Neutropenia frequently complicates infection due to human immunodeficiency virus (HIV). The etiology of neutropenia in this setting includes bone marrow infection or infiltration, myelosuppressive therapies, the presence of antibodies to HIV, and accelerated apoptosis. Protection against microbial invaders by neutrophils is further compromised by impaired chemotaxis and phagocytosis, production of toxic oxygen species, and expression of cellular adhesion molecules. Neutropenia is a significant risk factor for bacterial infection in HIV-infected patients. Endogenous cytokines, such as granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor, regulate neutrophil count and function. Treatment with recombinant human methionyl G-CSF (filgrastim) has lessened neutropenia in patients with HIV infection. Clinical trials have shown that the incidence of bacterial infections and the number of consequent days of hospitalization for HIV-infected patients receiving filgrastim therapy are lower. Filgrastim treatment also allows administration of larger doses of myelosuppressive agents.

Impaired cell-mediated immunity has long been considered the hallmark of HIV disease. It is now recognized that bacterial infections, especially bacteraemia, occur more frequently and may be refractory to therapy in HIV-infected patients [1–4]. Recent investigations of the effects of HIV disease on neutrophil count and function have led to an understanding of the importance of neutrophil impairments in the evolution of HIV-related bacterial infections and to new treatment strategies for correcting such impairments [5–9].

Neutropenia and Neutrophil Dysfunction in HIV Infection

Neutropenia is a commonly recognized consequence of HIV infection [10]. Neutropenia or monocytopenia has been reported to occur in 35%–75% of patients with AIDS and in 10%–20% of patients with AIDS-related complex [11]. Data compiled from a hospital database in Brussels showed that 560 (34%) of 1647 patients with HIV infection had had at least 1 episode of neutropenia (absolute neutrophil count [ANC], <1000 × 10³/L) [12].

The etiology of neutropenia is multifactorial. Direct bone marrow infection or infiltration may occur. In one series of patients with AIDS defined according to the Centers for Disease Control and Prevention, Mycobacterium avium/Mycobacterium intracellulare was recovered from 20% of bone marrow biopsy specimens [13]. Bone marrow stromal cells may also be directly infected with HIV [14], although this point remains controversial. In addition, neoplastic cells such as those of B-cell lymphoma may be present.

Treatment-related causes of neutropenia may compound infective and neoplastic causes. Frontline therapies for HIV disease, such as zidovudine, ganciclovir, and trimethoprim-sulfamethoxazole, are myelosuppressive, and therapy at suboptimal doses may be necessary [15, 16]. Myelosuppressive chemotherapeutic agents may be required for treatment of an associated neoplasm [17].

Nutritional deficiency, as reflected in declining vitamin B₁₂ levels [18], and the presence of antibodies to HIV envelope glycoprotein (gp120), which suppress bone marrow progenitors [19], also have been implicated as causal factors in neutropenia. Apoptosis, the normal mechanism of programmed cell death characterized by DNA fragmentation, is markedly accelerated in neutrophils in patients with HIV infection, tending to shorten cell survival [20].

Neutrophils are of major importance in the host defense against bacterial and fungal infections [21, 22]. The presence of decreased numbers of neutrophils in patients with HIV infection is accompanied by multiple abnormalities of neutrophil function, which compromise the ability to kill bacterial and fungal invaders. These abnormalities include impairments of chemotaxis and phagocytosis [5, 23], expression of cellular adhesion molecules at the surface of the neutrophil, production of toxic oxygen species, and actin shedding [24, 25]. Impaired
neutrophil function has been demonstrated in both symptomatic and asymptomatic patients with HIV infection [26, 27]. Additional factors may compromise host defense against microbes in HIV infection. An increased number of apoptotic neutrophils, which are unable to function as host defenders, are found in HIV-infected individuals [28]. Moreover, neutrophils obtained from HIV-infected patients at different stages of disease have impaired respiratory burst in response to in vitro stimulation [8].

Role of Granulocyte Colony-Stimulating Factor (G-CSF) in Neutrophil Regulation

Granulocyte colonies are regulated by a number of cytokines. Two of the 20 cytokines that have been identified, G-CSF and granulocyte-macrophage colony-stimulating factor (GM-CSF), play a major role in stimulation of granulopoiesis and regulation of microbicidal functions [29]. All neutrophils coexpress receptors for these factors, although subpopulations of circulating neutrophils may respond differently to colony-stimulating factors.

G-CSF is the major determinant of the number of circulating neutrophils. Mice genetically deficient in G-CSF are neutropenic, although some circulating neutrophils are present, probably in response to other growth factors [30]. In contrast, mice deficient in GM-CSF have normal levels of circulating neutrophils.

G-CSF is a major mediator of the response to situations that require increased neutrophils and host defense. Increased levels of endogenous G-CSF have been demonstrated in response to infection and trauma in otherwise normal individuals [31, 32]. The G-CSF level is elevated in neutropenia, as well as in fever, with and without neutropenia [33]. G-CSF levels also correlate with levels of bacteremia, especially bacteremia due to gram-negative organisms [33]. Furthermore, fever is accompanied by increased levels of IL-6 and G-CSF, but not of GM-CSF [33].

Understanding the role of G-CSF in neutropenia has led to investigations of the effect of exogenously administered recombinant G-CSF (rG-CSF) on neutrophil counts in neutropenic patients and normal volunteers. rG-CSF administered for several days increases neutrophil production and accelerates release of these cells into the peripheral circulation [34]. Moreover, sustained neutrophilia has been achieved with daily rG-CSF injections in patients with neoplasms [35–37].

In addition to increasing neutrophil counts, rG-CSF administration has been shown to improve the microbicidal activity of neutrophils. Several in vitro studies of neutrophil function have demonstrated that rG-CSF induces improvement in several functions necessary for bacterial killing [38–42]. These effects include enhancement of adherence, phagocytosis, respiratory burst, and degranulation. Improvement in chemotaxis has been reported by some investigators, although the effect of rG-CSF on this function is unclear [43–46].

Improvement in other aspects of neutrophil function with rG-CSF administration have also been demonstrated in vitro. Incubation of neutrophils from HIV-infected patients with rG-CSF results in suppression of apoptosis, with improved longevity and sustained function of neutrophils [20]. Antibody-dependent cell-mediated toxicity toward HIV-infected lymphocytes is also enhanced by both rG-CSF and recombinant GM-CSF [47].

Improvement in microbicidal activity by rG-CSF administration has been demonstrated in some in vivo studies, although the results are variable. In 1 study, neutrophils obtained after 5 days of rG-CSF administration had improved ability to kill Aspergillus or Rhizopus [48]. No effect was observed on killing of Candida albicans. In contrast, another study did not find enhanced killing of Staphylococcus aureus, Pseudomonas aeruginosa, or C. albicans in control subjects or patients with hematologic disorders following treatment with rG-CSF [49].

G-CSF in HIV Infection

Evidence suggests that the neutropenia and neutrophil dysfunction associated with HIV infection are at least partly mediated by abnormal regulation by cytokines. Whereas levels of endogenous G-CSF are increased in afebrile patients with chemotherapy-induced neutropenia, these levels in HIV-infected patients with neutropenia are lower than those in nonneutropenic HIV-infected patients and healthy control subjects [50]. Levels of endogenous GM-CSF have also been shown to be very low in patients with stage IV HIV infection who have low CD4+ T lymphocyte counts [51] and in HIV-infected injection drug users [52].

Stromal cultures enriched with microvascular endothelial cells (the most common bone marrow stromal cells infected with HIV [5%–20%]) have been shown to express normal levels of G-CSF and other hematopoietic growth factors, although the release of G-CSF in response to IL-6 is significantly reduced [14].

The role of endogenous G-CSF in HIV-related neutrophil dysfunction has led to the investigation of treatment of HIV-infected patients with recombinant human methionyl G-CSF (r-metHuG-CSF; filgrastim). This bacterially synthesized recombinant protein has been demonstrated to increase neutrophil counts in several clinical trials involving neutropenic patients with HIV infection [53–55]. Neutropenia was reversed in 98% of patients with ANCs <1000 × 10^9/L (median period to reversal, 2 days) [12]. A 10-fold increase in neutrophil counts was observed in 22 neutropenic HIV-infected patients treated with filgrastim for <2 weeks. A 24-week study of 258 HIV-infected patients with ANCs of 750–1000 × 10^9/L gound that filgrastim treatment provided an immediate and sustained increase in the mean ANC and significantly decreased the incidence of severe neutropenia [56].

Evidence suggests that dose reduction or discontinuation of
myelosuppressive therapies such as ganciclovir, trimethoprim-sulfamethoxazole, and pyrimethamine, as may be necessitated by neutropenia, are associated with disease progression and death [57–60]. Filgrastim treatment has been shown to support neutrophil counts during administration of myelosuppressive agents and to allow tolerance of greater dosages of these drugs [7, 9, 12, 61]. In a study of 200 HIV-infected patients, >80% of those treated with filgrastim were able to have ganciclovir, zidovudine, trimethoprim-sulfamethoxazole, or pyrimethamine therapy increased, maintained, or added to their regimen [12].

In addition to reversal of neutropenia, improvements in neutrophil function in the presence of HIV infection have been demonstrated following filgrastim administration. Defects in bacterial killing and in oxidative metabolism, as reflected in the chemiluminescent response of oxygenated luminogenic substrates, were corrected by filgrastim in a study of blood specimens from 77 HIV-infected patients at different stages of disease and from normal control subjects after administration of filgrastim daily or every other day for 8 days [8]. Moreover, the ratio of unprimed to primed opsonin-dependent chemiluminescence diminished, indicating that the chronic in vivo activation of neutrophils seen in HIV infection was decreased by filgrastim.

**Bacterial Infection in HIV-Infected Patients and Its Prevention with Filgrastim**

Decreased numbers of neutrophils with a decreased ability to provide defense against microbial invaders is reflected in the increased incidence of bacterial infections among patients with HIV infection [1, 2, 4]. Such infections, which are an important cause of morbidity and mortality in HIV disease, are directly associated with neutropenia. Although a study found that HIV-infected patients were not more likely to have a bacterial infection during neutropenic periods than during nonneutropenic periods [62], several other reports have indicated that neutropenia is an independent risk factor for bacteremia in HIV-infected patients [61, 63, 64]. For example, in a prospective observational study at a university teaching hospital, the relative risk of bacteremia was 14.9 for HIV-infected patients with ANCs <1000 × 10⁴/L compared with nonneutropenic HIV-infected control subjects [65].

The risk of infection also correlates with the degree of neutropenia [61, 64–66]. In a study of 118 neutropenic patients matched with nonneutropenic HIV-infected control subjects, the relative risk of bacterial infection was 2.33 for patients with ANCs <1000 × 10⁴/L and 7.92 for those with ANCs <500 × 10⁴/L [65]. The risk of hospitalization for bacterial infection and the number of days of hospitalization as an indicator of morbidity are also significantly correlated with the ANC. A retrospective analysis of 2047 HIV-infected patients revealed a significantly increased incidence of hospitalization for bacterial infection among patients with ANCs <750 × 10⁴/L [61]. Multivariate analysis revealed that the severity and duration of neutropenia are independent predictors of these events.

A recent clinical trial of therapy with filgrastim indicated that reversal of HIV-associated neutropenia decreases morbidity and mortality associated with bacterial infections and improves survival [56]. In that study, the incidence of bacterial infections was assessed among 258 HIV-infected patients with ANCs of 750–1000 × 10⁴/L. Patients received filgrastim treatment 1–3 times per week for 24 weeks to maintain the ANC at between 2000 and 10,000 × 10⁴/L. Filgrastim-treated patients developed 31% fewer bacterial infections than did control subjects. Moreover, the relative risk of severe bacterial infection was 0.46 for filgrastim-treated patients compared with control subjects. A significant decrease in the number of days of hospitalization, which was primarily due to the effect of decreased bacterial infections, was also demonstrated.

A preliminary report has indicated that filgrastim therapy improves survival in HIV-infected individuals [9]. After receiving filgrastim therapy, 71 neutropenic HIV-infected patients with CD4 cell counts <50 × 10⁴/L had significantly longer survival than did neutropenic HIV-infected controls. The filgrastim-treated patients also required fewer days of hospitalization than did the controls, suggesting that filgrastim improved both the length and quality of life in these patients.

**Conclusion**

Neutropenia and neutrophil dysfunction with compromised defense against bacterial invaders is an important cause of morbidity and mortality in patients with HIV infection. Falling neutrophil counts also prevent optimal use of aggressive therapies against HIV infection and its opportunistic and neoplastic complications. Understanding the role of cytokines, particularly G-CSF, has resulted in the development and evaluation of rG-CSF therapy, which sustains neutrophil counts, decreases the incidence of bacterial infection, and allows more aggressive treatment of patients with HIV infection. Preliminary studies indicate that filgrastim (r-metHuG-CSF) may prolong survival and improve the quality of life in patients with HIV infection.

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