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Neutropenia in primary immunodeficiency

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Abstract

Purpose of review—Neutropenia is a feature of several primary immunodeficiency diseases (PIDDs). Because of the diverse pathophysiologies of the PIDDs and the rarity of each disorder, data are often lacking, leading to the necessity of empiric treatment. Recent developments in the understanding of neutropenia in several of the PIDDs make a review of the data timely.

Recent findings—The category of severe congenital neutropenia continues to expand. Mutations in *G6PC3* have been identified as the cause of neutropenia in a minority of previously molecularly undefined cases. Recent advances have broadened our understanding of the pathophysiology and the clinical expression of this disorder. A possible function of the *C16orf57* gene has been hypothesized that may explain the clinical overlap between Clerucuzio-type poikiloderma with neutropenia and other marrow diseases. Plerixafor has been shown to be a potentially useful treatment in the warts, hypogammaglobulinemia, infection, and myelokathexis syndrome. Investigations of patients with adenosine deaminase deficient severe combined immunodeficiency have identified neutropenia, and particularly susceptibility to myelotoxins, as a feature of this disorder. Granulocyte-colony stimulating factor is the treatment of choice for neutropenia in PIDD, whereas hematopoietic cell transplantation is the only curative option.

Summary—The number of PIDDs associated with neutropenia has increased, as has our understanding of the range of phenotypes. Additional data and hypotheses have been generated helping to explain the diversity of presentations of neutropenia in PIDDs.

Keywords

granulocyte-colony stimulating factor; hematopoietic cell transplantation; neutropenia; primary immunodeficiency disorders

INTRODUCTION

The primary immunodeficiency diseases (PIDDs) include more than 150 different conditions [1■]. In the past 2 years, advances in this field have occurred in both myeloid and lymphoid immunodeficiencies. This review will address recent developments in these areas, with a

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Conflicts of interest

There are no conflicts of interest.

primary focus on entities that lead to neutropenia as an isolated finding or in the context of other immune defects (Table 1) [2,3■,4–7,8■,9–34,35■,36■,37–43,44■,45–47,48■,49■, 50–58], excluding marrow disorders presenting as pancytopenia and disorders only described in single patients or kindreds. Treatment of neutropenia in the setting of PIDD will also be discussed.

GLUCOSE-6-PHOSPHATASE CATALYTIC UNIT 3 DEFICIENCY

Glucose-6-phosphatase catalyzes the final steps of gluconeogenesis and glycogenolysis in the endoplasmic reticulum (ER). Three genes with this activity have been described, the most widely expressed of which is glucose-6-phosphatase catalytic unit 3 (*G6PC3*) [59,60]. Mutations in this gene were found to be a cause of severe congenital neutropenia in 2009 [7]. The neutrophils of patients with this disease, now known as severe congenital neutropenia type 4 (SCN4) [1■], have an increased sensitivity to apoptosis. Associated findings include structural heart defects, urogenital abnormalities, and venous angiectasia. In the past 2 years, extensive work has been done to delineate both the pathophysiology and the range of phenotypes of this syndrome.

The first patients described with *G6PC3* deficiency had an absence of mature neutrophils in the marrow, consistent with early apoptosis. In 2010, McDermott *et al.* [9] published a variant form of the disease showing myelokathexis. The two patients reported in this article were homozygous for a missense mutation at nucleotide 778 of *G6PC3*, coding for p.G260R. McDermott *et al.* reported decreased oxidase activity in their two patients, which was not identified in the original *G6PC3*-deficient cohort. Although the cohort of Boztug *et al.* [7] did include two patients with G260R, neither of these patients' bone marrows was assessed morphologically. Because of the finding of myelokathexis, McDermott *et al.* [9] examined the expression of CXCR4, the protein that is absent or mutated in warts, hypogammaglobulinemia, infection, and myelokathexis (WHIM) syndrome, in their patients and in *G6pc3*-knockout mice, finding it to be elevated in both cases. Treatment of the patients with granulocyte-colony stimulating factor (G-CSF) led to a decrease in CXCR4 expression along with an increase in absolute neutrophil count (ANC). Further tying the increased expression of CXCR4 to the patients' neutropenia, plerixafor, a specific CXCR4 antagonist, mobilized neutrophils into the circulation of *G6pc3*-knockout mice.

Neutropenia with *G6PC3* mutations was further described in 2011 by a British–Israeli team [61■]. All four reported patients were members of a single kindred of Palestinian citizens of Israel and shared the same missense mutation as the first family reported by Boztug *et al.* [7], c.758G>A leading to p.R253H. Three of the patients in this report were in their third decade, all older than the patients of Boztug *et al.* [7]. Consequently, Banka *et al.* [61■] describe their patients as representing the adult phenotype of SCN4. This phenotype includes venous varicosities and stasis ulcers, growth delay and small adult size, developmental delay or learning disabilities, and delayed sexual maturation in two of the three adult patients. The extent to which these findings represent the true adult phenotype of *G6PC3* mutation versus coinherited phenotypes in this highly consanguineous family is not clear, although venous varicosities and stasis ulcers could be related to the venous ectasia described by Boztug *et al.* The description of this phenotype may have important clinical

implications for patients with *G6PC3* mutations, because stasis ulcers would represent a substantial clinical problem in the setting of neutropenia.

Although not commented upon by the authors, the ANC of the Palestinian patients reported by Banka *et al.* [61] appear to be higher than those of the Aramean patients with the same mutation reported by Boztug *et al.* [7]. In the earlier paper, two out of five patients never had ANCs above 100 cells/ μ l, whereas the lowest ANC reported by the Israeli–British team was 200 cells/ μ l. The youngest patient was able to mount an ANC of 7700 cells/ μ l, although under what clinical circumstances is not clear. Banka *et al.* do not mention the extent to which their patients were treated with G-CSF, and if they do have higher neutrophil counts than the patients of Boztug *et al.* they may not be cytokine-dependent. This difference may be explained by other genomic factors, or it could represent the variability of the newly described disease.

Gatti *et al.* [62] presented a case report of the first South American patient with *G6PC3* deficiency in 2011. The mutation was a two base pair deletion leading to a frameshift. The child had lived 10 years without diagnosis or treatment. Between infections, the ANC could rise above 1000 cells/ μ l. The marrow showed a lack of mature neutrophils and was otherwise described as nonspecific.

Despite an apparently benign bone marrow examination, the patient had neutropenia below 200 cells/ μ l, anemia with reticulocytopenia, and thrombocytopenia. The two patients of McDermott *et al.* [9] were said to have iron deficiency anemia. In the report of Banka *et al.* [61], all four patients are said to be anemic, but reticulocyte counts or further evaluation are not mentioned, and patient number 1 appears to be persistently thrombocytopenic. Boztug *et al.* [7] mention mild thrombocytopenia in one of their patients, but otherwise do not describe findings in red cells or platelets in their initial report. The contribution of either inflammation or iron deficiency to the South American patient's anemia is not clear. Moreover, he was found to have antierythrocyte B19 IgM antibodies a month after the initial laboratory values were obtained. Nevertheless, it appears that patients with *G6PC3* deficiency may manifest cytopenias beyond simply neutropenia. The patient of Gatti *et al.* [62] could be maintained on a low dose of G-CSF, 1.8 μ g/kg/day. This, coupled with the patient's survival without treatment to age 10, may suggest that his mutation, despite being a frameshift, resulted in milder disease than that of some of the other patients described.

Boztug *et al.* [8] have more recently revisited the question of the *G6PC3*-deficient phenotype. Of 31 patients studied, 16 had homozygous or compound heterozygous mutations of *G6PC3*. Ten of these 16 had intermittent thrombocytopenia. The most common nonhematologic manifestation was venous ectasia, present in 14 of the 16 patients. Four patients had homozygous frameshift mutations, although there was no comment on their clinical course being better or worse than average. Fifteen of the 16 patients were maintained on G-CSF, with doses averaging 3.3 μ g/kg/day, and ranging from 0.7 to 14 μ g/kg/day. Twelve of the 15 used G-CSF less than once per day. In almost three centuries of cumulative follow-up, no patient developed leukemia, and this was found to be statistically different from an SCN cohort of 374 patients. No patient had myelokathexis. In some patients, the

authors noted an SCN4 phenotype without mutations in the coding region of *G6PC3*, suggesting that other genes may be involved in SCN4.

Three recent articles have investigated the pathophysiology of the *G6PC3* deficiency. Using a knockout mouse model [63], Jun *et al.* [64] showed that glucose transport out of the ER is deficient in neutrophils of *G6pc3*^{-/-} mice and *G6PC3*^{-/-} humans. Biochemical results of this deficiency included decreased glucose-6-phosphate in neutrophil cytoplasm, decreased lactate, and decreased ATP. In the murine model, neutrophils had decreased levels of the phagocyte oxidase proteins and inhibited oxidative burst, chemotaxis, and phagocytosis. In this respect, the knockout mice differ from the first kindred presented by Boztug *et al.* [7], who were homozygous for a missense mutation and had apparently normal neutrophil function. Recently, Jun *et al.* [65] showed that the neutrophil dysfunction of *G6pc3* knockout mice is ameliorated by G-CSF. Because McDermott *et al.* [9] had shown decreased respiratory burst activity in humans with *G6PC3* deficiency, this finding may have clinical importance.

Hayee *et al.* [66] showed a diffuse decrease in glycosylation in patients with *G6PC3* deficiency or with glycogen storage disease Ib/glucose-6-phosphate translocase (*G6PT*) deficiency. G6PT forms a complex with G6PC3 in the ER, where the former protein translocates glucose-6-phosphate from the cytoplasm, and the latter dephosphorylates the substrate. Given this profound glycomic disorder, the authors classify both diseases among the congenital disorders of glycosylation.

POIKILODERMA WITH NEUTROPENIA

In 2010, an Italian family with Clericuzio-type poikiloderma with neutropenia was found to have a mutation in *C16orf57* [67]. At that time, the gene's function was unknown. In 2012, Colombo *et al.* [68] reported on two novel *C16orf57* mutations. Further work *in silico* led the authors to hypothesize that *C16orf57* functions in RNA processing. If this hypothesis is correct, it could provide a pathophysiologic basis for the clinical overlap of poikiloderma with neutropenia, with dyskeratosis congenita with normal telomere length, and with Rothmund–Thomson syndrome [69].

NEUTROPENIA IN DISORDERS OF CXCL12/CXCR4 SIGNALING

The CXCR4 receptor is hyperfunctional in WHIM syndrome [70]. Based on the understanding of the molecular etiology of this disease as a gain-of-function mutation in *CXCR4* [71], McDermott *et al.* [72] demonstrated that the CXCR4 antagonist plerixafor could counteract this hyperfunctionality. In 2011, the same authors [49] and a separate group [48] showed that plerixafor could be used to increase neutrophil, lymphocyte, and monocyte counts in patients with WHIM syndrome. Both studies were dose escalation studies, showing an effective dose well below the dose approved by the US Food and Drug Administration for mobilizing peripheral blood hematopoietic stem cells, 0.24 mg/kg. In their report, the group from the National Institute of Allergy and Infectious Diseases discuss the potential for unintended consequences of chronic complete blockage of CXCR4, noting the knockout mice to be nonviable. The authors claim to have only partially blocked

CXCR4, estimating that at the lowest dose only about 30% of CXCR4 receptors were blocked. The data upon which this estimate is based are not presented. For this reason, and because the appropriate dose and schedule of plerixafor in WHIM syndrome have not been determined, G-CSF remains the treatment of choice [73].

In 2012, Liu *et al.* [74] presented the first case of WHIM syndrome caused by a point mutation in *CXCR4*, c.1027G->A, coding for p.343E->K. All previous reports of WHIM syndrome due to *CXCR4* mutations had been of truncating mutations. As is the case for truncated proteins, McDermott *et al.* found the missense mutation to cause CXCR4 to be hyperfunctional.

A potential second immunodeficiency involving CXCR4 and CXCL12 was identified in 2011 [75]. The reported patients had neutropenia, hypogammaglobulinemia, and recalcitrant warts, but did not have myelokathexis. Both patients had B-cell and natural killer cell lymphopenia, which is not typically associated with WHIM syndrome. Furthermore, no mutations in the *CXCR4* gene were identified. The patients' lymphocytes had reduced internalization of CXCR4 when stimulated with CXCL12, a finding which the authors had previously demonstrated in patients with WHIM syndrome [76].

NEUTROPENIA IN COMBINED IMMUNODEFICIENCY

In addition to the primary neutropenic immunodeficiencies, neutropenia can be found as a feature of what are primarily thought of as lymphoid immune deficiencies, including several subtypes of combined immunodeficiency (Table 1).

Recent work has shown a predisposition to neutropenia among children with adenosine deaminase deficient severe combined immunodeficiency (ADA-SCID). This was first identified in a trial of gene therapy [77], wherein two out of 10 patients had prolonged neutropenia after receiving 4 mg/kg of busulfan, less than half of the myeloablative dose [78]. A previous observation reported prolonged pancytopenia after a similar low dose of busulfan in a single patient [79]. Complicating the interpretation of this severe adverse event was a finding of a minority population of cells with trisomy 8 in marrow of the patient stored before gene therapy.

Our recent findings in a cohort of 13 patients with ADA-SCID further describe neutropenia in this condition [29]. Although none of the patients were profoundly neutropenic at the time of description, all of the patients had morphologic abnormalities of myeloid cells in the peripheral blood (Fig. 1), and of the six whose marrow was studied, all were found to have cytologic dysplasia. As was seen in two of the patients of Aiuti *et al.* [77], we observed prolonged neutropenia after low-dose busulfan given as conditioning prior to gene therapy for ADA-SCID. All three of the patients who received busulfan ultimately were treated with G-CSF in order to achieve a sustained ANC greater than 500 cells/ μ l. Additional findings included susceptibility to drug-induced neutropenia and an inverse correlation between ANC and deoxyadenosine metabolite percentage, a marker of metabolic burden of disease in ADA-SCID, at diagnosis.

Although these reports raise the suspicion of neutropenia as a feature of ADA-SCID, it is unclear whether this finding is a genuine manifestation of ADA deficiency, or whether it could be fully explained as an exaggerated response to myelotoxins, rather than an inherent myeloid abnormality. On the basis of our more recent findings, it can be argued that neutropenia is in fact a primary manifestation of ADA deficiency. We have made preliminary observations in two patients who became mixed chimeras after either allogeneic hematopoietic cell transplantation (HCT) or gene therapy for ADA-SCID [80]. In both cases, withdrawal of pegylated adenosine deaminase (PEG-ADA) months to years after cellular therapy led to an increase in the percentage of ADA-expressing lymphocytes. PEG-ADA withdrawal was accompanied by an expected increase and then fall of deoxyadenosine metabolites, during which neutropenia was observed. As metabolic control was regained with selection of ADA-expressing cells, the neutropenia improved. The patient who had had allogeneic HCT had 89% T-cell chimerism prior to PEG-ADA withdrawal. He had a transient neutropenia, whereas the gene therapy patient, who had 1% marking prior to PEG-ADA withdrawal, required prolonged administration of G-CSF before being able to maintain an ANC above 500 cells/ μ l. Before discontinuing the drug, the second patient used G-CSF as infrequently as once every 14 days.

Two groups described a new molecular etiology of combined immunodeficiency in April of 2012 [35■,36■]. The patients studied by Abdollahpour *et al.* [35■] were three members of a single Iranian family with stop mutations due to a single nucleotide substitution in exon 7 of *STK4*, also known as *MST1*, a gene whose product has antiapoptotic activity. In addition to deficiencies of B and T cell numbers, all three patients had neutropenia. Infections were both bacterial and viral. T cells and neutrophils showed increased apoptosis. Although these patients presented between ages 2 and 10, and were able to make specific antibodies against tetanus and diphtheria toxoids, two other members of the kindred died from sepsis in infancy.

Nehme *et al.* [36■] presented four Turkish patients from two consanguineous marriages with mutations in *STK4*. All patients had viral and bacterial infections, neutropenia, and autoimmunity. T-cell function was also impaired. Patients had elevated levels of IgG and IgA and made antibodies to polio, but not to tetanus or diphtheria toxoids, or to *Haemophilus influenzae* or *Streptococcus pneumoniae*. The authors characterized the syndrome as combined immunodeficiency rather than SCID. All four patients had truncating mutations of *STK4*. Additional findings included a decreased amount of IL7R α , a protein absent in a minority of autosomal recessive SCID patients. Two patients died after alternative donor HCT, and one was cured by the procedure.

TREATMENT OF NEUTROPENIA IN PRIMARY IMMUNODEFICIENCY DISEASE

Febrile neutropenia is a medical emergency in all cases. Although outpatient treatment with oral antibiotics has been advocated for low-risk patients expected to recover their white counts after cancer chemotherapy [81], the data for such an approach do not exist for neutropenia in PID, and this strategy cannot be recommended. Appropriate management

consists of empiric broad-spectrum antibiotics administered in an inpatient setting. As in postchemotherapy neutropenia, localizing signs and symptoms may be lacking in neutropenic patients with PID. However, unlike the case with postchemotherapy neutropenia, patients with PID and neutropenia are often able to increase their ANC in the face of an infectious challenge. Although this may make the outcomes of febrile neutropenia in PID less severe than in the post-chemotherapy setting, data for this hypothesis are lacking. Furthermore, patients with postchemotherapy neutropenia can be expected to recover their counts in a few days, whereas patients with neutropenic PID will not. The original data supporting empiric antibiotics for febrile neutropenia come from the postchemotherapy setting [82], and, in the absence of data specific to PID, it seems appropriate to extrapolate from these data in making treatment decisions.

Beyond the acute setting, treatment of neutropenia in PID depends on the underlying disorder, the overall health of the patient, and the goals of the patient and family. In the pre-cytokine era, patients with irreversible neutropenia who were not cured by HCT could be given prophylactic antibiotics. Although this approach is still advocated by some experts [13], it is not universally recommended [83], and other authors cite G-CSF as the treatment of choice for neutropenia in PID [45,53]. In the case of autoimmune neutropenia in humoral or combined immunodeficiencies, consideration can be given to corticosteroid treatment, although this must be done with caution in patients with PID and severe neutropenia. Alternative treatments include immunoglobulin replacement, G-CSF [84], and rituximab or alemtuzumab [46].

For the primary neutropenic disorders, G-CSF is the treatment of choice in the absence of curative HCT [83]. This treatment has reduced infectious morbidity [85] and mortality [86]. Although only 5% of patients with SCN have no response to G-CSF [87], the amount of cytokine needed varies greatly from less than 5 to 120 µg/kg/day. Those patients who do not respond to 120 µg/kg/day of G-CSF are unlikely to respond to higher doses [88] and are appropriate candidates for HCT. Included among this group are patients with a constitutive extracellular G-CSFR mutation [14,89,90], who are absolutely refractory to G-CSF. Patients who require more than 8 µg/kg/day of G-CSF have an increased risk for leukemic transformation [86].

The use of pegfilgrastim instead of filgrastim is theoretically attractive, and has been tried in isolated cases [91–94], but has not been routinely accepted, and may in fact lead to an increase in adverse events [95,96]. One obstacle to the use of this agent in the United States is the packaging of the commercially available product in a syringe prefilled with the adult dose of 6 mg. This would require either intentional overdosing or the cumbersome prospect of pharmacist re-packaging of the medicine if pegfilgrastim were used for children.

The experience of our group with neutropenia in ADA-SCID has been more variable. G-CSF is typically only needed after myelotoxic challenges, such as chemotherapy or myelotoxic drugs, and then only for a few weeks [29]. Antineutrophil antibodies have been found in several patients with ADA-SCID; however, the usual caveats of serologic diagnosis in patients on immunoglobulin replacement, as well as the known concerns about the poor specificity of the antineutrophil antibody assays, apply. There is no reported experience of

the use of immunosuppression in this situation. The utility of PEG-ADA to treat the neutropenia of ADA-SCID is not clear.

For most PIDDs, the only curative treatment is allogeneic HCT [97,98]. Although this procedure is clearly indicated in SCID [99■], with the possible exception of ADA-SCID without a matched related donor [100], it is more selectively applied in other PIDDs (Table 1). PIDDs with neutropenia in which HCT is generally considered to potentially have a favorable risk–benefit ratio include, in addition to SCID, X-linked hyper-IgM syndrome (CD40L deficiency), Chediak–Higashi syndrome, Griscelli syndrome, severe congenital neutropenia, and cyclic neutropenia [97].

Finally, genetically modified autologous HCT has been used as an investigational modality in several PIDDs [101–107], with notable successes in SCID, chronic granulomatous disease, and Wiskott–Aldrich syndrome. Gene therapy remains a potentially useful modality for PIDDs with neutropenia, but is still at the preclinical stage for most of them. Even in those disorders in which gene therapy has been carried out, its application must be judicious, given the potential for life-threatening or fatal adverse events [108–110] (and, press release from Hannover Medical School, http://www.asgct.org/UserFiles/file/Genethrapy_WAS_final_english.pdf, accessed 1 August 2012).

CONCLUSION

Neutropenia is a feature of several myeloid and lymphoid PIDDs. The many different pathophysiologies represented by the PIDDs lend themselves to, and in fact necessitate, a more diversified and nuanced treatment approach than the standard used for febrile neutropenia after cancer chemotherapy. Additional clinical observations and investigations into both the pathophysiology and the management of neutropenia in the different PIDDs, as an isolated complication and in the context of the underlying disease, are required and can be expected. Until such new data are presented, the management of neutropenia in PIDDs will require a flexible, empiric, and patient-centered approach based on the use of cytokines and HCT with consideration of antibiotic prophylaxis and gene therapy in the appropriate settings.

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- of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 72–73).

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KEY POINTS

- Neutropenia is a feature of several PIDDs, including those of myeloid and lymphoid lineage.
- The pathophysiology, clinical presentation, and management of neutropenia in PIDDs is more varied than in postchemotherapy neutropenia, and requires a more flexible approach.
- The database for managing neutropenia in any given PIDD is sparse, requiring the physician to extrapolate from the postchemotherapy setting.
- Febrile neutropenia is a medical emergency that should be treated by empiric broad-spectrum antibiotics.

FIGURE 1. Morphologic abnormalities in the peripheral blood of patients with adenosine deaminase deficient severe combined immunodeficiency: (a) trilobed eosinophil; (b) pyknotic neutrophil; (c) giant platelet, normal red blood cell can be seen next to the platelet for comparison; (d) pseudo-Pelger-Huet cell.

Table 1

Primary immunodeficiencies with neutropenia

Disease	Genes	Inheritance	Response to cytokines	Risk for leukemia	Reported use of HCT	Notes
Primary neutrophil defects						
Severe congenital neutropenia	<i>ELANE</i>	AD	G-CSF [2]	Increased [3■]	Yes [4]	Commonest form of SCN. Neutrophil functional defect [5]
	<i>HAX1</i>	AR	G-CSF [2]	Increased [3■]	Yes [6]	Kostmann syndrome
	<i>G6PC3</i>	AR	G-CSF [7]	Not reported [8■]	No [8■]	Neutrophil functional defect [9]
	<i>GFI1</i>	AD	G-CSF [10]	Not reported	No	<i>GFI136N</i> polymorphism associated with increased leukemia risk [11]. Increased expression of <i>GFI1</i> mRNA in CML [12]
	<i>CSFR3</i>	?	No [13]	Not reported	Yes [14]	
Cyclic neutropenia	<i>ELANE</i>	AD	G-CSF [15]	Not increased [16]	No	
X-linked neutropenia	<i>WASP</i>	XR	G-CSF [17]	Increased [18]	No	WASP is constitutively active [19]. All reported mutations in GTPase binding domain [20]
IRAK-4 deficiency	<i>IRAK4</i>	AR	Not reported	Not reported	No	Neutrophil functional defect [21,22]
Poikiloderma with neutropenia	<i>C16orf67</i>	AR	Not reported	Not reported	No	
Albinism with neutropenia						
Chediak–Higashi syndrome	<i>LYST</i>	AR	G-CSF [23]	Not reported	Yes [24]	Intermittent neutropenia. Neutrophil functional defect [25]
Griselli syndrome type 2	<i>RAB27A</i>	AR	Not reported	Not reported	Yes [24]	Intermittent neutropenia
Hermansky–Pudlak syndrome type 2	<i>AP3B1</i>	AR	G-CSF [26]	Not reported	No	
p14 deficiency	<i>P14</i>	AR	G-CSF [27]	Not reported	Yes [28]	
Primary T-cell defects						
Severe combined immunodeficiency	<i>ADA</i>	AR	G-CSF [29]	Not reported	Yes [24]	Neutropenia variably present. Increased susceptibility to myelotoxins [29]

Disease	Genes	Inheritance	Response to cytokines	Risk for leukemia	Reported use of HCT	Notes
	<i>PNP</i>	AR	Not reported	Not reported	Yes [24]	
	<i>RMRP</i>	AR	G-CSF [30]	Not increased [31,32]	Yes [32]	Cartilage-hair hypoplasia. 25% of patients have neutropenia [33]
	<i>AK2</i>	AR	GM-CSF [34]	Not reported	Yes [24]	Reticular dysgenesis
Combined immunodeficiency	<i>STK4/MST1</i>	AR	Not reported [35,36]	Not reported [35,36]	Yes [36]	
IPEX syndrome	<i>FoxP3</i> , unknown	XR	G-CSF [37]	Not reported	Yes [38,39]	
Primary B-cell defects						
Agammaglobulinemia	<i>BTK</i>	XR	G-CSF [40]	Not reported	Yes [41]	Neutropenia variably present. Transplants reported in English literature have been unsuccessful [41,42]
	<i>IgHM</i>	AR	Not reported	Not reported	No	Neutropenia variably present
X-linked hyper IgM	<i>CD40L</i>	XR	G-CSF [40]	Not reported	Yes [24]	Neutropenia in 2/3 of patients. Neutropenia can resolve with immunoglobulin replacement [43]
Common variable immune deficiency	<i>ICOS</i> , <i>TNFRSF13B</i> , <i>CD19</i> , <i>BAFFR</i> , unknown	AD, AR or sporadic	G-CSF [40]	Not reported	Yes [44]	Autoimmune neutropenia variably present [45]
Selective IgA deficiency	<i>IGAD1</i> , <i>TNFRSF13B</i> , unknown	AD, AR, or sporadic	Not reported	Not reported	No	Autoimmune neutropenia variably present [45]
Pan-leukocyte defect						
WHIM	<i>CXCR</i> , unknown [46]	AD	G-CSF, GM-CSF [40]	Not reported	Yes [47]	Neutropenia also responds to plerixafor [48,49]
Multisystem diseases with neutropenia						
Glycogen storage disease type Ib	<i>G6PT</i>	AR	G-CSF [50], GM-CSF [51]	Not reported	Yes [52]	Neutrophil functional defect [53]
Barth syndrome	<i>TAZI</i>	XR	Not reported	Not reported	No	
Cohen syndrome	<i>COH1</i>	AR	G-CSF [54,55]	Not reported	No	
Schinke immunosseous dysplasia	<i>SMARCAL1</i>	AR	G-CSF, GM-CSF [56]	Not reported	Yes [57,58]	Lymphopenia frequently present, neutropenia and other cytopenias variably present [56]

AD, autosomal dominant; AR, autosomal recessive; G-CSF, granulocyte-colony stimulating factor; HCT, hematopoietic cell transplantation; SCN, severe congenital neutropenia; WHIM, warts, hypogammaglobulinemia, infection, and myelokathexis; XR, X-linked recessive.