence heat map linking chronic neutropenia subtypes to (i) the number of reports and type of publications and (ii) the reported outcomes, including survival outcome, infectious complications, quality of life, malignant transformation, neutrophil response, and treatment-related adverse events. Of the observational studies, eight were before-after studies, seven were interrupted time series, and four were

[14]Cambridge Institute for Medical Research, University of Cambridge, Cambridge, UK
[15]Wellcome Trust-Medical Research Council Stem Cell Institute, University of Cambridge, UK
[16]Institute of Public Health, Faculty of Medicine and University Hospital, University of Cologne, Cologne, Germany
[17]Infectious Diseases Unit, Department of Pediatrics, IRCCS, Istituto Giannina Gaslini, Genova, Italy
[18]Department of Medicine, University of Washington, Seattle, Washington, USA
[19]Departments of Pediatrics and Molecular, Cell and Cancer Biology, UMass Chan Medical School, Worcester, MA, USA
[20]University Children's Hospital, Tübingen, Germany
[21]Hemopoiesis Research Laboratory, School of Medicine, University of Crete, Heraklion, Greece
[22]Department of Hematology, University Hospital of Heraklion, Crete, Greece
*Helen A. Papadaki and Carlo Dufour shared senior author position.

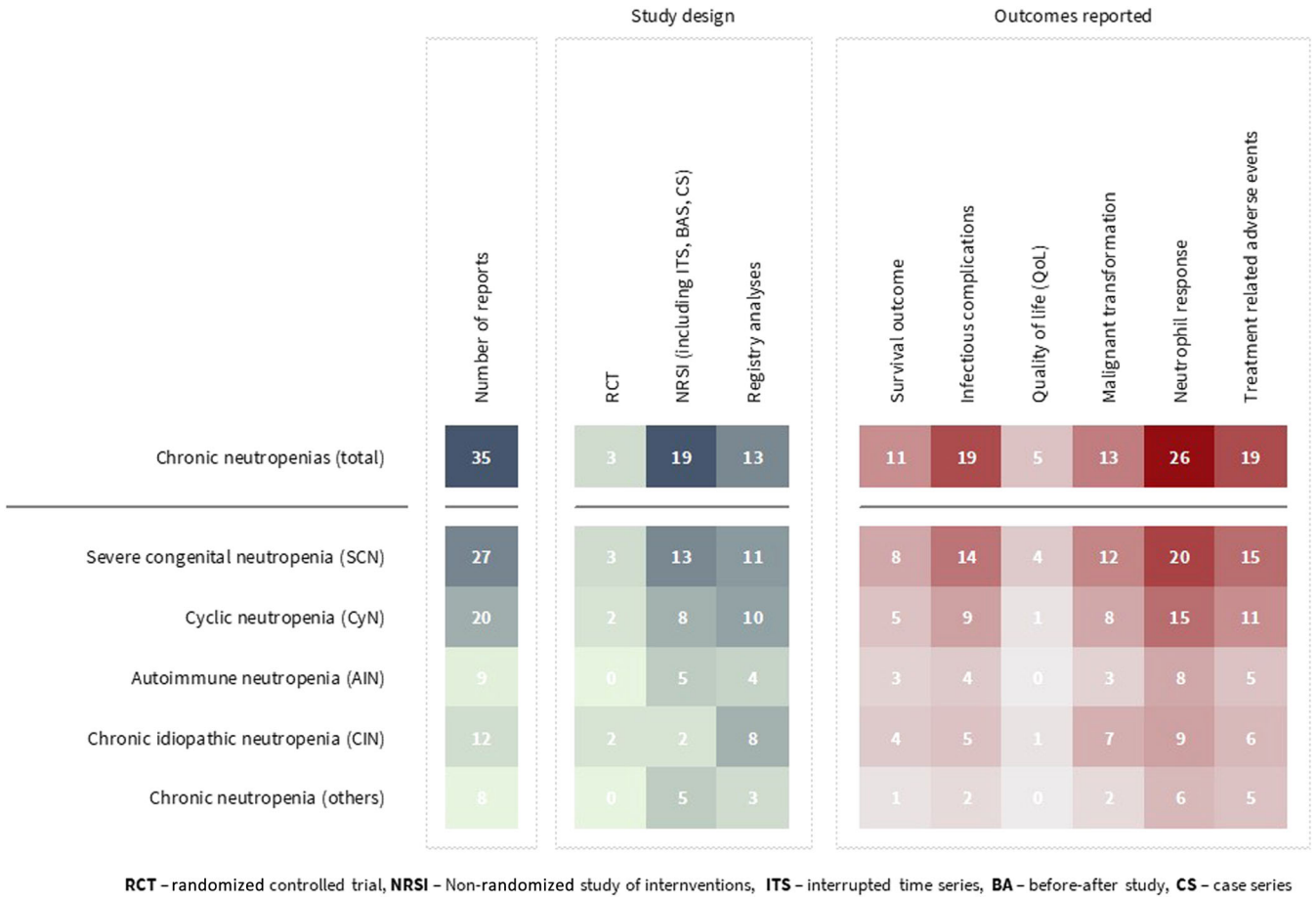

FIGURE 1 Evidence heat map.

case series. The largest body of evidence could be identified for the intervention of G-CSF in severe CN, followed by CyN and CIN. Considering the disease rarity and trial nature, the focus of RCTs was largely on surrogate and potential early outcomes of neutrophil response, infectious complicationsm and immediate adverse events, while long-term follow-up registry analyses supplied real-world data on the outcomes of mortality and malignant transformation. The paucity and indirectness of data, stemming from different disease biologies (as elucidated in later sections), ethical considerations, whereby withholding effective therapy (i.e., G-CSF) in the absence of valid alternatives largely forbade experimental trials and the high risk of double-counting due to registry re-analyses, led to a constellation of most outcomes being supported only by weak evidence.

Recognizing evidence gaps and the need for guidance, the expert panel chose to formulate consensus recommendations primarily based on their collective live experience in treating chronic neutropenia patients, while integrating the systematically accrued evidence. Following the structured consensus-finding approach of the Delphi method, derived recommendations were shared among the expert panel and voted on, as described previously.[12–15] In accordance with the EHA guideline methodology, a recommendation was consented if the agreement among experts exceeded 75%.[15] The resulting recommendations were supplemented by the level of agreement expressed in percentages.

NEUTROPENIA: INFECTIONS OCCURRENCE AND MANAGEMENT

As mentioned earlier, patients affected with neutropenia are prone to develop bacterial infections rather than fungal or due to viruses, with a variable clinical course (from mild to severe) and different presentation patterns (i.e., acute/persistent or recurrent). Life-threatening infections are more common in severe CN rather than in acquired neutropenia (AIN and CIN), although a small proportion of patients with acquired neutropenia may still experience a relatively significant infectious burden. Common sites of infection include the skin, ear, mouth, and mucosa. In cases involving fluctuating ANC levels, such as CyN, infections may exhibit periodicity.[1,2,7,8]

The atypical chemokine receptor-1/Duffy antigen receptor for chemokines gene (*ACKR1/DARC*)-associated neutropenia (ADAN; previously defined as ethnic neutropenia), which is common in individuals of African or Middle Eastern descent, seems not to be associated with an increased propensity to infection even in the rare cases with severe neutropenia.[16]

The propensity to infection and the infective episodes in patients with chronic neutropenia are usually managed with G-CSF, which increases the number of mature circulating neutrophils. Some studies on the use of alternative or adjunctive treatments (corticosteroids, immunoglobulin, and granulocyte transfusion) are available in the literature.

The following sections will discuss the use of the most common therapies to manage neutropenia according to subtypes, indication of HSCT, and the emerging frontier of gene therapy.

G-CSF

G-CSF indications

Severe CN and CyN

G-CSF is a cytokine that enhances the production of mature neutrophils by promoting the proliferation of myeloid committed progenitors and the marrow mitotic pool (from myeloblast to myelocyte) by shortening the maturation time from metamyelocyte to neutrophil and increasing the half-life of neutrophils.[17] G-CSF is generally able to overcome the maturation arrest due to apoptosis of the progenitors at the promyelocyte stage in severe CN and CyN and it is also useful to optimize neutrophil maturation in acquired neutropenia where immature (left shifted) neutrophils are commonly seen.[5] Since its introduction in clinical practice, the natural history of severe CN has dramatically improved.[18]

Indeed, long-term data coming from the two biggest neutropenia registries (the SCNIR and French) show that severe CN and CyN patients treated with rhG-CSF have a considerable survival benefit and a lower rate of infection-related complications compared to historical controls from the pre-G-CSF era, which is reflected in decreased antibiotic use and hospital admissions.[18–20] Regarding quality of life (QoL), patients have reported improvement in perceived health status, disease-related symptoms, and activity limitation despite experiencing significant inconvenience from regular injections.[21–24] A long-acting pegylated filgrastim (Pegfilgrastim), which requires weekly rather than daily subcutaneous injections, would overcome this issue and will be discussed later (Box 1).[25]

Other types of chronic neutropenias

The efficacy and the safety of G-CSF have been assessed in neutropenias other than CN. Common types of acquired neutropenias affecting both children and adults, such as AIN and CIN, usually display a more benign course with fewer infective episodes and better outcomes compared to CN patients.[26–28]

Although in AIN and CIN patients available studies do not provide clear evidence that continuous treatment with G-CSF leads to survival benefit, improved QoL, or reduced severe infective complications, therapy with G-CSF is considered useful to manage acute or chronic infections. The low evidence is attributed by the panel to the fact that only a minority of AIN and CIN patients actually need treatment with G-CSF, thus accounting for the lack of a large series containing these subjects. As for *ACKR1/DARC*-associated neutropenia characterized by no increased infection propensity, there is no clear indication for the routine use of G-CSF (Box 2).[16]

Primary goal of G-CSF treatment

The primary aim of G-CSF treatment in neutropenic patients is the control of infections by increasing the ANC, and the minimization of reported side effects in the forms of bone pain and splenomegaly.[29–35]

The ANC nadir, typically measured before any subsequent injections, is an important determinant of the success of treatment in CN. G-CSF response may be variable; there are no established rules on the number of nadir samples needed to reach the desired neutrophil threshold. As a general principle, the ANC threshold should be as stable as possible, before finalizing the ultimate G-CSF schedule.[1,12]

On the contrary, in AIN and CIN, other features such as the frequency and severity of infections are more relevant in guiding the need for G-CSF treatment and its schedule.[36,37] The desirable ANC target for G-CSF has been adjusted downward over time, thus requiring lower G-CSF doses. In the pivotal phase 3 RCT by Dale et al. in 1993, the threshold to label the neutrophil response as complete was an ANC of more than 1.5×10^9/L.[10] In later years, a lower target ANC of 1.0 to 1.5×10^9/L was deemed sufficient by the advisory board of the SCNIR.[37] According to current knowledge, the desirable threshold of ANC is 1.0×10^9/L because neutrophils above this level are generally considered adequate to protect against infections. According to the available evidence, up to 90% of CN, CyN, CIN, and AIN patients respond to G-CSF treatment.[18,36–39] In CyN, infectious burden is generally lower than the one described in CN, thus enabling

BOX 1: G-CSF treatment in severe congenital and cyclic neutropenia.

Overall, the panel considers that G-CSF treatment either in severe CN or in CyN is beneficial because it reduces the frequency and severity of infection and improves the quality of life (reduced use of antibiotics, hospitalization, and infection-related complications).
Consensus agreement 100%

As a consequence, the panel recommends the use of G-CSF in severe CN and in CyN, particularly in those patients with recurrent or severe infections.
Consensus agreement 100%

Abbreviations: CN, congenital neutropenia; CyN, cyclic neutropenia; G-CSF, granulocyte-colony stimulating factor.

BOX 2: G-CSF treatment in neutropenias other than severe congenital and cyclic neutropenia.

The panel does not recommend the continuous use of G-CSF, based only on the ANC, in patients with CIN or AIN.
Consensus agreement 100%

The panel recommends an individual approach for patients with CIN or AIN and the final decision regarding continuous G-CSF should be based on the history and severity of infections rather than the ANC.
Consensus agreement 100%

The panel encourages the continuous use of G-CSF in rare patients with CIN or AIN who present with frequent and/or severe infections. The panel also suggests evaluating the occasional use of G-CSF in CIN or AIN patients during severe infective episodes.
Consensus agreement 100%

The panel does not recommend the use of G-CSF in *ACKR1/DARC*-associated neutropenia (ADAN, previously defined as ethnic neutropenia) due to the lack of infection propensity.
Consensus agreement 100%

Abbreviations: *ACKR1*, atypical chemokine receptor-1 gene; AIN, autoimmune neutropenia; ANC, absolute neutrophil count; CIN, chronic idiopathic neutropenia; *DARC*, Duffy antigen receptor for chemokines gene; G-CSF, granulocyte-colony stimulating factor.

to accept ANC levels lower than 1500/mmc for very short periods (Box 3).[1]

G-CSF types

Different forms of G-CSF analogs have been investigated for the treatment of chronic neutropenias. Most publications report on the use of the non-glycosylated form of G-CSF analog filgrastim or its biosimilars. The glycosylated form of G-CSF lenograstim has been studied in three patient cohorts in four published reports.[40–43] The noninferiority of the glycosylated G-CSF (lenograstim) compared to the non-glycosylated G-CSF (filgrastim) formula with regard to neutrophil response, recovery, and incidence of infections has been demonstrated.[21,41]

Pegfilgrastim, a pegylated G-CSF formulation with a longer half-life than the first-generation G-CSF, has been compared with filgrastim and lenograstim in terms of ANC responses and rate of infectious complications and no significant differences were identified in the two published studies.[44,45] However, an improvement of QoL was shown with pegfilgrastim versus filgrastim in severe CN patients.[45] Notably, there are no reported studies on the use of pegfilgrastim in CIN or AIN patients (Box 4).

G-CSF doses and frequency

G-CSF dose estimate reporting is inconsistent across publications, with some studies indicating average or median daily G-CSF dose in different types of neutropenia around or above 5 mcg/kg/d in severe CN and below 5 mcg/kg/d in AIN and CIN.[5,27,44,50–53] Patients with CyN are effectively treated with G-CSF, usually at doses of 1–5 mcg/kg/d (median dose 2.5 mcg/kg/d).[21]

BOX 3: Absolute neutrophil count (ANC) threshold during G-CSF administration.

The panel considers ANC over 1.0×10^9/L as the protective threshold against infections. For CyN, a lower nadir may be accepted.
Consensus agreement 100%

As a general concept, the panel suggests using the lowest effective dose of G-CSF for infection control (usually coinciding with ANC ≥ 1.0×10^9/L) and to minimize marrow stimulation and potential side effects (bone pain and splenomegaly).
Consensus agreement 93%

Abbreviations: CyN, cyclic neutropenia; G-CSF, granulocyte-colony stimulating factor.

BOX 4: G-CSF types.

Filgrastim and lenograstim may be interchangeably used in patients with severe CN. Pegfilgrastim might be considered in cases of poor adherence to G-CSF treatment.
Consensus agreement 100%

Abbreviations: CN, congenital neutropenia; G-CSF, granulocyte-colony stimulating factor.

According to SCNIR data, patients requiring higher G-CSF doses (i.e., above 8 mcg/kg/d) to achieve a sufficient ANC response are at a higher risk of developing MDS/AL with a cumulative incidence at 15 years of 34% (95% confidence interval [CI]: 21–47), which unfavorably compares to patients who need less than 8 mcg/kg/d, who display a lower cumulative incidence at 15 years of 15% (95% CI: 4–25).[20]

In addition to cumulative dose of G-CSF, specific genetic variants may also contribute to malignant clonal evolution. In this respect, the French Registry found a correlation between the incidence of MDS/AL and the type of neutropenia (with a higher incidence in severe CN and Shwachman–Diamond Syndrome [SDS])[19] and confirmed that not only the dose but also duration of exposure to G-CSF were risk factors for MDS/AL development in patients with CN.

Moreover, the SCNIR outlined that in severe CN, specific mutations of the *ELANE* gene (mutations G214R or C151Y) are associated with a higher risk of evolution to AL.[45–49]

Therefore, it looks that genetic background, in addition to G-CSF dose itself and duration of exposure, plays a key role in the risk of MDS/AL development in chronic neutropenia associated with *ELANE* mutations.[48,49]

Neutropenia in SDS is associated with an increased risk of developing myeloid malignancies due to inherited deficiency of the ribosome maturation protein SBDS. Longitudinal data from multiple international registries confirmed that SDS predisposes patients to an increased risk of myeloid malignancy with an estimated incidence ranging from 9.8% to almost 30% by the age of 30 years. Strict hematologic surveillance of SDS patients is required, and the minimal effective dose of G-CSF is preferred (1–4 mcg/kg/d).[50]

Glycogen storage disease type Ib (GSD-Ib) is a metabolic disorder associated with neutropenia and neutrophil dysfunction leading to an increased incidence of recurrent infections and development of enterocolitis. In most of these patients, G-CSF increases ANC, mitigates the infectious burden, and ameliorates gastrointestinal manifestations. However, doses must be limited due to the potential contribution of G-CSF to spleen enlargement in the long term with consequent abdominal pain (Box 5).[51]

To minimize the exposure to G-CSF, it is important to consider not only the dose but also the frequency of administration. Instead of daily dosing, an intermittent schedule (e.g., every other day, one or two injections per week, etc.) could be applied and tailored to the individual's medical history, diagnosis, drug side effects, and period of life. In some cases, mainly in CIN and AIN, treatment could be time limited (sporadic) and not continuous.[7]

The G-CSF options, at least as for the starting doses, to be increased according to the "desired ANC threshold" in different neutropenia types are summarized in Table 1 (Box 6).

CORTICOSTEROIDS

The increase of neutrophils following the administration of steroids is a well-known effect due to the accelerated release of neutrophils from the bone marrow into the circulation, reduction in the migration of neutrophils out of the circulation, and increased demargination from the vessels.[52] Additionally, steroids induce lymphocytopenia, as a result of redistribution of circulating lymphocytes into other lymphoid compartments (e.g., spleen, lymph nodes, thoracic duct, and bone marrow).[52]

Weak evidence from the literature indicates that corticosteroid treatment may temporarily lead to a recovery in ANC in up to half of patients with AIN or CIN.[26,27] However, outcomes such as mortality, QoL, malignant transformation, infectious complications, and

BOX 5: G-CSF dosing according to the underlying disease.

In severe CN, the panel suggests initiating treatment with the standard dose of 5 mcg/kg/d.
Consensus agreement 94%

In CyN, G-CSF doses may be lower than in severe CN. The standard dose should be ≤3 mcg/kg/d continuously. G-CSF may be also given every other day. Dosage may be adjusted to avoid nadir $<0.5 \times 10^9$/L and clinical conditions such as mouth ulcers, fevers, or infections.
Consensus agreement 94%

In diseases carrying a high intrinsic risk of transformation such as SDS or of splenomegaly such as GSD-1b, minimal effective dose of G-CSF to prevent infections should be used.
Consensus agreement 100%

In AIN and CIN, no studies have established the dose of G-CSF to use. If G-CSF is needed, we suggest beginning at 1 mcg/kg/d.
Consensus agreement 93%

ANC > 5.0×10^9/L is usually not necessary to prevent infection. In patients with CyN, a higher ANC at peak can be expected.
Consensus agreement 93%

Abbreviations: AIN, autoimmune neutropenia; ANC, absolute neutrophil count; CIN, chronic idiopathic neutropenia; CN, congenital neutropenia; CyN, cyclic neutropenia; G-CSF, granulocyte-colony stimulating factor; GSD-Ib, glycogen storage disease type Ib; SDS, Shwachman–Diamond syndrome.

TABLE 1 Summary on starting G-CSF doses according to different neutropenia types.

	CN	CyN	SDS/GSD-1b	AIN/CIN
G-CSF starting dose	5 mcg/kg/d	≤3 mcg/kg/d	1 mcg/kg/d	1 mcg/kg/d

BOX 6: G-CSF administration schedule

Sporadic therapy is reserved for those patients (mainly with AIN or CIN) who require a transient boost of the ANC but are generally infection-free without intervention.
Consensus agreement 87%

Continuous therapy is indicated for those patients persistently at risk of developing severe infections due to intrinsic/severe impairment of neutrophil production/maturation.
Consensus agreement 80%

In G-CSF-treated patients with AIN and CIN, the possibility of spontaneous remission of neutropenia, and consequently no further need for G-CSF treatment, should be taken into consideration by cautiously interrupting the treatment for 1–3 weeks.
Consensus agreement 87%

Abbreviations: AIN, autoimmune neutropenia; CIN, chronic idiopathic neutropenia; G-CSF, granulocyte-colony stimulating factor.

treatment-related adverse events consequent to corticosteroid therapy have not been reported in these studies. Notably, there are no published studies and lack of evidence reporting corticosteroids in the treatment of severe CN or CyN (Box 7).

BOX 7: Use of corticosteroids in neutropenia.

The panel does not recommend the use of corticosteroids in any type of neutropenia as the lymphocyte depletion effect may worsen the propensity to infections.
Consensus agreement 93%

BOX 8: Granulocyte transfusions.

The panel considers that, at present, due to the lack of evidence on efficacy and possible side effects, granulocyte transfusions should not be considered a therapeutic option for severe infections in any chronic neutropenia condition outside well-designed clinical trials.
Consensus agreement 86%

GRANULOCYTE TRANSFUSION

Data on granulocyte transfusion in patients with CN, CIN, or AIN are not available in the literature; thus, there is no evidence to determine whether this treatment approach is beneficial or harmful for the treatment or prevention of infections in these disorders. The existing knowledge in the field derives from the restricted use of granulocyte transfusion post-chemotherapy or after HSCT.

Although some authors suggest a role for granulocyte transfusion in association with antimicrobial therapy, especially in the presence bacterial or fungal infection, there are no conclusive data from RCT that the use of granulocyte transfusions reduces mortality in neutropenic patients with severe infections.[53,54] Furthermore, large-scale RCT must be encouraged to support or reject the use of the granulocyte transfusion in neutropenia disorders.

Mild-to-moderate adverse reactions (such as fever, shivering, or changes in blood pressure) are described in up to 41% of cases following granulocyte transfusions; also, more severe reactions including respiratory distress and transfusion-related acute lung injury may occur.[55,56] Other described problems include infectious complications such as cytomegalovirus or West Nile Virus infection and the development of anti-HLA and anti-neutrophil antibodies in the recipient.[57,58] Furthermore, one of the concerns is the limited number of harvested cells that is often insufficient to counteract the infections. Finally, it has to be considered that G-CSF, when used to increase cell collection from healthy granulocyte donors, might raise ethical concerns related to potential side effects,[59] thus representing a further discouraging element toward the standard use of this procedure (Box 8).

SUPPORTIVE MEASURES

Antibiotic therapy and prophylaxis

Infections are more common in neutropenic patients compared to the healthy population, and their clinical pattern is usually more severe in CN disorders rather than acquired forms, as discussed earlier.[1,2,7,37,60] Infrequently, infective episodes may be lethal as shown by the cumulative incidence of lethal sepsis in patients with severe CN, which

is reported to be 10% after 15 years of treatment with G-CSF, according to the SCNIR data.[20]

Management of infectious complications, in case of acute illness, should be similar to that recommended for neutropenia following anti-leukemia chemotherapy.[61,62]

In particular, blood cultures should be performed at the onset of fever, and urinalysis and urine culture should be considered in patients where a clean-catch, mid-stream specimen is readily available. Imaging, preferentially chest CT scan, should be performed only in patients with respiratory signs or symptoms, while other diagnostic imaging should be performed according to the presence of localized clinical signs.

Particular attention has to be paid to neutropenic patients showing abdominal pain to detect any possible infection caused by opportunistic and/or anaerobic agents (i.e., *Clostridium difficile*).

Initial empirical treatment could be represented by monotherapy with piperacillin–tazobactam (mainly in patients with abdominal symptoms) or cefepime, while meropenem should not be routinely used since it could represent the best antibiotic change in case of no clinical response or of resistance.[63]

The choice of oral antibacterial therapy may be more appropriate in clinically stable patients. Amoxicillin–clavulanate or levofloxacin could be considered for this purpose.[61]

However, it has to be highlighted that the choice of treatment should be better tailored to local epidemiological conditions, also considering the possible colonization by antibiotic-resistant pathogens.[64]

In case of persistent fever, a diagnostic workup according to the clinical picture inclusive at least of imaging, bronchoalveolar lavage (BAL), repeated cultures, galactomannan antigen detection, or anything else indicated by clinical findings should be considered.[65]

In case of recurrent infections, secondary antibacterial prophylaxis could be considered on an individual basis, taking into account the number of recurrences, the involved site(s), the isolated pathogen (s), and antibiotic susceptibility bearing in mind that prolonged administration of antibiotics is associated with the risk selecting bacterial resistances. In case of neutropenia concomitant to persistent lymphocyte count below the threshold for age, prophylaxis against opportunistic agents such as *Pneumocystis jirovecii* (PJP) with low-dose trimethoprim–sulfamethoxazole might be considered.[66]

Considering the low incidence of invasive fungal diseases in neutropenia patients compared with that observed in ALs or following stem cell transplantation, primary antifungal prophylaxis is also not recommended.[65]

However, if a patient has additional host defense defects involving the adaptive immune system, viral or fungal infections should be considered for appropriate investigation and treatment (Box 9).

BOX 9: Antibiotic treatment and prophylaxis.

Infections in neutropenic patients should be promptly evaluated and treated immediately with broad-spectrum antibiotics and hospitalization may be needed. The choice of antibiotics depends on the local policies, hospital bacterial flora, antibiotic resistance patterns, and possible known colonization of patients with specific microbes.
Consensus agreement 100%

Based on the lack of data on efficacy and on the risk of microbiological resistance, the panel suggests avoiding antibiotic prophylaxis in any type of neutropenia.
Consensus agreement 87%

Dental hygiene

Severe CN is a condition that favors infections including periodontal disease, with a severity proportional to the depth and duration of neutropenia. It has been reported that optimal dental health is obtained through ANC maintenance above the threshold needed to fight infections as mentioned in Box 3.[67,68]

As regards the underlying pathophysiology, low ANC leads to impaired cytokine balance (both proinflammatory and anti-inflammatory) in the peri-gingival fluid with the consequence of alveolar bone loss and periodontal disease.[69,70]

Adults and children with untreated or refractory neutropenia suffer from chronic periodontal disease and this requires good dental hygiene to prevent infections of the mucosa and teeth with regular treatment by dental health professionals.[69,70] The benefit from good dental hygiene which can prevent tooth loss, is by far higher than the theoretical risk of bacteremia as a result of local trauma. Normal saline and hydrogen peroxide rinses in combination with local anesthetic gels and gargles can be used for pain control related to oral and gingival lesions (Box 10).[71]

Psychological support

Dedicated studies on the QoL and psychological needs in neutropenic patients are particularly limited. Neutropenia is a persistent condition, and appropriate support both from health professionals and patient/parent groups may alleviate the psychological burden of a chronic illness.[72,73] Moreover, some types of neutropenia may be associated with neurodevelopment delay (i.e., HAX neutropenia) that require either psychological support or rehabilitation programs.[3]

The psychosocial effects of severe neutropenia in individuals and their families, as in other chronic conditions, are present at any stage of childhood and adulthood and can disrupt normal life due to unpredicted illness and infection. Affected patients and their families may feel isolated from their community and friends and joining support groups might alleviate these feelings. Adolescence is a period in which patients with severe neutropenia may realize that they are different from their peers and it might be difficult for them to maintain a positive self-image. Parents should be vigilant to recognize signs of depression or unusual anger in their children and seek advice from professionals (Box 11).[72,73]

Vaccination

Subjects affected with chronic neutropenia are more susceptible to invasive infections than the general population, highlighting the importance of protecting them through serial vaccination boosters. No dedicated studies on the safety and effectiveness of vaccination in

BOX 10: Suggestions for dental hygiene.

Given the increased incidence of periodontal inflammation in severe CN and CyN, frequent periodontal examinations and maintenance of good oral hygiene is recommended. The panel suggests maintaining a target ANC $\geq 1.0 \times 10^9$/L for optimal dental health.
Consensus agreement 100%

Abbreviations: ANC, absolute neutrophil count; CN, congenital neutropenia; CyN, cyclic neutropenia.

BOX 11: Psychological support

Psychological support is highly advisable in chronic neutropenia patients to improve their quality of life.
Consensus agreement 93%

Special support and rehabilitation programs for patients with neurodevelopmental disabilities is suggested.
Consensus agreement 100%

BOX 12: Advice on vaccination.

Subjects affected with chronic neutropenia in whom underlying T-cell, B-cell, and natural killer cell immunodeficiency/dysregulation have been ruled out, should receive all routine inactivated, and live attenuated vaccines according to specific national schedules.
Consensus agreement 100%

Consultation with an immunologist is indicated for neutropenic patients with an underlying immunodeficiency.
Consensus agreement 100%

All patients with chronic neutropenia should be advised to receive an approved influenza and COVID-19 vaccine.
Consensus agreement 100%

Whenever possible, it is worth considering immunization of close contacts of a patient with neutropenia against all vaccine-preventable diseases.
Consensus agreement 100%

the neutropenic population exist, and the immunization policy is extrapolated from the literature on "phagocytic cell defects."[72,74,75] Patients with severe CN usually have an intact adaptive immune system, which is sufficient to produce protective antibodies following the standard vaccination schedule for their age.[74] It is often emphasized that the adult population, especially immunocompromised patients, are significantly under-vaccinated, highlighting the importance of close surveillance of vaccination schedules.[75]

For patients with chronic neutropenia without any additional immune defect, routine inactivated and live attenuated vaccines against bacterial and viral diseases are indicated according to the respective national regulations.

Live viral vaccines are indicated if immunodeficiency is excluded (defined by CD4+ > 0.5×10^9/L in adults, CD4+ > 1.0×10^9/L in ages 1–6 years, or CD4+ cells > 1.5×10^9/L in children under 1 year of age).[76–78] In cases where neutropenia is associated with immune deficiency/dysregulation, expert advice by an immunologist on vaccination procedures is recommended (Box 12).

HSCT

Neutropenia in severe CN patients is generally managed with subcutaneous G-CSF injections. This approach, however, is not curative. In contrast, HSCT is potentially curative,[79–86] also offering the "benefit" of preventing possible leukemic transformation in patients with high-risk genetic/cytogenetic abnormalities and/or in those who are poor G-CSF responders (requiring more than 10 mcg/kg/d).[87] However, HSCT carries an associated risk of mortality, which has been assessed at 17%, in the largest cohort of severe CN transplanted patients studied to date.[85] In general, HSCT for severe CN has better outcomes in patients younger than 10 years and in those transplanted after the year 2000. Matched sibling and matched related donors appear to have an advantage over mismatched donors and bone marrow is considered a better stem cell source than cord blood or peripheral blood.[79–86] In the case of a sibling donor, an underlying germline etiology for CN should be excluded by genetic testing, even in the absence of neutropenia. The outcomes of severe CN patients transplanted with overt leukemia at the time of HSCT are still a matter of debate because the available data are not conclusive.[82,85]

For all the aforementioned reasons, the decision to proceed with HSCT must be carefully evaluated on an individual basis for each CN patient and should take into consideration several factors: response to G-CSF, compliance with subcutaneous injections, ability to manage infections, age of the patient, availability of a suitable donor, and the expertise of the center in managing CN patients and transplant procedures (Box 13).[85–87]

G-CSF alternative/target treatments

In patients with severe CN patients, G-CSF therapy has proven to be effective, safe, and well tolerated in the majority of cases over the years. Side effects are rare and generally include rash, bone pain, osteopenia, splenomegaly, and occasional cases of vasculitis usually

BOX 13: HSCT in severe congenital neutropenia.

The panel suggests carefully evaluating the pros and cons of HSCT, tailoring the decision on an individual case basis, and sharing the decision with the patient/family. The expertise of the center in performing HSCT and in managing CN patients is an important consideration in the final decision.
Consensus agreement 93%

Strong indications for HSCT include:
(1) Established transformation to MDS/Acute Leukemia or bone marrow dysplastic features with high-risk acquired cytogenetic abnormalities (monosomy 7, trisomy 8, and trisomy 21) or with a combination of acquired leukemia-associated somatic mutations (e.g., *RUNX1*, *ASXL1*, and *SETBP1*). *CSF3R* mutations alone are not an indication of HSCT.
(2) CN due to mutations carrying an intrinsic high risk of leukemic transformation per se, i.e., *GATA2* mutations, high-risk *ELANE* mutations, or clones with biallelic *TP53* mutations in SDS.
(3) No response to G-CSF (doses > 20 mcg/kg/d to reach ANC of 1.0×10^9/L), poor response to G-CSF (doses between 10 and 20 mcg/kg/d failing to reach ANC of 1.0×10^9/L) or poor control of infection irrespective of the G-CSF dose.
Consensus agreement 100%

Potential indications to HSCT adequate management of infections with G-CSF at "intermediate doses" (10–15 mcg/kg/d) with availability of a healthy HLA-identical sibling or HLA identical matched donor.
Consensus agreement 93%

Weak indication of HSCTG-CSF response at doses up to 10 µg/kg/d, good tolerability and compliance to daily subcutaneous injections, infections control, and unavailability of HLA-matched donors.
Consensus agreement 100%

Abbreviations: ANC, absolute neutrophil count; CN, congenital neutropenia; G-CSF, granulocyte-colony stimulating factor; HSCT, hematopoietic stem cell transplantation; SDS, Shwachman–Diamond syndrome.

not necessitating drug discontinuation.[88] A common problem of G-CSF treatment is poor patient compliance with daily subcutaneous injections. For these subjects, pegfilgrastim may represent a valid alternative option to improve the QoL. Notably, the cost of treatment with pegfilgrastim has been estimated as similar to the equivalent exposure to classical G-CSF.[45]

Alternatives or additive therapeutic approaches to filgrastim and pegfilgrastim are under evaluation and have shown promising results in some cases. For example, there have been successful attempts to design novel granulopoietic proteins with activities similar to G-CSF, which are easy to produce, stable, and resistant to cleavage by proteases; however, no clinical studies have been reported so far.[89,90] Another study has shown that treatment of severe CN patients with high-dose nicotinamide (NA) may result in the reduction of the therapeutic dose of G-CSF in patients with severe CN as well as of frequency of bacterial infections.[91,92] NA was well tolerated and was continued in some patients for more than 1 year. The introduction of NA into the therapy regimens of CN patients was based on the involvement of the NA pathway in the G-CSF-triggered emergency granulopoiesis.[85]

For specific categories of neutropenia such as WHIM syndrome (Warts, Hypogammaglobulinemia, Infections, and Myelokathexis) or those caused by mutations in the gene encoding for glucose-6-phosphatase catalytic subunit 3 (G6PC3) and GSD-Ib, novel approaches have been approved or investigated. WHIM syndrome is commonly caused by autosomal dominant mutations in the C-X-C chemokine receptor 4 (CXCR4) associated with hyperactive receptor hyperactive. Mavorixafor is an oral, selective CXCR4 antagonist, approved in April 2024 as the first oral therapy for WHIM syndrome in the United States for patients aged ≥12 years.[93,94] The approval was based on a randomized, double-blind, placebo-controlled, phase 3 clinical trial which showed that mavorixafor provides a significantly longer duration of neutrophil and lymphocyte counts above the threshold compared to placebo.[95] Treatment with mavorixafor was safe and reduced the frequency, severity, duration of infections, and antibiotic use. The results of this phase 3 study were supported by efficacy data from an open-label, multinational, phase 2 dose-finding study in adults with genetically confirmed WHIM syndrome.[96,97] Clinical development of mavorixafor for chronic neutropenic disorders is ongoing.

For neutropenia associated with GSD-Ib and G6PC3 mutations, treatment with a renal sodium-glucose cotransporter type 2 (SGLT-2) inhibitor such as empaglifozin results in the improvement of neutropenia and neutrophil dysfunction in the affected patients.[98] The underlying mechanism for this effect is associated with SGLT-2 inhibitor-mediated urinary excretion of 1,5-AG and inhibition of renal glucose reabsorption, resulting in a decrease of the 1,5-anhydroglucitol (1,5-AG) concentration in blood.[99] This effect rescues neutrophils from energy deprivation and apoptosis in patients with GSD-Ib and G6PC3 mutations. Recently, in a consensus-based report, the authors proposed SGLT-2 inhibitors for the treatment of neutropenia in GSD-1b patients, but the literature on patients with GSPC3-related neutropenia is still relatively limited.[99,100] However, the promising results of SGLT-2 inhibitors in ameliorating neutropenia in patients with germline GSD-1b and GSPC3 mutations open the way for multicenter follow-up studies and clinical trials to evaluate the long-term efficacy and safety of these compounds.[101,102]

Gene therapy for CN neutropenia—aiming at the correction or inhibition of mutated genes—might provide an alternative curative approach to bone marrow transplantation. Recent developments in inhibiting or correcting *ELANE* mutations in the hematopoietic stem cells of CN patients offer hope to patients and clinicians. This approach is based on CRISPR/Cas9-mediated gene-editing technology, which specifically cuts the *ELANE* gene to induce the degradation of *ELANE* mRNA, leading to an *ELANE* knockout (*ELANE* KO).[103,104] Part of the mutated ELANE DNA is cut by the Cas9 nuclease and subsequently corrected by homology-directed repair (HDR) mechanisms.[105] To successfully achieve correction, an HDR template of WT *ELANE* must be delivered into cells using single-stranded oligodeoxynucleotides or adeno-associated virus-based constructs.[106]

The gene therapy approach is certainly promising but still experimental, and further steps are actually needed for its application in clinical practice.

Overall, the present article synthesizes the available knowledge on neutropenia enriched and strenghtened by a comprehensive and accurate discussion by a group of experts in the field that produced consensus recommendations. The final output has the intent to support at best decisions in any aspect of management of neutropenia patients in everyday clinical practice.

ACKNOWLEDGMENTS

The authors thank Dr Francesco Cerisoli, Dr Anna Daniel, Ms Olesea Mirza, Ms Anastasia Naoum, and Ms Xiamo Wang, staff of the European Hematology Association (EHA) Executive Office, for their scientific and organizational support of the EHA/EuNet-INNOCHRON Guidelines project. Ina Monsef is also acknowledged for setting up the search strategies and conducting the database searches. Open access funding was provided by BIBLIOSAN.

AUTHOR CONTRIBUTIONS

All authors participated in the meetings for the production of the guidelines described in the article. All authors contributed to the writing of the article.

CONFLICT OF INTEREST STATEMENT

Jan Palmblad Chiesi Canada Ltd: Advisory Board. X4, Boston, USA: Safety Board Member. Francesca Fioredda X4: Advisory Board. AlanJ Worren SDS Therapeutics: Consultant. Newburger X4: Advisory Board.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

FUNDING

This article is based on the work from Cooperation in Science and Technology (COST) Action CA18233 "European Network for Innovative Diagnosis and treatment of Chronic Neutropenias, EuNet- INNOCHRON" (https://www.eunet-innochron.eu/) supported by COST. A.J.W. was supported by Cancer Research UK (DRCNPG-Jun24/100002), the UK Medical Research Council (MR/T012412/1).

ORCID

Francesca Fioredda http://orcid.org/0000-0002-7096-4580
Helen A. Papadaki https://orcid.org/0000-0002-5146-9699
Carlo Dufour https://orcid.org/0000-0002-5980-5474

REFERENCES

1. Dale DC. How I diagnose and treat neutropenia. *Curr Opin Hematol*. 2016;23:1-4.
2. Skokowa J, Dale DC, Touw IP, Zeidler C, Welte K. Severe congenital neutropenias. *Nat Rev Dis Primers*. 2017;3:17032.
3. Fioredda F, Skokowa J, Tamary H, et al. The European Guidelines on Diagnosis and Management of Neutropenia in Adults and Children: a

consensus between the European Hematology Association and the EuNet-INNOCHRON COST Action. *HemaSphere*. 2023;7:e872.
4. Fioredda F, Beccaria A, Casartelli P, et al. Late-onset and long-lasting neutropenias in the young: a new entity anticipating immune-dysregulation disorders. *Am J Hematol*. 2024;99:534-542.
5. Donadieu J, Beaupain B, Fenneteau O, Bellanné-Chantelot C. Congenital neutropenia in the era of genomics: classification, diagnosis, and natural history. *Br J Haematol*. 2017;179:557-574.
6. Fioredda F, Calvillo M, Burlando O, et al. Infectious complications in children with severe congenital, autoimmune or idiopathic neutropenia: a retrospective study from the Italian Neutropenia Registry. *Pediatr Infect Dis J*. 2013;32:410-412.
7. Rotulo GA, Plat G, Beaupain, et al. Recurrent bacterial infections, but not fungal infections, characterise patients with ELANE-related neutropenia: a French Severe Chronic Neutropenia Registry study. *Br J Haematol*. 2021;194:908-920.
8. Tsaknakis G, Galli A, Papadakis S, et al. Incidence and prognosis of clonal hematopoiesis in patients with chronic idiopathic neutropenia. *Blood*. 2021;138:1249-1257.
9. Chatta G, Price T, Allen R, Dale D. Effects of in vivo recombinant methionyl human granulocyte colony-stimulating factor on the neutrophil response and peripheral blood colony-forming cells in healthy young and elderly adult volunteers. *Blood*. 1994;84:2923-2929.
10. Dale D, Bonilla M, Davis M, et al. A randomized controlled phase III trial of recombinant human granulocyte colony-stimulating factor (filgrastim) for treatment of severe chronic neutropenia. *Blood*. 1993;81:2496-2502.
11. Welte K. Forty years of human G-CSF: a short history in time. *Br J Haematol*. 2024;205:1296-1298.
12. Fioredda F, Onofrillo D, Farruggia P, et al. Diagnosis and management of neutropenia in children: the approach of the Study Group on Neutropenia and Marrow Failure Syndromes of the Pediatric Italian Hemato-Oncology Association (Associazione Italiana Emato-Oncologia Pediatrica - AIEOP). *Pediatr Blood Cancer*. 2022;69:e29599.
13. National Institute for Health and Care Excellence (NICE). The Guidelines Manual: 6.5 summarising evidence, 2014. Updated January 18, 2022, www.nice.org.uk/process/pmg20
14. German Association of the Scientific Medical Societies (AWMF). Standing Guidelines commission. AWMF Guidance Manual and Rules for Guideline Development, 1st ed. 2012. English version. http://www.awmf.org/leitlinien/awmf-regelwerk.html
15. European Hematology Association (EHA). EHA guidelines methodology for diagnosis and therapy of blood disorders. https://ehaweb.org/assets/Guidelines/EHA-Guidelines-Methodology-3.pdf
16. Palmblad J, Sohlberg E, Nilsson CC, et al. Clinical and immunological features in ACKR1/DARC-associated neutropenia. *Blood Adv*. 2024;8:571-580.
17. Bronchud M, Potter M, Morgenstern G, et al. In vitro and in vivo analysis of the effects of recombinant human granulocyte colony-stimulating factor in patients. *Br J Cancer*. 1988;58:64-69.
18. Bonilla MA, Gillio AP, Ruggeiro M, et al. Effects of recombinant human granulocyte colony-stimulating factor on neutropenia in patients with congenital agranulocytosis. *N Engl J Med*. 1989;320:1574-1580.
19. Donadieu J, Leblanc T, Bader MeunierMeunier, B, et al. Analysis of risk factors for myelodysplasias, leukemias and death from infection among patients with congenital neutropenia. Experience of the French Severe Chronic Neutropenia Study Group. *Haematologica*. 2005;90:45-53.
20. Rosenberg PS, Zeidler C, Bolyard AA, et al. Stable long-term risk of leukaemia in patients with severe congenital neutropenia maintained on G-CSF therapy. *Br J Haematol*. 2010;150:196-19937.
21. Dale DC, Bolyard A, Marrero T, et al. Long-term effects of G-CSF therapy in cyclic neutropenia. *N Engl J Med*. 2017;377:2290-2292.
22. Fazio MT, Glaspy JA. The impact of granulocyte colony-stimulating factor on quality of life in patients with severe chronic neutropenia. *Oncol Nurs Forum*. 1991;18:1411-1414.
23. Jones EA, Bolyard AA, Dale DC. Quality of life of patients with severe chronic neutropenia receiving long-term treatment with granulocyte colony-stimulating factor. *JAMA*. 1993;270:1132-1133.
24. Cleary PD, Morrissey G, Yver A, Oster G. The effects of rG-CSF on health-related quality of life in children with congenital agranulocytosis. *Qual Life Res*. 1994;3:307-315.
25. Molineux G. Pegfilgrastim: using pegylation technology to improve neutropenia support in cancer patients. *Anticancer Drugs*. 2003;14:259-264.
26. Bux J, Behrens G, Jaeger G, Welte K. Diagnosis and clinical course of autoimmune neutropenia in infancy: analysis of 240 cases. *Blood*. 1998;91:181-186.
27. Farruggia P, Fioredda F, Puccio G, et al. Idiopathic neutropenia of infancy: data from the Italian Neutropenia Registry. *Am J Hematol*. 2019;94:216-222.
28. Sicre de Fontbrune F, Moignet A, Beaupain B, et al. Severe chronic primary neutropenia in adults: report on a series of 108 patients. *Blood*. 2015;126:1643-1650.
29. Heil G, Hoelzer D, Sanz MA, et al. A randomized, double-blind, placebo-controlled, phase III study of filgrastim in remission induction and consolidation therapy for adults with de novo acute myeloid leukemia. *Blood*. 1997;90:4710-4718.
30. Beksac M, Ali R, Ozcelik T, et al. Short and long term effects of granulocyte colony-stimulating factor during induction therapy in acute myeloid leukemia patients younger than 65: results of a randomized multicenter phase III trial. *Leuk Res*. 2011;35:340-345.
31. Godwin JE, Kopecky KJ, Head DR, et al. A double-blind placebo-controlled trial of granulocyte colony-stimulating factor in elderly patients with previously untreated acute myeloid leukemia: a Southwest oncology group study (9031). *Blood*. 1998;91:3607-3615.
32. Usuki K, Urabe A, Masaoka T, et al. Efficacy of granulocyte colony-stimulating factor in the treatment of acute myelogenous leukaemia: a multicentre randomized study. *Br J Haematol*. 2002;116:103-112.
33. Platzbecker U, Prange-Krex G, Bornhäuser M, et al. Spleen enlargement in healthy donors during G-CSF mobilization of PBPCs. *Transfusion*. 2001;41:184-189.
34. Stroncek D, Shawker T, Follmann D, Leitman SF, et al. G-CSF-induced spleen size changes in peripheral blood progenitor cell donors. *Transfusion*. 2003;43:609-613.
35. Nuamah NM, Goker H, Kilic YA, Dagmoura H, Cakmak A. Spontaneous splenic rupture in a healthy allogeneic donor of peripheral-blood stem cell following the administration of granulocyte colony-stimulating factor (g-csf). A case report and review of the literature. *Haematologica*. 2006;91(5 Suppl):ECR08.
36. Dale DC, Bolyard AA, Shannon JA, et al. Outcomes for patients with severe chronic neutropenia treated with granulocyte colony-stimulating factor. *Blood Adv*. 2022;6:3861-3869.
37. Dale DC, Bolyard AA, Schwinzer BG, et al. The Severe Chronic Neutropenia International Registry: 10-year follow-up report. *Support Cancer Ther*. 2006;3:220-231.
38. Dale DC, Bolyard AA. An update on the diagnosis and treatment of chronic idiopathic neutropenia. *Curr Opin Hematol*. 2017;24:46-53.
39. Donadieu J, Fenneteau O, Beaupain B, Mahlaoui N, Chantelot C. Congenital neutropenia: diagnosis, molecular bases and patient management. *Orphanet J Rare Dis*. 2011;6:26.
40. Boxer LA, Hutchinson R, Emerson S. Recombinant human granulocyte-colony-stimulating factor in the treatment of patients with neutropenia. *Clin Immunol Immunopathol*. 1992;62:S39-S46.
41. Donadieu J, Boutard P, Bernatowska E, et al. A European phase II study of recombinant human granulocyte colony-stimulating factor (lenograstim) in the treatment of severe chronic neutropenia in children. *Eur J Pediatr*. 1997;156:693-700.

42. Smith MA, Smith JG. Clinical experience with the use of rhG-CSF in secondary autoimmune neutropenia. *Clin Lab Haematol*. 2002;24:93-97.
43. Carlsson G, Åhlin A, Dahllöf G, Elinder G, Henter J-I, Palmblad J. Efficacy and safety of two different rG-CSF preparations in the treatment of patients with severe congenital neutropenia. *Br J Haematol*. 2004;126:127-132.
44. Beaupain B, Leblanc T, Reman O, et al. Is pegfilgrastim safe and effective in congenital neutropenia? An analysis of the French Severe Chronic Neutropenia registry. *Pediatr Blood Cancer*. 2009;53:1068-1073.
45. Fioredda F, Lanza T, Gallicola F, et al. Long-term use of pegfilgrastim in children with severe congenital neutropenia: clinical and pharmacokinetic data. *Blood*. 2016;128:2178-2181.
46. Freedman MH, Bonilla MA, Fier C, et al. Myelodysplasia syndrome and acute myeloid leukemia in patients with congenital neutropenia receiving G-CSF therapy. *Blood*. 2000;96:429-436.
47. Dale DC, Cottle TE, Fier CJ, et al. Severe chronic neutropenia: treatment and follow-up of patients in the Severe Chronic Neutropenia International Registry. *Am J Hematol*. 2003;72:82-93.
48. Makaryan V, Zeidler C, Bolyard AA, et al. The diversity of mutations and clinical outcomes for ELANE-associated neutropenia. *Curr Opin Hematol*. 2015;22:3-11.
49. Tesakov1, Makaryan V, Bolyard AA, et al. Genotype-phenotype correlations in patients with severe chronic neutropenia harboring ELANE mutations. e-poster at 21ST Biennal Meeting of the European Society for Immunodeficincies Marseille, October 16-19, 2024
50. Reilly CR, Shimamura A. Predisposition to myeloid malignancies in Shwachman-Diamond syndrome: biological insights and clinical advances. *Blood*. 2023;141:1513-1523.
51. Dale DC, Bolyard AA, Marrero T, et al. Neutropenia in glycogen storage disease Ib: outcomes for patients treated with granulocyte colony-stimulating factor. *Curr Opin Hematol*. 2019;26:16-21.
52. Fauci AS, Dale DC, Balow JE. Glucocorticosteroid therapy: mechanisms of action and clinical considerations. *Ann Intern Med*. 1976;84:304-315.
53. Gurlek Gokcebay D, Akpinar Tekgunduz S. Granulocyte transfusions in the management of neutropenic fever: a pediatric perspective. *Transfus Apher Sci*. 2018;57:16-19.
54. Jaiswal SR, Bhakuni P, Bhagwati G, Joy A, Chakrabarti A, Chakrabarti S. Impact of preemptive granulocyte infusions during febrile neutropenia in patients colonized with Carbapenem-resistant Gram-negative bacteria undergoing haploidentical transplantation. *Biol Blood Marrow Transplant*. 2019;25:1621-1628.
55. Estcourt LJ, Stanworth SJ, Hopewell S, Doree C, Trivella M, Massey E. Granulocyte transfusions for treating infections in people with neutropenia or neutrophil dysfunction. *Cochrane Database Syst Rev*. 2016;4:CD005339.
56. Price TH, Boeckh M, Harrison RW, et al. Efficacy of transfusion with granulocytes from G-CSF/dexamethasone-treated donors in neutropenic patients with infection. *Blood*. 2015; 29 126:2153-2161.
57. Arslan D, Yildizdas D, Horoz OO, Aslan N, Leblebisatan G. Transfusion-associated acute lung injury following donor granulocyte transfusion in two pediatric patients. *J Pediatr Intensive Care*. 2019;8:251-254.
58. Meny GM, Santos-Zabala L, Szallasi A, Stramer SL. West Nile virus infection transmitted by granulocyte transfusion. *Blood*. 2011;117:5778-5779.
59. Gea-Banacloche J. Granulocyte transfusions: a concise review for practitioners. *Cytotherapy*. 2017;19:1256-1269.
60. Farruggia P, Fioredda F, Puccio G, et al. Autoimmune neutropenia of infancy: data from the Italian neutropenia registry. *Am J Hematol*. 2015;90:E221-E222.
61. Lehrnbecher T, Robinson PD, Ammann RA, et al. Guideline for the management of fever and neutropenia in pediatric patients with cancer and hematopoietic cell transplantation recipients: 2023 update. *J Clin Oncol*. 2023;41:1774-1785.
62. Lehrnbecher T, Averbuch D, Castagnola E, et al. 8th European Conference on Infections in Leukaemia: 2020 guidelines for the use of antibiotics in paediatric patients with cancer or post-haematopoietic cell transplantation. *Lancet Oncol*. 2021;22:e270-e280.
63. Castagnola E, Bagnasco F, Mesini A, et al. Assessing the theoretical efficacy of combination therapy against Gram-negative infections in neutropenic pediatric cancer patients: insights from the statistical analysis of survey data. *Antibiotics*. 2024;13:1160.
64. Castagnola E, Bagnasco F, Mesini A, et al. Antibiotic resistant bloodstream infections in pediatric patients receiving chemotherapy or hematopoietic stem cell transplant: factors associated with development of resistance, intensive care admission and mortality. *Antibiotics*. 2021;10:266.
65. Groll AH, Pana D, Lanternier F, et al. 8th European Conference on Infections in Leukaemia: 2020 guidelines for the diagnosis, prevention, and treatment of invasive fungal diseases in paediatric patients with cancer or post-haematopoietic cell transplantation. *Lancet Oncol*. 2021;22(6):e254-e269.
66. Maschmeyer G, Helweg-Larsen J, Pagano L, Robin C, Cordonnier C, Schellongowski P. ECIL guidelines for treatment of Pneumocystis jirovecii pneumonia in non-HIV-infected haematology patients. *J Antimicrob Chemother*. 2016;71:2405-2413.
67. Okada M, Kobayashi M, Hino T, Kurihara H, Miura K. Clinical periodontal findings and microflora profiles in children with chronic neutropenia under supervised oral hygiene. *J Periodontol*. 2001;72:945-952.
68. Acar B, Cagdas D, Tan Ç, et al. Evaluation of periodontal status and cytokine/chemokine profile of GCF in patients with severe congenital neutropenia. *Odontology*. 2021;109:474-482.
69. Park MS, Tenenbaum HC, Dror Y, Gloguaer M. Oral health comparison between children with neutropenia and healthy controls. *Spec Care Dentist*. 2014;34:12-18.
70. Szczawinska-Poplonyk A, Gerreth K, Breborowicz A, Borysewicz-Lewicka M. Oral manifestations of primary immune deficiencies in children. *Oral Surg Oral Med Oral Pathol Oral Radiol Endodontol*. 2009;108:e9-e20.
71. Tirali RE, Yalçınkaya Erdemci Z, Çehreli SB. Oral findings and clinical implications of patients with congenital neutropenia: a literature review. *Turk J Pediatr*. 2013;55:241-245.
72. Michniacki TF, Merz LE, McCaffery H, Connelly JA, Walkovich K. Quality of life and patient-reported outcomes in chronic severe neutropenia conditions. *Int J Hematol*. 2021;113:735-743.
73. Newburger PE, Dale DC. Evaluation and management of patients with isolated neutropenia. *Sem Hematol*. 2013;50:198-206.
74. Zeidler C, Boxer L, Dale DC, Freedman MH, Kinsey S, Welte K. Management of Kostmann syndrome in the G-CSF era. *Br J Haematol*. 2000;109:490-495.
75. Eibl MM, Wolf HM. Vaccination in patients with primary immune deficiency, secondary immune deficiency and autoimmunity with immune regulatory abnormalities. *Immunotherapy*. 2015;7:1273-1292.
76. American Academy on Pediatric (ACIP). https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html
77. Janczar S, Zalewska-Szewczyk B, Bąbol-Pokora K, Paśnik J, Zeman K, Młynarski W. Vaccination in children with chronic severe neutropenia - review of recommendations and a practical approach. *Cent Eur J Immunol*. 2020;45:202-205.
78. Neutropenia Support Association Inc. Accessed March 25, 2025. https://neutropenianet.org
79. Ferry C, Ouachée M, Leblanc T, et al. Hematopoietic stem cell transplantation in severe congenital neutropenia: experience of the French SCN register. *Bone Marrow Transplant*. 2005;35:45-50.
80. Nakazawa Y, Sakashita K, Kinoshita M, et al. Successful unrelated cord blood transplantation using a reduced-intensity conditioning regimen in a 6-month-old infant with congenital neutropenia complicated by severe pneumonia. *Int J Hematol*. 2004;80:287-290.

81. Mino E, Kobayashi R, Yoshida M, Suzuki Y, Yamada M, Kobayashi K. Umbilical cord blood stem cell transplantation from unrelated HLA-matched donor in an infant with severe congenital neutropenia. *Bone Marrow Transplant*. 2004;33: 969-971.
82. Zeidler C, Welte K, Barak Y, et al. Stem cell transplantation in patients with severe congenital neutropenia without evidence of leukemic transformation. *Blood*. 2000;95:1195-1198.
83. Carlsson G, Winiarski J, Ljungman P, et al. Hematopoietic stem cell transplantation in severe congenital neutropenia. *Pediatr Blood Cancer*. 2011;56:444-451.
84. Oshima K, Hanada R, Kobayashi R, et al. Hematopoietic stem cell transplantation in patients with severe congenital neutropenia: an analysis of 18 Japanese cases. *Pediatr Tranplant*. 2010;14:657-663.
85. Fioredda F, Iacobelli S, van Biezen A, et al. Stem cell transplantation in severe congenital neutropenia: an analysis from the European Society for Blood and Marrow Transplantation. *Blood*. 2015;126:1885-1892.
86. Choi SW, Boxer LA, Pulsipher MA, et al. Stem cell transplantation in patients with severe congenital neutropenia with evidence of leukemic transformation. *Bone Marrow Transplant*. 2005;35: 473-477.
87. Peffault de Latour R, Peters C, Gibson B, et al. Recommendations on hematopoietic stem cell transplantation for inherited bone marrow failure syndromes. *Bone Marrow Transplant*. 2015;50: 1168-1172.
88. Morstyn G, Keech J, Sheridan W, et al. Effect of granulocyte colony stimulating factor on neutropenia induced by cytotoxic chemotherapy. *Lancet*. 1988;331(8587):667-672.
89. Hernandez Alvarez B, Skokowa J, Coles M, et al. Design of novel granulopoietic proteins by topological rescaffolding. *PLoS Biol*. 2020;18:e3000919.
90. Skokowa J, Hernandez Alvarez B, Coles M, et al. A topological refactoring design strategy yields highly stable granulopoietic proteins. *Nat Commun*. 2022;13:2948.
91. Skokowa J, Lan D, Thakur BK, et al. NAMPT is essential for the G-CSF-induced myeloid differentiation via a NAD(+)-sirtuin-1-dependent pathway. *Nature Med*. 2009;15:151-158.
92. Deordieva E, Shvets O, Voronin K, et al. Nicotinamide (vitamin B3) treatment improves response to G-CSF in severe congenital neutropenia patients. *Br J Haematol*. 2021;192:788-792.
93. Hoy SM. Mavorixafor: first approval. *Drugs*. 2024;84:969-975.
94. Zmajkovicova K, Pawar S, Sharapova SO, et al. A novel transmembrane CXCR4 variant that expands the WHIM genotype-phenotype paradigm. *Blood Adv*. 2024;8:3754-3759.
95. Badolato R, Alsina L, Azar A, et al. A phase 3 randomized trial of mavorixafor, a CXCR4 antagonist, for WHIM syndrome. *Blood*. 2024;144:35-45.
96. Dale DC, Firkin F, Bolyard AA, et al. Results of a phase 2 trial of an oral CXCR4 antagonist, mavorixafor, for treatment of WHIM syndrome. *Blood*. 2020;136:2994-3003.
97. Warren JT, Dickerson KE, Sharathkumar AA, et al. Mavorixafor for patients with chronic neutropenic disorders treated with G-CSF: preliminary response data and G-CSF dose reduction in an ongoing phase 2, open-label, multicenter study support reduction in G-CSF dosing. *Blood*. 2023;142(suppl 1):1160.
98. Veiga-da-Cunha M, Wortmann SB, Grünert SC, Van Schaftingen E. Treatment of the Neutropenia Associated with GSD1b and G6PC3 Deficiency with SGLT2 Inhibitors. *Diagnostics*. 2023;13: 1803.
99. Veiga-da-Cunha M, Chevalier N, Stephenne X, et al. Failure to eliminate a phosphorylated glucose analog leads to neutropenia in patients with G6PT and G6PC3 deficiency. *Proc Natl Acad Sci*. 2019;116:1241-1250.
100. Grünert SC, Derks TGJ, Mundy H, et al. Treatment recommendations for glycogen storage disease type IB- associated neutropenia and neutrophil dysfunction with empagliflozin: consensus from an international workshop. *Mol Gen Metab*. 2024; 141:108144.
101. Lédeczi Z, Pittner R, Kriván G, Kardon T, Legeza B. Empagliflozin restores neutropenia and neutrophil dysfunction in a young patient with severe congenital neutropenia type 4. *J Allergy Clin Immunol Pract*. 2023;11:344-346.e1.
102. Boulanger C, Stephenne X, Diederich J, et al. Successful use of empagliflozin to treat neutropenia in twoG6PC3-deficient children: impact of a mutation in SGLT5. *J Inherit Metab Dis*. 2022;45: 759-768.
103. Nasri M, Ritter M, Mir P, et al. CRISPR/Cas9-mediated ELANE knockout enables neutrophilic maturation of primary hematopoietic stem and progenitor cells and induced pluripotent stem cells of severe congenital neutropenia patients. *Haematologica*. 2020;105: 598-609.
104. Rao S, Yao Y, Soares de Brito J, et al. Dissecting ELANE neutropenia pathogenicity by human HSC gene editing. *Cell Stem Cell*. 2021;28: 833-845.e5.
105. Tran NT, Graf R, Wulf-Goldenberg A, et al. CRISPR-Cas9-mediated ELANE mutation correction in hematopoietic stem and progenitor cells to treat severe congenital neutropenia. *Mol Ther*. 2020;28: 2621-2634.
106. Skokowa J. Circumventing mutation to nix neutropenia. *N Engl J Med*. 2021;384:1956-1958.