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Review Article

Assessment of Congenital Neutropenia in Children: Common Clinical Sceneries and Clues for Management

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Abstract. A disparate group of rare hematological diseases characterized by impaired maturation of neutrophil granulocytes defines congenital neutropenias. Neutropenic patients are prone to recurrent infections beginning in the first months of life. Of interest is "cyclic neutropenia," an ultra-rare disorder revealed by sinusoidal variations in the neutrophil count and recurring infections every 21 days. Diagnosis of these disorders is frequently obscured by the multiple causes of recurrent fevers in children. The aim of this overview is to outline the physical assessment of children presenting with early-onset symptomatic neutropenia, identify the disease between the many medical conditions and even emergencies which should enter in differential diagnosis, hint at the potential management with granulocyte-colony stimulating factor, define the risk of evolution to hematologic malignancy, and summarize inter-professional team strategies for improving care coordination and outcomes of patients.

Keywords: Congenital neutropenia; Cyclic neutropenia; Myelopoiesis; Neutrophil elastase; Periodic fever; Autoinflammation; PFAPA syndrome; Innovative biotechnologies; Granulocyte-colony stimulating factor; Personalized medicine.

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Introduction. Neutrophil granulocytes are the primary mediators of host innate immunity against bacterial pathogens, and genetically determined neutrophil disorders confer a predisposition to infections. Failure in either neutrophil number or neutrophil function can be disclosed by the occurrence of infections in several clinical settings. The most common etiologies of neutropenia, defined as a reduction of the absolute number of circulating neutrophils, are acquired and include sequestration, viral infections, chemotherapy, and drug reactions.[1] The inherited etiologies of neutropenia are much less common, though often more severe.[2] Congenital neutropenias are rare disorders of myelopoiesis characterized by impaired neutrophil differentiation with maturation arrest at the promyelocyte stage.[3] A congenital neutropenia consists of "statically" low neutrophil counts and is largely observed in the first infancy, while cyclic neutropenia is defined by regularly "cyclic" episodes of neutropenia which recur every three weeks in toddlers.[4]

The decrease of neutrophils in both bone marrow and bloodstream can reach a nadir below 200 neutrophils/mm^3 during febrile neutropenic days.[5] This recurrence of fever flares in children might have dramatic consequences on the overall quality of life of patients and their caregivers, displaying a negative interference with school attendance or daily activities, and might generate a deep sense of frustration in the families.[6] A significantly increased risk of myelodysplastic syndrome and acute myeloid leukemia has been reported for severe congenital neutropenia, but treatment options are limited and no reliable tools predict this kind of progression. Moreover, the delay to a definite diagnosis may be of several months or even years, and children are frequently exposed to redundant and unnecessary diagnostic procedures. Hence, the importance of considering and properly identifying congenital neutropenia warrants the updated overview herein presented.

The Entwined Molecular Mechanisms of Neutropenia. Congenital neutropenia encompasses a family of disorders characterized by neutropenia, either permanent or intermittent, both mild and severe when the neutrophil count is below 500/mm^3: the inner working of neutropenia has been extensively investigated, and different pathways that control programmed cell death in neutrophils have been studied. The exact physiological basis of neutropenia remains unclear, though many authors have confirmed an interrupted cell production in the bone marrow.[7] There is a continuum between permanent neutropenia *versus* intermittent neutropenia and different mutations at the locus 19p13.3 of the gene encoding the enzyme neutrophil elastase, referred to as *ELANE* (or *ELA2*), have been disclosed in most cases of congenital neutropenia.[8] The molecular machinery by which *ELANE* mutations disrupt myelopoiesis is unknown. However, we know that neutrophil elastase, a 238-amino acid protein with broad proteolytic activities, is packaged into azurophil granules within neutrophils as a fully active enzyme after being processed in the Golgi apparatus.[9] The regular oscillation of white blood cell counts in cyclic neutropenia is attributed to the excessive cell turnover in the early neutrophil compartments and to a potential autoregulatory loop with an inverse correlation between circulating cells and humoral regulators of the neutrophil balance.[10] Mir et al. analyzed the subpopulations of bone marrow cells at both peak and nadir of the neutrophil cycle in patients with cyclic neutropenia, detecting a higher proportion of hematopoietic stem cells at the nadir, as opposed to the peak. In particular, they found that mRNA expression levels of *ELANE* and unfolded protein response-related genes were elevated at the nadir, differently from anti-apoptotic genes, which were reduced, and hypothesized that some stem cells escaped the unfolded protein response-stress: these escaper cells responded to granulocyte colony-stimulating factor (G-CSF), generating either neutrophils between nadir and peak or new progenitor cells during the cycle.[11] However, the exact mechanisms governing the clock-like timing of hematopoiesis and unfolded protein response remain to decipher and are a matter of ongoing research.

Furthermore, accelerated apoptosis with cell cycle arrest in the G0/G1 phase has been described in promyelocytes of patients with severe congenital neutropenia: this can result from misfolded elastase proteins and subsequent activation of the unfolded protein response. In these patients *ELANE* mutations lead to the mislocalization and accumulation of unfolded proteins, creating endoplasmic reticulum stress, which affects the survival and differentiation of granulocytes.[12] More specifically, CD34+CD45+ hematopoietic progenitor cells deriving from pluripotent stem cell lines of patients with congenital neutropenia display elevated levels of reactive oxygen species and a high number of promyelocyte leukemia protein nuclear bodies, which are hallmarks of acute oxidative stress.[13] In general terms, by the perturbation of mitochondrial energy metabolism, uncontrolled vesicle trafficking, or unbalanced oxidative stress, the disease causes a maturation arrest in myeloid precursor cells, reducing the number of circulating neutrophils and making patients vulnerable to recurrent infections.

The Spyglass of Genotype Studies in Congenital Neutropenias. Severe congenital neutropenia is a bone marrow failure syndrome characterized by neutropenia present from birth, leading to frequent infections of different severity. *ELANE*-related neutropenia includes severe congenital neutropenia (also known as Kostmann syndrome) and cyclic neutropenia, which are primary disorders characterized by similar phenotype: recurrent fevers, skin, and oropharyngeal inflammation. *ELANE* mutations have been found in 80-to-100% of cases with cyclic neutropenia and in 35-to-63% of cases with severe congenital neutropenia.[14] While *ELANE* mutations have been proved as the nearly-exclusive cause of cyclic neutropenia, several mutations in other genes can explain the pathogenesis of Kostmann syndrome. Autosomal dominant gain-of-function *ELANE* mutations transmit cyclic neutropenia, but sporadic cases may arise from new germline mutations. Kostmann syndrome, first described by the Swedish pediatrician Rolf Kostmann, who coined the term 'infantile genetic agranulocytosis' in 1950, is a primary immunodeficiency associated with increased apoptosis of myeloid cells and includes different disorders caused by protean genetic abnormalities: the mutated genes encompass the one encoding neutrophil elastase, but also the proteins HAX1, G6PC3, WAS and GFI1.[15]

The distinction between congenital neutropenia and

cyclic neutropenia is primarily based on clinical findings and secondly on a molecular approach, including single-gene testing or multigene panels. Patients' siblings or other at-risk relatives should be evaluated by *ELANE* genetic testing. In general terms, *ELANE* pathogenic variants include missense and nonsense variants, small deletions or insertions in exons, splicing defects, and changes in the *ELANE* regulatory region.[16] Genotype-phenotype correlations have been roughly defined for *ELANE*-related neutropenias. Although the patterns of pathogenic variants in congenital neutropenia and cyclic neutropenia are distinct on a population basis, these variants might overlap, indicating that the distinction between the two conditions should remain clinical and only later based on the genotype analysis.[17] Some pathogenic *ELANE* variants have been associated with an overall good prognosis, and some of these appear to be solely associated with cyclic neutropenia, having a minimal risk of hematologic malignancies.[18]

Some patients with severe congenital neutropenia can have homozygous or compound heterozygous mutations in the *HAX1* gene, coding for the HCLS1-associated protein X-1 or HAX1, an ubiquitously expressed multifunctional protein predominantly localized in mitochondria. Klein et al. showed that HAX1 is critical for maintaining the inner mitochondrial membrane potential and protecting myeloid cells from apoptosis, suggesting that this protein is a major regulator of myeloid homeostasis and neutrophil apoptosis.[19] A minority of patients with *HAX1*-related neutropenia might have also neurodevelopmental delay and epilepsy.[20] Biallelic (homozygous or compound heterozygous) *G6PC3* pathogenic variants can cause a phenotypic spectrum that ranges from nonsyndromic isolated severe congenital neutropenia to "classic" neutropenia associated with cardiovascular and/or urogenital abnormalities, endocrine dysfunctions, intermittent thrombocytopenia, lymphopenia, thymic hypoplasia, recurrent bacterial infections, failure to thrive and poor postnatal growth, which define the glucose-6-phosphatase catalytic subunit 3 (G6PC3) deficiency, also named Dursun syndrome.[21]

An X-linked form of congenital neutropenia is caused by gain-of-function mutations in the *WAS* gene, coding for the actin regulator WASp (Wiskott-Aldrich syndrome protein), which are different from those causing Wiskott-Aldrich thrombocytopenia, and defined by impaired cytoskeleton activity leading to aberrant generation of neutrophils with reduced chemotactic capacity.[22] Moreover, the Gfi-1 zinc finger transcriptional repressor oncoprotein Gfi-1 has been related to myelopoiesis, and heterozygous germline mutations in the *GFI1* gene cause a severe form of congenital neutropenia.[23] A different ethnic form of neutropenia linked to the genetic deletion of the Duffy antigen receptor for chemokines (DARC-null genotype) has been reported among Africans, having potential effects on the development of different infectious diseases in these individuals.[24] Additional diseases characterized by reduced white blood cell count which do not have a genetic basis are benign familial neutropenia, idiopathic neutropenia of unknown cause and autoimmune neutropenia, for which anti-neutrophil antibodies need to be demonstrated.

The Common Outlet of Infections in Congenital Neutropenia. *ELANE*-related neutropenia represents a disease spectrum encompassing congenital neutropenia, cyclic neutropenia, and intermediate findings between the two phenotypes. Patients with cyclic neutropenia display a clinical syndrome with fever, oral and mucosal ulcers or opportunistic infections during the neutropenic phase. Stomatological infections are very frequent after 2 years of age, and if neutropenia is severe they are characterized by erosive, hemorrhagic or painful gingivitis associated with aphthae and oral furuncles of the tongue and cheek mucosa. Chronic and severe infections in the lung, liver or soft tissues occurring at irregular intervals are more typical of severe congenital neutropenia. Fever, malaise, oral aphthosis and mild sore throat every three weeks is the usual presentation of cyclic neutropenia in children: the typical onset is in the first year of life. Symptoms may range from mild to severe, depending on the degree and duration of neutropenia.[25] Infections of the paranasal sinuses, upper- and lower respiratory tract and skin, including the perianal area, may occur if the absolute neutrophil count drops near to 0, and such an extremely low count may last for up to 3-to-5 days, giving rise to severe infections. Cellulitis may occur during periods of neutropenia, even perianal cellulitis, but bacteremia is infrequently proved. Abdominal pain and signs of acute abdomen, suggesting sepsis and bacteremia from colonic ulcers, have been also reported.

Tonsillitis, pharyngitis, gingivitis, swollen lymph nodes, and dermatological infections are frequently encountered in toddlers and older children. More than 60% of patients have skin and pharyngeal symptoms, cervical lymphadenopathy, fever, and fatigue more than 5 times a year. Some children might exhibit periodontitis with alveolar bone fragility, and some may even display early loss of permanent teeth.[26] Between the neutropenic periods, children are generally healthy and grow well. Although congenital neutropenia is usually discovered in childhood, the disease lasts throughout the lifetime. However, the overall course of cyclic neutropenia is benign, compared with other neutropenias.[27] The systemic symptoms usually diminish after adolescence, but adult patients may continue to experience oral ulcers, gingivitis, periodontitis, and other mild infections.[28] Most infections are caused by common organisms lining

on patients' body surfaces, including *Clostridia* species and anaerobes of the intestinal microbiota. In contrast, bacterial infections can be severe in congenital neutropenia and may even occur in the neonatal period, when early-onset omphalitis could be the first disease symptom. In addition to the risk of bacterial infections, human papillomavirus infections can occur. The cumulative incidence of hematologic malignancies is scarce in cyclic neutropenia, differently from severe congenital neutropenia.[29]

The risk of developing myelodysplasia or acute myelogenous leukemia might vary considerably depending on the specific *ELANE* variant, and a consultation with a clinical geneticist should be warranted.[30] In addition to leukemic transformation, solid tumors may also develop early in life, such as kidney tumors and papilloma virus-induced carcinoma. In the past, the risk of mortality for patients with congenital neutropenia was related to the occurrence of necrotizing enterocolitis, peritonitis, or sepsis involving *Escherichia coli* or *Clostridium* species.[31]

Today, the development of blood malignancy is the major cause of mortality in patients with congenital neutropenia, though the spectrum of somatic mutations contributing to leukemic transformation has not been characterized.[32] Patients who present with poor growth and fatty stools need testing for the pancreatic function to rule out Shwachman-Diamond syndrome, an autosomal recessive disorder with multisystemic abnormalities, including exocrine pancreatic insufficiency, short stature, and neutropenia (with hyposegmented neutrophils); assessment of pancreatic function can be useful for diagnosis[33] A congenital form of neutropenia can be also found in glycogen storage disease type 1b, in a specific form of immunodeficiency with oculo-cutaneous albinism called Chediak-Higashi syndrome (in which neutrophils contain abnormal cytoplasmic granulations), in Griscelli syndrome type 2 (with partial albinism) and in other metabolic diseases or bone marrow failure syndromes. **Table 1** lists the most relevant causes of congenital neutropenia and other conditions accompanied by neutropenia.

Searching for Diagnostic Hints of Congenital Neutropenia. Post-infectious and drug-related are the most frequent etiologies of neutropenia, but they have no frankly specific features. The congenital neutropenia syndromes are taken into consideration if there are recurrent infections in patient's history, if neutropenia is severe, and if any associated anomalies suggest a genetic disorder. Diagnosis of cyclic neutropenia depends on serial measurements of the absolute neutrophil count over several weeks: all affected children have a neutrophil count below 200/mm^3 for three-to-five days at approximately three-week intervals. This disease is usually diagnosed within the first year of life, based on the pattern of recurrent fevers, skin inflammation, and oral ulcerations with serial blood cell count assessment. Bone marrow examination is not needed for establishing the diagnosis, but should be performed to rule out malignant hemopathies in the case of additional hematological abnormalities; oscillations of other cells such as lymphocytes, eosinophils, and platelets may also be observed. A reciprocal increase in blood monocytes and reticulocytes can occur during the neutrophil nadir.[34]

A proband with a suggestive clinical scenery that recurs over time requires genetic testing, and diagnosis follows the identification of one heterozygous pathogenic variant in the *ELANE* gene. Testing a panel of genes rather than a single gene may be useful since distinct genetic disorders can be associated with variably cycling neutrophil counts. The differential diagnosis between severe congenital neutropenia and cyclic neutropenia is important, as the severity of infections may be higher in the first and because of the risk of developing potentially life-threatening diseases, such as myelodysplastic syndrome and acute myeloid leukemia.[35,36] Cyclic neutropenia is usually not associated with malignant transformation to hematologic cancer, except for very few cases.[37,38] Rosenberg et al. studied the risk of sepsis mortality and incidence of leukemia in a population of 374 people with severe congenital neutropenia, receiving long-term therapy with G-CSF, finding that mortality due to sepsis was stable at 0.9% per year, while the risk of developing myelodysplastic syndrome or acute myeloid leukemia increased significantly over time, from 2.9% per year after 6 years to 8% per year after 12 years of therapy with G-CSF.[39,40] Investigations such as complete blood cell count, bone marrow biopsy, tumoral markers, serum level of G-CSF, chest X-ray or chest ultrasound, and computerized tomography scan of the chest should be done to rule out other immunodeficiency disorders. Autoinflammatory disorders should be also considered if the recurrent episodes of fever are combined with organ-specific sterile inflammatory manifestations.[41] In children aged 1-3 years with neutropenia not-caused by cyclic neutropenia or Kostmann syndrome, the presence of neutrophil-specific autoantibodies results in a peripheral destruction of neutrophils. Although these infants lack peripheral blood neutrophils, they usually do not suffer from severe infections.[42] **Table 2** shows some critical hints for diagnosing congenital neutropenia.

Assessing the Risk of Evolution to Hematologic Malignancy. Myelodysplastic syndromes are diseases affecting patients prevalently over 65 years. In contrast, the genetic susceptibility to myelodysplastic syndrome and acute myeloid leukemia can be rarely demonstrated in children. A malignant progression of congenital neutropenia has seldom been seen in the pre-growth factor era, but the number of patients progressing to

Table 1. List of the most relevant causes of congenital neutropenia and other conditions potentially giving rise to neutropenia.

Disorder	Affected Gene	Locus	Clinical Sceneries
Cyclic neutropenia	*ELANE*	19p13.3	recurrent fevers, skin and oropharyngeal infections every 3 weeks
ELANE-related congenital neutropenia	*ELANE*	19p13.3	recurrent infections of varying severity
HAX1-related congenital neutropenia	*HAX1*	1q21.3	recurrent infections, neurodevelopmental delay, epilepsy
G6PC3 deficiency associated with severe congenital neutropenia (Dursun syndrome)	*G6PC3*	17q21.31	recurrent infections, cardiovascular and/or urogenital abnormalities, intermittent thrombocytopenia, thymic hypoplasia, failure to thrive
WAS-related congenital neutropenia	*WAS*	Xp11.23	recurrent infections
GFI1-related congenital neutropenia	*GFI1*	1p22.1	recurrent infections
Shwachman-Diamond syndrome	*SBDS*	7q11.21	cytopenia, pancreatic dysfunction, short stature, metaphyseal dysostosis
Glycogenosis type Ib (glucose-6-phosphate translocase deficiency)	*SLC37A4*	11q23.3	hypoglycemia, hyperlactatemia, hyperlipidemia, hyperuricemia, recurrent infections
Chediak-Higashi syndrome	*LYST*	1q42.3	variable degrees of oculo-cutaneous albinism, easy bruisability and bleeding, recurrent infections
Griscelli syndrome type 2	*RAB27A*	15q21.3	partial albinism, immunodeficiency with or without neurologic impairment
Hermansky-Pudlak syndrome type 2	*AP3B1*	5q14.1	developmental delay, hypopigmentation, thrombocytopenia
Charcot-Marie-Tooth disease	*DNM2*	19p13.2	progressive weakness and atrophy of the peroneal muscles and distal muscles of the arms
P14 deficiency	*MAPBPIP*	1q22	short stature, hypopigmentation, coarse facies and frequent bronchopulmonary infections
Cartilage-hair hypoplasia	*RMRP*	9p13.3	dwarfism with skeletal abnormalities, hypotrichosis and immune deficiency that can lead to recurrent infections
WHIM syndrome	*CXCR4*	2q22.1	hypogammaglobulinemia, infections, warts (due to papillomavirus infections), myelokathexis (increased granulocyte pool with dystrophic neutrophils)
Reticular dysgenesis (adenylate kinase 2 deficiency)	*AK2*	1p35.1	severe combined immunodeficiency, agranulocytosis, sensorineural deafness
X-linked immunodeficiency with hyper-IgM syndrome	*CD40L*	Xq26.3	defective CD40 signaling by B cells, affecting class-switch recombination of immunoglobulin heavy chains
22q11 deletion syndrome (DiGeorge syndrome, velo-cardio-facial syndrome, conotruncal anomaly face syndrome)	Contiguous 22q11 deletion	22q11	variable cognitive delay, immunodeficiency, hypoparathyroidism, congenital heart disease, palatal, gastrointestinal and renal abnormalities

Table 2. Pivotal keys to the diagnosis of congenital neutropenia in children.

Family history of neutropenia combined with consanguinity
Serial assessment of white blood cell count and/or specific cytological abnormalities on the peripheral blood smear
Presence of any severe infections, bacterial or fungal, detectable at the time of assessment
Presence of stomatitis in the clinical history
Evaluation of immunological tests (immunoglobulin assay, lymphocyte immunophenotyping, anti-neutrophil antibody)
Evaluation of pancreatic markers (serum trypsinogen, fecal elastase) and liposoluble vitamin levels (A, E and D)

blood cancer has increased with the improved life expectancy achieved after G-CSF introduction as treatment. The development of myelodysplastic syndrome and acute myeloid leukemia in congenital neutropenia remains the major cause of mortality in these patients.[43] This risk is shared by both *ELANE*-related and *HAX1*-related severe congenital neutropenia, and specific *ELANE* mutations (e.g. G214R and C151Y) have a higher risk of progression to acute myeloid leukemia.[44] Apart from allogeneic hematopoietic stem cell transplantation, treatment options are limited, and there are neither reliable biomarkers that predict progression, nor effective prevention strategies.

Myelodysplastic syndromes secondary to severe congenital neutropenia are frequently associated with monosomy 7 and abnormalities of chromosome 21, which are relatively uncommon in *de novo* myeloid leukemia. The accumulation of mutations in hematopoietic stem cells with increasing age results in the production of a genetically heterogeneous cell population, with each stem cell possessing its own unique set of private mutations. Selective clonal hematopoiesis due to mutations in the tumor suppressor *TP53* gene has been found in almost 50% of patients with

Shwachman-Diamond syndrome, but not in those with severe congenital neutropenia: in particular, Shwachman-Diamond patients have an impaired ribosome biogenesis driving the expansion of hematopoietic stem cells which carry *TP53* mutations. Factors that increase the rate at which mutations accumulate in stem cells may increase the frequency of clonal hematopoiesis and blood cancer uprising. The acquisition of *TP53* mutations can be framed as an early event for the transformation of Shwachman-Diamond-related neutropenia into myelodysplastic syndrome or acute myeloid leukemia.[45]

Different neutropenic patients with risk of leukemic progression can show hematopoietic clones with somatic mutations in the *CSF3R* gene, encoding the G-CSF receptor, resulting in a truncated form of the G-CSF receptor, leading to defective internalization and aberrant signaling properties of the receptor: these clones may persist for months and even years before myelodysplastic syndrome or acute myeloid leukemia becomes overt. Of note, no increase in clonal hematopoiesis due to other gene mutations can be observed, demonstrating the highly selective nature of *CSF3R*-dependent clonal expansion in severe congenital neutropenia and clearly suggesting that *CSF3R* mutations contribute to the development of myelodysplastic syndrome and acute myeloid leukemia.[46]

In recent times, mutations in some oncogenes have been linked to familial myelodysplastic syndrome and acute myeloid leukemia. For instance, the *GATA2* gene, located at the chromosome 3, encoding for a nuclear transcription factor, has been identified as a potential trigger to develop blood malignancy in neutropenic patients, mostly if germline *GATA2* mutations are associated with partial or complete deletion of chromosome 7.[47] Somatic *RUNX1* mutations on chromosome 21 have been found in approximately 10% of patients with *de novo* acute myeloid leukemia, but are more common in secondary forms of myelodysplastic syndrome and acute myeloid leukemia, mostly if originating from certain types of leukemia-prone neutropenic syndromes. How *RUNX1* mutations and how the Runt-related transcription factor contribute to the pathobiology of secondary hemopathies, often characterized by adverse prognosis and refractoriness to treatment, is still unknown.[48]

Therefore, although we have gained significant knowledge of the heterogeneous genetic origin of congenital neutropenia, it is still undeciphered how these mutations predispose to leukemia and molecular mechanisms eliciting the transformation of neutropenia to myelodysplastic syndrome or acute myeloid leukemia are poorly understood. Additional treatment strategies using small molecule inhibitors with selectivity for the mutant genes to eradicate the mutant clones shortly after they appear or gene therapies correcting the underlying genetic defect in hematopoietic stem cells should be explored in real-life sceneries.

How to Put Children with Recurrent Fevers in Differential Diagnosis. Cyclic neutropenia represents a diagnostic dilemma, as most patients exhibit non-specific signs or symptoms dominated by recurrent fevers. Evaluation of children with cyclic neutropenia is based on the recognition of pivotal recurrent symptoms, disease duration, history of hereditary inheritance, and periodic assessment of the leukocyte count to prompt a differential diagnosis.[49,50] This clinical picture should remind several causes of recurring fevers in pediatrics, such as recurrent tonsillitis, infectious diseases, and Behçet's disease, but diagnosis of cyclic neutropenia is confirmed if the periodic oscillation of neutrophil count (every 21 days) is demonstrated at a sufficient number of time points (at least three times per week over 6 weeks), which is sometimes challenging for children.[51] Many diseases share recurrent fever as a common presenting feature in childhood: in particular, if fevers are not truly periodic (i.e., do not have a quite regular interval between febrile episodes) the monogenic periodic fever syndromes, caused by activation of the innate immune system, should be scrutinized.[52] These syndromes are different expressions of a primary dysfunction of innate immunity and are collectively named "autoinflammatory disorders", complex and heterogeneous diseases in which there is no evidence of adaptive immunity involvement, neither high-titre autoantibodies nor antigen-specific T cells, and no relationship with infectious triggers.[53] Children with hereditary autoinflammatory disorders display periodically-recurring features consisting of fever and organ-specific inflammation, with symptom-free intervals of different duration between attacks.

Among autoinflammatory disorders, familial Mediterranean fever and mevalonate kinase deficiency need to be taken into consideration as their manifestations may overlap with those of cyclic neutropenia.[54] The first is characterized by periodic short-lasting febrile episodes combined with serositis and/or arthritis in patients of Arabian, Armenian, non-Ashkenazi Jewish or Turkish descent.[55,56] The second is characterized by variably recurrent self-limiting febrile episodes of 3-7 days combined with concurrent debilitating symptoms which involve the muco-cutaneous, gastrointestinal and musculoskeletal system and last about one week.[57,58] On the other hand, recurrent flares of longlasting fever combined with recurrent inflammation in the muscles, joints, gastrointestinal tube and skin are the leading features of tumor necrosis factor receptor-associated periodic syndrome.[59] There is no specific laboratory examination to support the diagnosis of autoinflammatory disorders, except for the genetic analysis; their onset is usually during the first

Table 3. List of the most relevant systemic autoinflammatory disorders entering in differential diagnosis with cyclic neutropenia.

Disorder	*Affected Gene*	*Locus*	*Protein Encoded*	*Clinical Peculiarity*
Familial Mediterranean fever	*MEFV*	16p13.3	Pyrin	Recurrent serositis combined with self-limited joint symptoms
Mevalonate kinase deficiency	*MVK*	12q24	Mevalonate kinase	Onset in the first year of life with febrile attacks characterized by skin/gastrointestinal signs, lymphadenopathy and splenomegaly
Tumor necrosis factor receptor-associated periodic syndrome	*TNFRSF1A*	12p13	p55 receptor of tumour necrosis factor	Long duration of febrile attacks (more than 1 week) with muscle/gastrointestinal signs, periorbital edema and conjunctivitis occurring during attacks
Periodic fever/aphthous stomatitis/pharyngitis/cervical adenitis (PFAPA) syndrome	-	-	-	Periodically recurring high fever episodes with "clockwork" periodicity at intervals of 3-6 weeks

decade in about 50% of cases and symptoms may also start in the first months of life, requiring a strict differentiation with other childhood emergencies.[60]

During a typical attack of autoinflammatory disorders blood tests show a generalized increase of inflammatory parameters with a parallel neutrophil leukocytosis (until and over 20.000/mm^3).[61] This feature should help clinicians in differentiating autoinflammatory disorders from neutropenia, in which cyclic and "sterile" inflammatory phenomena outside the oral cavity are not usually encountered. Chronic inflammation in autoinflammatory disorders may also cause irreversible damage in multiple organ systems, such as visual loss, deafness, joint restriction and amyloidosis.[62]

Conversely, the periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (or PFAPA) syndrome, the most common non-inherited cause of periodic fever in childhood, is very similar to cyclic neutropenia and similarly may affect patient's family quality of life.[63] PFAPA children display inflammatory symptoms restricted to the oropharyngeal and neck lymphoid tissue with "clockwork" regularity every to 3-to-6 weeks: their fevers lasting 3-to-6 days recur combined with aphthous ulcers, pharyngitis and/or tonsillitis and cervical lymph node enlargement.[64] In contrast with cyclic neutropenia, these children have high white blood cell counts with preponderance of neutrophils and high levels of inflammatory markers during febrile episodes, while the neutrophil count turns to normal in the interfebrile periods.[65] Procalcitonin, a significant marker of bacterial infections, does not increase during PFAPA attacks, while serum immunoglobulins are usually normal during attacks.[66] The discrimination between PFAPA syndrome and cyclic neutropenia may be particularly challenging, as it requires a painstaking collection of clinical and laboratory data, and this challenge also involves the area of internal medicine, as PFAPA symptoms have been reported even in adulthood.[67-69] There is a need for universal diagnostic criteria of PFAPA syndrome, which can be valid for both children and adults. Febrile flares of mevalonate kinase deficiency can closely resemble PFAPA syndrome and cyclic neutropenia, but the presence of significant diarrhea or vomiting, lymphadenopathy outside of the cervical area and episodes triggered by immunizations may steer the diagnosis towards mevalonate kinase deficiency.[70] **Table 3** lists the most relevant general features of hereditary periodic fever syndromes and PFAPA syndrome, which require consideration in the differential diagnosis with cyclic neutropenia. Unfortunately, many questions related to PFAPA pathogenesis or a potential genetic basis for PFAPA symptoms and the reason why inflammation is localized at the oral cavity and neck, similar to cyclic neutropenia, remain unsolved.

Clues for the Specific Management of Children with Congenital Neutropenia. Over the past years, different hematologists have collaborated to optimize the management of patients with congenital neutropenia, finding that a multidisciplinary approach including immunologists, radiologists, and dentists is crucial through regular patients' follow-up visits to improve the overall outcome. Treatment of severe chronic neutropenia should focus on the prevention of infections, managing organ dysfunction, and preventing leukemic transformation.[71] All fevers and infections require prompt evaluation and treatment, while abdominal pain requires excluding peritonitis. Severe infections are rare in cyclic neutropenia, and most infections usually respond to antibiotics. Longer-term follow-up studies of patients with cyclic neutropenia showed that the most relevant complications were spontaneous peritonitis, segmental bowel necrosis, and septicemia, though they occurred rarely.[72]

Children suffering from severe congenital neutropenia require long-term administration of recombinant human G-CSF, given by subcutaneous injections daily or every other day, which is also the same treatment for patients suffering from cyclic neutropenia. Treatment with G-CSF (either filgrastim or pegfilgrastim) is safe and well-tolerated and is effective for elevating the neutrophil count in both congenital and cyclic neutropenia, ameliorating disease symptoms and reducing most infectious complications.[73] In cyclic neutropenia G-CSF shortens the periods of neutropenia as well as the length of the neutropenic

cycle: once the absolute neutrophil count normalizes, the resistance to infections improves. Common side effects of G-CSF include bone pain, headache, splenomegaly, and osteoporosis, but no adverse effects on growth and development have been reported in children. Therefore, G-CSF treatment enables patient's participation to school and recreational activities without any concerns. The optimal dosage of filgrastim in cyclic neutropenia is 2-to-3 μg/kg/day: this dose is lower than that used for severe congenital neutropenia (5-10 μg/kg/day) or for chemotherapy-associated neutropenia, and may require adjustments based on the therapeutic response.[74] Treatment combined with broad-spectrum antibiotics is important and even lifesaving in the case of complicated serious infections, which may be caused by mixed anaerobic/aerobic pathogens. Trying to synchronize filgrastim treatment to coincide with the period of neutropenia in cyclic neutropenia is hard, but administrations of G-CSF will usually change the periodicity of neutropenia. The drug is effective from as early as 6 months of age and treatment should continue lifelong, as needed. The main goal of treatment is to maintain the nadir of the absolute neutrophil count over 500/mm^3, which substantially reduces the risk of infections and affects health of the oral cavity, improving both masticatory ability and comfortable eating.[75] The long-acting pegylated formulation of G-CSF, pegfilgrastim, is also effective and convenient, but is difficult to dose in children and often leads to more severe bone pain as a side effect.[76] Although granulocyte-macrophage colony-stimulating factor has been administered for severe chronic neutropenia, it is less effective than G-CSF and associated with more adverse effects.[77]

It has been found that in *JAGN1*-mutant granulocytes, characterized by ultrastructural defects, paucity of granules, aberrant glycosylation of multiple proteins and increased apoptosis, in which the production of the JAGN1 protein located in the endoplasmic reticulum is deficient, the response to G-CSF may be poorer.[78]

As children grow and become adults, the dose of G-CSF should be adjusted in accordance with symptoms and blood cell count, rather than depending on the body weight. Because levels of neutrophils fluctuate in cyclic neutropenia, the neutrophil count has to be periodically monitored for several weeks after starting G-CSF. Sometimes, neutrophil cycling may be replaced by a mild chronic neutropenia in the third decade. An old report suggested that a combination therapy of G-CSF and high-dose immunoglobulins could be effective to induce the disappearance of neutrophil oscillations in cyclic neutropenia, but this therapeutic protocol has not been confirmed.[79]

Lastly, hematopoietic stem cell transplantation is the ultimate radical treatment for congenital neutropenia, as it can permanently correct the disease, being the long-term option for patients who do not respond to G-CSF.[80] Because G-CSF may promote leukemic transformation, patients requiring higher doses of G-CSF to prevent infections are candidates for stem cell transplantation, while patients not-undergoing transplantation require long-term surveillance to reveal a malignant transformation of the disease. Reassuringly, there are preclinical data giving proof of concept for treatment of congenital neutropenia through autologous transplantation of gene-edited cells for patients who did not show any response to G-CSF and for whom bone marrow transplantation had failed.[81]

Supportive care is also important to reduce the risk and severity of infections and should include oral hygiene and dental care through regular health assessments at intervals of 6 months and twice-daily oral rinsing with chlorhexidine after tooth brushing.[82] Bone density should be checked for the risk of osteoporosis during prolonged treatment with G-CSF, as osteoporosis is a possible side effect of this medication, and monitoring vitamin D levels should be also provided.[83] Furthermore, it is important to maintain an age-appropriate schedule of immunizations, while there is no need to avoid public places with people aggregation since most infections are caused by resident organisms from the intestinal microbiota. Common viral infections may be complicated with bacterial infections; however, prophylactic antibiotics are not recommended, as this might eventually select resistant organisms.[84]

General Conclusive Remarks. Despite the great steps in understanding congenital neutropenia, the constellation of clinical symptoms and recurrent fevers occurring in this protean disease generate frustration and grievous interactions among the clinician and patient's family members. In conclusion, among the rare primary disorders of the hematopoietic stem cell, it is crucial to consider cyclic neutropenia, transmitted with autosomal dominant inheritance, which is characterized by a biological clock responsible for sinusoidal variations of the neutrophil count every 21 days and recurrent infections. This disorder is distinct from permanent neutropenia, the classic feature of Kostmann syndrome, which starts in infancy. Infectious complications of cyclic neutropenia are rarer than those occurring in the severe congenital neutropenia. However, treatment with G-CSF can be largely effective, though the dose required to normalize neutrophils may vary. A strict differentiation of cyclic neutropenia from hereditary monogenic autoinflammatory disorders and PFAPA syndrome is mandatory in children.

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