Idiopathic, Immune, Infectious, and Idiosyncratic Neutropenias

Jan E.W. Palmblad and Albert E.G.Kr. von dem Borne

In idiopathic and immune neutropenias the susceptibility to infectious agents is highly variable, but the reason why some patients exhibit no undue susceptibility whereas others contract life-threatening infections is poorly understood. An important factor is the efficacy of delivery of neutrophils to the tissues. Recent investigations of the mechanisms for mild to moderate chronic neutropenias have shown the significance of interactions between myelopoiesis and the immune system, as for example, in relation to immunoglobulin aberrations and the cytokine network. Antibody-mediated neutropenias (alloimmune, autoimmune) are now well-characterized diseases. If infections occur, apart from antibiotics, granulocyte colony-stimulating factor (G-CSF) is the treatment of choice, while intravenous or monoclonal immunoglobulins and cyclosporine are reserved for refractory cases.

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N EUTROPENIA REFERS to the existence of a blood absolute neutrophil count (ANC) of less than 1,500/µL (in blacks < 1,200/µL). The ANC in mild cases is 1,000 to 1,500/µL, in moderate cases 500 to 1,000/µL, and in severe neutropenia (often called agranulocytosis) less than 500/µL.17,28 This subdivision is useful for predicting the risk of pyogenic infection.

Acute or transient neutropenias are most often caused by cytotoxic drugs or due to idiosyncratic drug-induced reactions. Some infectious agents may also cause transient neutropenia.

Chronic idiopathic neutropenia is a disorder with isolated neutropenia of unknown origin to which no other pathology can be associated. Being a diagnosis of exclusion, it is highly dependent on the quantity and quality of the diagnostic procedures. Chronic immune neutropenia is diagnosed based on the presence of antibodies against neutrophils or myeloid progenitors30 or when other findings strongly point to an immune process that probably (also) includes neutrophils. The introduction of better assays for autoantibodies and alloantibodies has allowed for more specific diagnoses of alloimmune and autoimmune neutropenias.51

Infections

The major risk in neutropenia is infection and, in general, this risk is inversely proportional to the ANC.27 This relation has been best documented in neutropenic patients following cytoreductive therapy and in human immunodeficiency virus (HIV) patients.34 The incidence of infections in idiopathic neutropenias has not been well documented. Nonetheless, some patients with idiopathic severe chronic neutropenia may be surprisingly free of symptoms, while others with only mild neutropenia present with frequent infections. Risk is enhanced when neutropenia is accompanied by monocytopenia, lymphocytopenia, and/or severe hypogammaglobulinemia.

Clearly, it is not the ANC itself that is the interesting variable but the delivery of neutrophils to the tissues, reflected in the ability to produce pus. Because assessments of that delivery, for instance by means of skin windows, is impractical, simpler methods are needed. One, employing the number of neutrophils in mouthwashes, offers advantages.73 Another is based on the plasma levels of the soluble FcγRIIb or CD16: neutropenic patients with frequent infections have low values, whereas other patients with equally low ANCs but higher CD16 concentrations fare far better.41

A recent study of a group of patients with mild/moderate neutropenia of various causes found no relation between an ANC between 500 and 1,500/µL and the frequency or severity of infections.37 Increasing knowledge of the etiology and pathophysiology as well as the impact of simultaneously occurring defects of host defense indicate that the infection-prone phenotype might depend on a combination of aberrations. Low proliferation of myeloid precursors and poor bone marrow reserves enhance infection risks, whereas increased peripheral destruction of...
neutrophils combined with unperturbed production lowers the risk, even at similar ANC52.

An interesting albeit yet poorly understood phenomenon is coexisting polymorphism or mutations for other determinants of host defense: IgG-FcR polymorphisms and/or complement component deficiencies,66 immunoglobulin or IgG subclass deficiencies,37 lack of mannose-binding lectin,23 and other pattern recognition systems,21 as well as age, malnutrition, and various other factors.14,54 Consequently, specific treatment of chronic neutropenias must be based on the clinical presentation as much as on the ANC.

The infections in chronic neutropenic patients involve organisms normally residing in the nasopharynx, on the skin, or as part of the intestinal flora. The types of infections in a well-defined group of patients with infantile autoimmune neutropenia are listed in Table 1.

**Table 1. Infections in Infantile Autoimmune Neutropenia at the Time of Diagnosis**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory infections</td>
<td>19%</td>
</tr>
<tr>
<td>Otitis media</td>
<td>17%</td>
</tr>
<tr>
<td>Pyoderma</td>
<td>12%</td>
</tr>
<tr>
<td>Fever of unknown origin</td>
<td>12%</td>
</tr>
<tr>
<td>Abscess</td>
<td>10%</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>10%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>7%</td>
</tr>
<tr>
<td>Lymphadenitis coli</td>
<td>4%</td>
</tr>
<tr>
<td>Sepsis</td>
<td>3%</td>
</tr>
<tr>
<td>Urogenital infections</td>
<td>3%</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>2%</td>
</tr>
<tr>
<td>Phlegmonia</td>
<td>1%</td>
</tr>
<tr>
<td>Meningitis</td>
<td>1%</td>
</tr>
</tbody>
</table>

*Note. Mean age at diagnosis, 8 months. The total number of events is 260.*

Chronic Acquired Idiopathic Neutropenia

These children and adults present with an isolated neutropenia (and sometimes anemia secondary to infections). Other blood cell lineages are normal and the spleen is usually not enlarged. The bone marrow may be normal or may show neutrophilic hypoplasia or an ineffective neutrophil granulocytopenia (“maturation arrest”). There are no chromosomal abnormalities or signs of myelodysplasia (MDS). In vitro, the formation of granulocyte-macrophage colony-forming units (CFU-GM) is usually normal. In the diagnostic work-up it is important to exclude large granular lymphocytosis (LGL syndromes), primary immune neutropenias, hematologic disorders (MDS, lymphomas, B12 deficiency), autoimmune diseases (systemic lupus erythematosus [SLE], Sjögren’s syndrome, primary biliary cirrhosis) and infections (Table 2).

Severe Chronic Idiopathic Neutropenias

Understanding of the mechanisms for these cases has not improved during the last few years. Most patients need treatment with granulocyte colony-stimulating factor (G-CSF) and respond with increased ANCs at doses that are lower than those required for patients with congenital or cyclic neutropenia. The condition(s) appears to be stable over time, not evolving into MDS, acute leukemias, or aplasia.

Nonimmune Mild and Moderate Idiopathic Neutropenias

These are probably most frequent in adults, characterized by polymorphonuclear leukocyte counts between 500 and 1,500/µL for more than 3 months. The most common form is a benign ethnic neutropenia, observed in a variety of populations: Africans, West Indians, Yemenite and Ethiopian Jews, black Beduin Arabs, and Jordanians.28 The etiology is probably genetic. There has also been an interest in neutropenias in athletes.4,67

Non-ethnic neutropenia may persist for years, even throughout life, and is very rarely complicated by lupus erythematosus, rheumatoid arthritis, or any other systemic disease.37,43,57 While acute myeloid leukemia was recently reported in four Caucasian patients,3,58 the relation to neutropenia is unclear. G-CSF administration will increase neutrophils in most patients and is useful in case of recurrent fever and infections.

The prevalence of non-ethnic neutropenia in Caucasians in general is largely unknown. However, in a Greek population it has been estimated to 1.67%, primarily affecting middle-aged women and with a preponderance for the tissue antigens HLA-DRB1*1302.56 One series of studies characterized these patients and the mechanisms for neutropenia.58 They were usually asymptomatic but frequently displayed an increased splenic volume on ultrasonography55 and low bone mineral density.58 There was a decrease of myeloid precursors, such as CD34+7/CD33+ cells in the bone marrow, as well as CFU-GM in the maturating pool of neutrophils. These findings might be explained by bone marrow stromal cells that failed to sustain granulopoiesis in vitro and produced increased amounts of negative regulators of myelopoiesis, such as transforming growth factor beta-1 (TGF-β1).58

A number of other features suggest that there is an intimate, yet complex, interaction between myelopoiesis and the immune system. Thus, the Greek patients displayed a moderate T-memory cell lym-
phopenia as well as an increase of bone marrow B, plasma, and CD57/H11001 cells,58 sometimes coupled with the appearance of a monoclonal gammaglobulin component.58 Many patients displayed a polyclonal rise in serum IgG that was unexpectedly associated with low IgG3 levels.57 Interestingly, among 30 Swedish patients with mild/moderate neutropenia, due to various reasons, approximately half exhibited low IgG3 levels, supporting the idea that B-cell reactions are important for development of these neutropenias.37 Contrary to expectations, those with the combination of neutropenia and IgG3 deficiency did not have a greater risk of bacterial infections.37 Further studies on the Greek patients have shown a low-grade activation of cytokine and chemokine networks. Serum levels of many of macrophage-derived proinflammatory mediators (including interleukin [IL]-1β, tumor necrosis factor [TNF]-α, soluble TNF-RI (p55), TGF-β1, IL-6, RANTES, and IL-8) were significantly increased, while the levels of lymphocyte-derived mediators (soluble CD23, IL-4, IL-2R and interferon-gamma) appeared normal.58 Other findings in the Greek patients pointed to the existence of an activated endothelium, which may enhance neutrophil emigration into the tissues, thus contributing to neutropenia.58 Thus, neutropenia in Greek patients may result from a combination of factors, such as reduced neutrophil production and as a consequence of accelerated neutrophil extravasation or sequestration.58 These findings point to new explanations of the mechanisms of chronic mild/moderate neutropenias.

Treatment was rarely needed, but most patients respond to G-CSF.58 Case reports indicate beneficial effects of chloramphenicol on the ANC.1,20

**Table 2. Diseases Associated With Secondary Autoimmune Neutropenia**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune blood disorders (Evans syndrome)</td>
<td></td>
</tr>
<tr>
<td>Autoimmune thrombocytopenia, hemolytic anemia</td>
<td></td>
</tr>
<tr>
<td>Generalized and organ-specific autoimmune disorders</td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematosus, rheumatoid arthritis/Felty’s syndrome,</td>
<td></td>
</tr>
<tr>
<td>scleroderma, Sjögren’s syndrome</td>
<td></td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Malignant lymphoproliferative disorders</td>
<td></td>
</tr>
<tr>
<td>Leukemia, lymphoma (Hodgkin, non-Hodgkin)</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>Infectious mononucleosis (Epstein-Barr virus), Castleman’s disease (human herpes virus 8), HIV-infection, leishmaniasis</td>
<td></td>
</tr>
<tr>
<td>Hypogammaglobulinemia</td>
<td></td>
</tr>
<tr>
<td>Autoimmune lymphoproliferative syndrome (Canale-Smith syndrome)</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3. Types of Immune Neutropenia**

| Neutrophil-specific alloantibodies                                      |           |
| Autoimmune neonatal neutropenia                                        |           |
| Neutrophil-specific autoantibodies                                     |           |
| Primary autoimmune neutropenia (of infancy, adults)                   |           |
| Secondary autoimmune neutropenia (systemic lupus erythematosus, rheumatoid arthritis, organ-specific autoimmune disease, other blood autoimmune diseases, malignant lymphoproliferative diseases) |           |
| Circulating immune complexes                                           |           |
| Systemic lupus erythematosus, rheumatoid arthritis (Felty syndrome)   |           |
| Large granular lymphocytosis/neutropenia*                             |           |
| Idiopathic, rheumatoid arthritis, clonal                              |           |

* Reported in references 5 and 49.
allotypic variants of the phosphatidylinositol glycan–
linked neutrophil FcγRIIb. One series of 18 subjects
found anti–NA1-specific antibodies in five sera, anti-
NA2 in four, and anti-NB1 in two. Isoantibodies,
antibodies directed against the whole receptor (anti–
pan-FcγRIIb), occur when the receptor is missing
(gene deletion) from the mothers’ neutrophils, a con-
dondition known as isooimmune neonatal neutropenia. In
the past the FcγRIIb antigen was described as
ND1.69 Less than 1% of Caucasians have a deletion of
this gene and may become immunized against it.18

Autoimmune Neutropenia

Autoimmune neutropenia (AIN) is defined as a
(chronic) neutropenia in which autoantibodies
against neutrophil autoantigens can be detected by
methods such as leukoagglutination, neutrophil im-
munofluorescence, and/or monoclonal antibody im-
mobilization of neutrophil antigens (MAINA). Neu-
trophil-bound autoantibodies are present and the
autoantibodies show glycoprotein or even antigenic
specificity. AIN is a relatively benign, nonfamilial
disorder.

Idiopathic or primary AIN (or benign neutropenia
of childhood) is rare, found predominantly in chil-
dren below 2 years of age,46,47 and is more frequent in
females (54%) than males (46%).8,11 The disease is
characterized by mild to moderately severe recurrent
infections, including benign bacterial infections of
the skin or the oropharynx, but rarely pneumonia.
Infections start 1 to 15 months after birth and recov-
ery is spontaneous in 7 to 73 months.15

The total leukocyte count may be normal but there
is severe neutropenia (median ANC, 250/μL), often
with monocytosis and sometimes eosinophilia. The
bone marrow is normal or hypercellular and often
shows a marked reduction of segmented forms. Se-
rum G-CSF levels are normal, increasing only during
active infections.9 Skin windows reveal a delayed
appearance of neutrophils. The neutrophil count may
rise upon administration of corticosteroids, epineph-
rine, or G-CSF, or when infection is present.

Treatment is usually not necessary; however, most
patients are given prophylactic cotrimoxazole.8 Im-
munosuppressive therapy is not required, although
corticosteroids may be effective in inducing a remis-
ion. In case of infection, antibiotics and high-dose
intravenous immunoglobulin (IVIG) or G-CSF are
the treatments of first choice.7,16 Upon discontinua-
tion of these drugs, relapse often occurs.

Neutrophil-specific autoantibodies are detectable by
leukoagglutination and/or immunofluorescence in
most patients, and are autoanti-NA1 or sometimes
autoanti-NA2. We studied 28 patients and detected
specific anti–NA1 or sometimes anti-NA2 in only the
21 cases with primary AIN, presenting at less than 1
year of age6 (Table 6). All eventually recovered sponta-
neously. We also found an increased incidence of
the NA1-phenotype, in contrast to secondary AIN
found in seven children (in association with Evans
syndrome, autoimmune hemolytic anemia, thrombo-
cytopenia or thyroiditis or insulin-dependent dia-
betes mellitus, combined immune deficiency), pre-
senting at an age of 0.5 to 15 years, who all had
pan-reactive autoanti-FcγRIIb antibodies and a
chronic course. Due to its prenatal onset, AIN has
also been reported as congenital AIN in two prema-
ture neonates.13

Table 4. Clinically Important Human Neutrophil Alloantigens

<table>
<thead>
<tr>
<th>Glycoprotein</th>
<th>Antigens*</th>
<th>Frequency (%)</th>
<th>Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>FcγRIIb</td>
<td>HNA-1a (NA1)</td>
<td>58</td>
<td>FCGR3B*01</td>
</tr>
<tr>
<td></td>
<td>HNA-1b (NA2)</td>
<td>88</td>
<td>FCGR3B*02</td>
</tr>
<tr>
<td></td>
<td>HNA-1c (SH or NA3)†</td>
<td>5-38</td>
<td>FCGR3B*03</td>
</tr>
<tr>
<td>Glycoprotein 50-64 (CD177)†</td>
<td>HNA-2a (NB1)</td>
<td>94</td>
<td>CD177*01</td>
</tr>
<tr>
<td>Glycoprotein 70-95</td>
<td>HNA-3a (MART)</td>
<td>99</td>
<td>CD11B*1</td>
</tr>
<tr>
<td>CD11b integrin αL chain</td>
<td>HNA-5a (OND)</td>
<td>96</td>
<td>CD11A*1</td>
</tr>
</tbody>
</table>

NOTE. More detailed genetic analysis has revealed that one alternate allele of NA1 (NA1*02) and four alternate alleles of NA2 (NA2*02, NA2*03, NA2*04, and NA2*05) exist, notably occurring in blacks.53
* Based on Bux.12 Previously used nomenclature is given in parenthesis.
† Appears closely related to or identical with PRV-1, a novel member of the uPAR receptor superfamily.39,63
‡ Expression of the human neutrophil alloantigen (HNA)-1c is often accompanied by triplication of the FcγRIIb gene.41

Table 5. Specificity of Neutrophil Alloantibodies in AIN

<table>
<thead>
<tr>
<th>Specificity</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti–HNA-1a</td>
<td>5</td>
</tr>
<tr>
<td>Anti–HNA-1b</td>
<td>2</td>
</tr>
<tr>
<td>Anti–pan-FcγRIIb (ND1)</td>
<td>4</td>
</tr>
<tr>
<td>Anti–HNA-2a</td>
<td>1</td>
</tr>
<tr>
<td>Anti–HNA-3a</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>8</td>
</tr>
</tbody>
</table>

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Primary AIN is a very peculiar disease. As yet no explanation exists for its early and transient occurrence or its typical specificity. We did not find an increase of NA2-positive mothers in our series (unpublished data), making a transplacental origin unlikely.

Secondary AIN with an associated disorder (autoimmune disorder of the blood or of organs, or a systemic autoimmune disease; see Table 6) is more frequent in adults, peaking at age 40 to 60 years, and known as adult autoimmune neutropenia.

**Autoimmune Lymphoproliferative Syndrome**

Children with secondary AIN should be tested for autoimmune lymphoproliferative syndrome (ALPS), a rare childhood disorder characterized by lymphadenopathy, splenomegaly, and autoimmunity (Table 7). The autoimmune diseases include autoimmune neutropenia, hemolytic anemia, and thrombocytopenia (Evans syndrome). Patients with ALPS have increased numbers of circulating double-negative T cells (>20%) and profoundly impaired apoptosis of activated T cells incubated with an anti-Fas antibody. ALPS is caused by Fas mutations (all heterozygous), which impair signal transduction. Autoimmune manifestations of the disease persist into adolescence. Neoplasms (malignant lymphoma, hepatocellular carcinoma) may develop in adulthood.

**Adult AIN**

AIN in adults is also rare. Patients with idiopathic neutropenia often have a positive direct neutrophil immunofluorescence test (NIFT) but negative sera and/or neutrophil eluates. Thus, false-positive tests are frequent, due, for example, to occupancy of surface FcR by immune complexes or immunoglobulins, simulating antibodies to neutrophils. Only in a few cases are neutrophil-antigen-specific autoantibodies found: autoanti-NA1, -NB1, -pan-FcR-IIIb, and -CD11b/CD18 (CR3) complex have been detected (and our unpublished data).

Precursor autoantibodies causing ablation of the whole neutrophil series (pure white blood cell aplasia) have also been postulated to occur, but this remains to be confirmed.

**Treatment of Adult AIN**

An important motto in the treatment of adult AIN is: *Do not treat a neutrophil count but a patient!* The classical therapeutic approach (corticosteroids, high-dose IVIG, splenectomy, azathioprine, cyclophosphamide) is rarely indicated today. When infections occur, antibiotics together with G-CSF is the treatment of first choice. An important effect of G-CSF is that by stimulating neutrophil production, in vivo absorption and consumption of autoantibodies also occurs, leading to their disappearance from the circulation.
A number of patients with severe AIN have demonstrated only transient responses with corticosteroids, antilymphocyte globulin, and G-CSF, and are resistant to treatment with azathioprine, cyclosporin, and IVIG. A course of intravenous Campath-1H monoclonal antibody in these patients resulted in prolonged hematologic responses.\textsuperscript{38,71}

**Neonatal Pre-eclampsia–Associated Neutropenia**

Absolute neutropenia (ANC < 1,500/μL), lasting longer than 72 hours after birth, may occur in very low birthweight neonates with a maternal history of severe pregnancy-induced hypertension.\textsuperscript{26} Treatment with recombinant G-CSF increases neutrophil counts strongly and reduces the incidence of neonatal sepsis.\textsuperscript{40,44}

**Idiosyncratic Reactions and Infections**

Acute, and thus transient, neutropenias are often idiosyncratic drug-induced reactions, although a causative drug is not always identified. In other cases, infections might have caused the reaction.

**Drugs**

Traditionally, idiosyncratic drug-induced neutropenias were believed to be caused by toxic or immune/allergic reactions.\textsuperscript{62} However, we have a poor understanding of which mechanism leads to an individual case of agranulocytosis. There are some well-characterized pathophysiology: antineutrophil antibodies related to aminopyrine, cytotoxic T cells, haptns, autoimmune reactions, polymorphism for drug-metabolizing enzymes or for cytokine and HLA systems, and oxidative and other modifications of drugs. Some drugs, such as penicillin and thyrostatics, have been suggested to cause agranulocytosis by several mechanisms. Few laboratory methods are validated, partly because of the unexpected appearance of these rare patients. For clozapine-induced neutropenia,\textsuperscript{70} multiple steps include the patient’s genetics (for example, polymorphisms in the TNF and HLA systems) as a prerequisite,\textsuperscript{64,74} and subsequent activation of proinflammatory cytokines leads to generation of superoxide ions and hydrogen peroxide, which is necessary for the metabolism of clozapine to the reactive nitrosonium ion in neutrophils.\textsuperscript{59} This ion causes glutathione and adenosine triphosphate depletion, a process that has been shown to cause neutrophil apoptosis. Treatment is often with G-CSF, although no evidence-based clinical data support its use.\textsuperscript{22,61} IVIG has also been advocated.\textsuperscript{65}

**Infections**

Many infectious agents can cause transient neutropenia.\textsuperscript{36} HIV infection as well as its treatment is associated with neutropenia. Infections may limit therapy, but respond to G-CSF in lower doses than required for chronic severe neutropenia.\textsuperscript{2} Although several reports address the possibility that parvovirus B19 can cause neutropenia, few fulfill Koch’s postulate in order to assign a causative role.\textsuperscript{29,32}

Apart from acute viral infections (influenza, measles, rubella, hepatitis), some bacteria might also confer acute neutropenia. In severe sepsis, particularly in alcoholics,\textsuperscript{35} neutropenia is a sign of poor prognosis. Mechanisms are not well characterized but might include sequestration of neutrophils in the capillary beds of the lungs. It is also possible that ethanol per se has myelotoxic effects and impairs the ability of a major contributor of G-CSF to generate this growth factor.\textsuperscript{35} G-CSF treatment might be of value for those patients.

Human granulocytic erlichiosis was recently identified as a cause of transient neutropenia (and thrombocytopenia).\textsuperscript{25} Likewise, leishmaniasis should be suspected in patients with neutropenia, thrombocytopenia, and splenomegaly who have traveled in endemic regions.

**Conclusion**

With the introduction of new assays for auto- and alloantibodies it has been possible to characterize immune neutropenias better and allow reclassification of many cases with a previous diagnosis of idiopathic neutropenia. Likewise, signs of activation of the immune and inflammatory systems in other cases with idiopathic neutropenias suggest that such reactions are involved in the emergence and perpetuation of this condition. Although some insight as to mechanisms for drug-induced neutropenias has also been gained in recent years, much is still to be understood in order to predict and identify the causative drug.

**References**


