The transfusion of neutrophils, or granulocyte transfusion therapy, has long been considered as a logical approach to the treatment of severe bacterial and fungal infections in patients with prolonged neutropenia or intrinsic defects in neutrophil function. However, despite numerous clinical trials, the efficacy and safety of granulocyte transfusion therapy remain controversial. Efficacy has been compromised largely by the inability to transfuse sufficient quantities of functionally active neutrophils to patients. The recent use of recombinant granulocyte colony-stimulating factor (G-CSF) to mobilize neutrophils in donors before centrifugation leukapheresis has rekindled interest in the potential clinical applications of granulocyte transfusion therapy. This review focuses on the use of G-CSF for donor stimulation and summarizes the current status of granulocyte transfusion therapy for treatment of infectious diseases.

Neutrophils (polymorphonuclear leukocytes [PMNL]) play an integral role in host defense against potential bacterial and opportunistic fungal pathogens. The expanding use of dose-intensive cancer treatment strategies, such as high-dose chemotherapy and bone marrow and hematopoietic stem cell transplantation, has increased the frequency of prolonged neutropenia and, consequently, the risk of severe infections in affected patients [1]. Furthermore, opportunistic fungal infections and antibiotic-refractory bacterial infections remain important causes of morbidity and mortality in neutropenic individuals [2]. These factors have prompted investigators to explore alternative or adjunctive approaches to the management of infections during profound and prolonged neutropenia, including new methodologies for the collection and transfusion of PMNL.

The PMNL is the most common leukocyte in the peripheral blood of healthy persons, and healthy individuals weighing 70 kg produce \( \sim 10^{11} \) PMNL per day [3]. PMNL have a life span of \( \sim 9-10 \) days (from the premature myeloblast to death) and spend their lives in 3 main areas of the body as they pass from bone marrow to peripheral blood and into tissues [4]. The circulating and margilated pools are in a dynamic equilibrium, with PMNL moving back and forth between the 2 pools. During infection, PMNL in the blood are attracted to sites of infection by chemo-tactic factors or chemotaxins, which are generated by the interaction of host cells and factors with pathogens [5].

Historical Background

The possibility of enhancing host defenses by the infusion of neutrophilic granulocytes has been explored for \( >65 \) years. In 1934, Strumia [6] injected a “leukocyte cream” intramuscularly into patients with neutropenia, and the injection increased the peripheral PMNL count in 9 of 10 patients. Normal leukocytes were first transfused in 1953 and involved lethally irradiated dogs who received isogeneic leukocytes [7]. The same investigators also demonstrated that rat leukocytes retained some physiological activity when injected into neutropenic mice [8]. In the 1960s, Freireich et al. [9] used patients with untreated chronic myelogenous leukemia (CML) as donors for PMNL; however, because of a lack of donors, the possibility of cell engraftment, and the risk of transmission of potential pathogens, the collection of PMNL from CML patients failed to become established [10, 11].

In general, 2 methods, namely filtration leukapheresis and centrifugation leukapheresis, historically have been used to obtain cells from healthy donors for granulocyte transfusion therapy. Filtration leukapheresis, using nylon fibers, yields a large number of PMNL, but, unfortunately, the filters traumatize and activate cells, thereby promoting granule release and complement activation [12]. Cells obtained by filtration leukapheresis also have a shortened life span and an impaired tissue response [12]. Furthermore, on-line collection by filtration leukapheresis has been associated with transient, profound neutropenia in the donor during the first 30 min of leukapheresis, which suggests the possibility of PMNL pulmonary sequestration during the procedure [13].

Continuous-flow centrifugation leukapheresis, which cur-
rently is the standard methodology for collection of PMNL for clinical purposes, was developed in the 1960s. To elevate the peripheral blood PMNL count and increase collection yield, donors were routinely treated with corticosteroids. With the use of hydroxyethyl starch to accelerate erythrocyte sedimentation, the collection of $10 \times 10^9$ to $30 \times 10^9$ PMNL (10%–30% of the normal daily production of an adult) was possible [14]. However, this number of cells was not consistently sufficient for the effective treatment of infections in neutropenic patients. Because of inconsistent efficacy, along with improvements in antibiotic therapy and reports of adverse events, including serious pulmonary injury that is possibly attributable to granulocyte transfusion therapy, interest in this form of therapy significantly waned in ensuing years [10].

The basis for renewed interest in granulocyte transfusion therapy is 2-fold. First, there is a need for effective treatment of infections in severely neutropenic patients receiving dose-intensive cancer therapy regimens. Second, the discovery of the potential of recombinant human granulocyte colony-stimulating factor (G-CSF) and advances in collection techniques have made it possible to transfuse a larger number of cells.

G-CSF

The number and function of PMNL are regulated by cytokines, including CSFs, especially G-CSF [15]. The essential role of G-CSF in the normal regulation of PMNL development was demonstrated in studies conducted with the G-CSF knock-out mouse. Mice rendered G-CSF deficient by targeted disruption of the G-CSF gene in embryonic stem cells develop chronic neutropenia associated with a 50% reduction of PMNL precursor cells in the bone marrow. G-CSF knock-out mice exhibit a markedly impaired ability to control infection by *Listeria monocytogenes* and do not develop sepsis-related neutrophilia [16].

The G-CSF gene is located on chromosome 17 q21-22, near other genes involved in the development of neutrophilic granulocytes [17]. In its native form, the G-CSF protein is O-glycosylated with a molecular mass of 20 kDa. Structurally, it is composed of 4 helices connected by amino acid loops, which contribute importantly to the molecule’s 3-dimensional structure [18]. Approved pharmaceutical forms of G-CSF for human use include a recombinant nonglycosylated protein expressed in *Escherichia coli* (filgrastim; Amgen) and a glycosylated form expressed in CHO cells (lenograstim; Chugai Pharmaceuticals). Both forms have similar biological activities and bioavailability after subcutaneous (sc) or intravenous administration.

In addition to its critical role in the regulation of granulopoiesis, G-CSF also improves specific PMNL functional responses when administered in vitro and in vivo. G-CSF has been shown to enhance PMNL chemotaxis, respiratory (oxidative) burst, phagocytosis, and bactericidal activity and to stimulate surface expression of CD11b/CD18, FcγRII (CD32), and FcγRIII (CD64) on PMNL [19–22].

Currently, G-CSF is widely used therapeutically for the treatment of neutropenia, including neutropenia secondary to chemotherapy, radiotherapy, or myelosuppressive drugs, as well as leukemia, idiopathic neutropenia, and aplastic anemia [23–25]. On the basis of randomized trials conducted in patients with chemotherapy-induced neutropenia, G-CSF has been approved for the acceleration of marrow recovery after standard-dose therapy for solid tumors and myeloid malignancies [26, 27]. However, G-CSF administration in patients with severe neutropenia after dose-intensive chemotherapy is less effective because of the lack of responsive hematopoietic precursor cells [28, 29]. In these patients, a period of $\geq 2$ weeks of severe neutropenia is not unusual, and life-threatening bacterial or fungal infections remain a major problem [30]. For infections in this patient population, granulocyte transfusion therapy would appear to be a logical therapeutic approach.

**Technical Considerations**

*Granulocyte donors.* Before the discovery and the development of human growth factors for clinical use, the inability to collect adequate numbers of functional PMNL from healthy donors hindered the development of granulocyte transfusion therapy. Without substantial neutrophilia in the donor, the yield of PMNL obtained by leukapheresis is limited. Corticosteroids conventionally have been used to mobilize PMNL in granulocyte donors. As mentioned previously, this practice allows for the collection of a relatively small number of PMNL ($10 \times 10^9$ to $30 \times 10^9$/leukapheresis), which usually results in only a transient increase in the blood PMNL count when transfused in neutropenic patients [3, 10].

In hematologically normal individuals, administration of G-CSF has been found to be safe and well tolerated. After multiple doses of daily G-CSF, most leukocytes in the peripheral blood of the donor remain mature PMNL; however, small numbers of bands, promyelocytes, metamyelocytes, and myelocytes do begin to appear in the circulation with repetitive G-CSF administration [31]. A slight increase in the absolute number of lymphocytes is also observed, but monocyte counts do not change appreciably. After a 5-day treatment with G-CSF at a dose of 2 $\mu$g/kg/day, no severe adverse effects were reported in 1 study [32]. Moreover, no long-term adverse events have been reported after the administration of G-CSF to healthy individuals. In a study of 19 donors, blood counts 1 year after the collection of G-CSF–stimulated peripheral blood stem cells (PBSC), and the results of a second mobilization and collection were analyzed [33]. Subjects in this study received a regimen of 2–10 $\mu$g of G-CSF/kg/day for 5 days on 2 occasions, separated in time by $\geq 12$ months. One year after the administration of G-CSF, blood counts were normal and unchanged, and the yield of PBSC from the second leukapheresis procedure was similar to the yield achieved from the first collection.

Several studies have demonstrated that the administration of
300 µg of G-CSF sc can elevate the peripheral blood PMNL count 5–6-fold within 12–24 h, compared with a 2–3-fold increase observed after corticosteroid therapy [31, 34]. In addition, recent evidence indicates that the administration of corticosteroids significantly increases the level of neutrophilia induced in normal subjects by single-dose G-CSF [34]. In 1 study, healthy volunteers were randomly assigned to receive each of the following 5 single-dose regimens: (1) G-CSF, 300 µg given sc; (2) G-CSF, 600 µg sc; (3) dexamethasone, 8 mg given orally; (4) G-CSF, 300 µg sc, plus dexamethasone, 8 mg orally; and (5) G-CSF, 600 µg sc, plus dexamethasone, 8 mg orally [34]. All 5 drug regimens induced a rapid neutrophilic response in the subjects, which was evident within 6 h after drug administration and sustained through 24 h. Except for the administration of dexamethasone alone, the maximal PMNL count observed after each regimen occurred at the 12-h time point. Mobilization of PMNL was greatest after the administration of G-CSF (600 µg) and dexamethasone (8 mg); the PMNL count increased >12-fold from a mean baseline value of 3594/µL to 43,017/µL at 12 h. All the drug regimens were well tolerated. The most commonly reported side effects were myalgia and arthralgia, followed by headache. These side effects resolved within 24 h, and no donors requested or required dismissal from the study protocol as a result of these effects.

Enhanced PMNL mobilization in donors effectively results in an enhanced yield of PMNL by centrifugation leukapheresis. Regardless of whether G-CSF or corticosteroids are used for donor stimulation, mature PMNL constitute >75% of the leukocytes in the granulocyte concentrate (authors’ unpublished data). In a recent study, 16 normal subjects received G-CSF (600 µg sc) and dexamethasone (8 mg orally) 12 h before leukapheresis [35]. A mean of 77.4 ± 10⁶ PMNL was collected with each leukapheresis. The functional properties of the PMNL remained normal or near normal. Specifically, the respiratory burst in response to PMA, FMLP, tumor necrosis factor (TNF)-α, and lipopolysaccharide was assessed in PMNL from venous blood after the administration of G-CSF and dexamethasone before leukapheresis and in PMNL obtained from the concentrate after leukapheresis. In the latter case, PMNL retained the respiratory burst activity in response to all 4 stimuli. PMNL isolated from venous blood after the administration of G-CSF and dexamethasone were primed to undergo an enhanced respiratory burst in response to either TNF-α or lipopolysaccharide. In the concentrate, the bactericidal capacity against *Staphylococcus aureus* was normal, and the surface expression of CD11b, CD18, CD14, CD32, and CD64 was increased. In 5 subjects, PMNL were infused ~2–3 h after collection. The half-life for the infused cells was significantly longer than that of normal blood PMNL (20.3 ± 2.1 h vs. 9.6 ± 1.2 h) [35].

A single-dose G-CSF regimen of 450 µg recently was shown to be as effective as 600 µg for the mobilization of PMNL within 12 h in healthy individuals [36]. Use of the lower dose of G-CSF for donor stimulation in granulocyte transfusion programs would result in significant cost savings (~$80 US/donor) for blood banks, without compromising the yield of PMNL in the granulocyte product. In the near future, on the basis of this evidence, the standard regimen for granulocyte donor stimulation probably will be the administration of 450 µg G-CSF sc and 8 mg dexamethasone orally.

**Table 1. Polymorphonuclear leukocyte (PMNL) yield by centrifugation leukapheresis in response to granulocyte colony-stimulating factor (G-CSF)–based donor stimulation regimens.**

<table>
<thead>
<tr>
<th>Reference, author, year</th>
<th>Stimulation regimen</th>
<th>No. of aphereses/donor</th>
<th>Mean no. of PMNL/leukapheresis, ×10⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>[31], Bensinger et al., 1993</td>
<td>G-CSF: 5 µg/kg/day sc ×12 (9–14)</td>
<td>4-12</td>
<td>42</td>
</tr>
<tr>
<td>[37], Caspar et al., 1993</td>
<td>G-CSF: 300 µg sc ×1</td>
<td>1</td>
<td>44</td>
</tr>
<tr>
<td>[38], Hester et al., 1995</td>
<td>G-CSF: 5 µg/kg/day sc ×5</td>
<td>4-5</td>
<td>32-66</td>
</tr>
<tr>
<td>[39], Dale et al., 1998</td>
<td>G-CSF: 600 µg sc ×1, plus dexamethasone, 8 mg po ×1</td>
<td>1</td>
<td>77</td>
</tr>
<tr>
<td>[39], Jendricho et al., 1998</td>
<td>G-CSF: 5 µg/kg/day sc ×5</td>
<td>4-5</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>Prednisone, 60 mg/day po ×5</td>
<td></td>
<td>29</td>
</tr>
<tr>
<td>[40], Peters et al., 1999</td>
<td>G-CSF: 5 µg/kg/d sc ×5</td>
<td>5</td>
<td>2kg²</td>
</tr>
<tr>
<td>[41], Price et al., 2000</td>
<td>G-CSF: 600 µg sc ×1, plus dexamethasone, 8 mg po ×1</td>
<td>1</td>
<td>82</td>
</tr>
<tr>
<td>[42], Adkins et al., 2000</td>
<td>G-CSF: 10 µg/kg sc days 1, 4, 6, and 8</td>
<td>4</td>
<td>56-99</td>
</tr>
<tr>
<td>[43], Hübel et al., 2000</td>
<td>G-CSF: 600 µg sc ×1</td>
<td>1</td>
<td>73</td>
</tr>
</tbody>
</table>

NOTE: iv, intravenous; po, by mouth; sc, subcutaneously.

a Every other day.

b Related to patient’s body weight.
ploy continuous-flow centrifugation leukapheresis, which selectively removes a leukocyte fraction containing predominantly PMNL and returns the red cells and platelets to the donor [45]. Blood from one antecubital vein travels to a pump, where a sedimenting agent, usually hydroxyethyl starch with citrated anticoagulant, is added. The use of hydroxyethyl starch, which increases erythrocyte sedimentation by causing rouleaux formation, doubles the efficiency of leukapheresis and significantly increases the quantity of erythrocytes returned to the donor [10, 46]. Setting the centrifuge apparatus to a higher interface offset improves the collection yield without significant effects to the donor [47].

Granulocyte storage. In current practice, PMNL are collected and transfused as quickly as possible. However, delays in the transfer of the cells from blood bank to recipient are inherent, and daily collection can be difficult. The ability to effectively store PMNL in a functionally active state would be a significant step to improve the feasibility of granulocyte trans- fusion therapy programs in blood banks. One of the factors contributing to the decline in the activity of stored PMNL is spontaneous apoptosis. PMNL die rapidly via apoptosis in vivo and in vitro, and apoptotic cells demonstrate a reduced ability to degranulate, to generate an oxidative burst, or to undergo shape changes in response to external stimuli [48]. Among its physiological effects, G-CSF significantly decreases the rate of PMNL apoptosis in vitro, thereby extending the functional life span of PMNL in culture [49].

Several groups of investigators have explored methods and conditions to maintain PMNL viability and function during storage. In 1 study, chemotaxis and oxidase activity in response to PMA or FMLP, with or without platelet-activating factor in stored PMNL obtained from volunteers who received G-CSF (10 μg/kg/day) for 5 days, were compared with PMNL from subjects without G-CSF treatment [50]. The granulocyte concentrate was stored in apheresis bags at room temperature for up to 48 h. There was a slight decrease of chemotactic activity in the G-CSF–mobilized cells after 24-h storage. PMNL oxidase activity in response to PMA and FMLP plus platelet-activating factor was reduced after leukapheresis compared with that in venous blood PMNL. This activity was reduced further during 48-h storage. In contrast, the FMLP response was increased in the G-CSF–mobilized cells and remained elevated during 24-h storage. Addition of supplemental G-CSF ex vivo to these granulocyte products did not further improve preservation of PMNL function.

The storage of granulocyte products by centrifugation leukapheresis of 9 healthy donors 12 h after the administration of 1 dose of 600 μg G-CSF recently was compared at room temperature (22°C) and at a reduced temperature of 10°C [43]. Although surface expression of β2-selectin declined substantially during storage in both conditions, expression levels of CD11b, CD18, CD14, CD16, CD32, and CD64 were maintained at values >50% of baseline during 48-h storage at 22°C and 10°C. In contrast, although respiratory burst activity was relatively preserved at 22°C, the inducible respiratory burst was greatest in granulocyte product stored at 10°C. Similarly, bac tericidal activity against S. aureus was preserved during storage at subphysiological temperatures, with activity statistically superior at 10°C versus 22°C after storage for 48 h. The granulocyte products retained fungicidal activity against Aspergillus fumigatus, Rhizopus arrhizus, and Candida albicans during storage for 48 h at 10°C. However, despite these promising results, controlled studies must be conducted to assess the circulation kinetics, migration properties, and safety of stored granulocytes when reinfused in vivo.

Clinical Efficacy of Granulocyte Transfusion Therapy

Overall efficacy for the treatment of infections in neutropenic patients. The clinical utility of granulocyte transfusion therapy remains controversial. In 1995, Strauss [51] analyzed 32 studies that reported the outcome of granulocyte transfusion therapy for the treatment of infections in severely neutropenic patients. Overall, 127 (62%) of 206 patients with bacterial sepsis and 39 (83%) of 47 patients with localized bacterial infections responded to granulocyte transfusion therapy. In contrast, granulocyte transfusion therapy failed in 45 (71%) of 63 patients with invasive fungal infections (table 2). However, because most of these 32 reports described uncontrolled studies of small numbers of patients with a diversity of underlying diseases, types of infections, antimicrobial therapy, and management of granulocyte transfusion therapy, interpretation of the pooled data is inherently difficult. Several of the studies included in this analysis were compromised by relatively small quantities of PMNL (< 30 × 10^9 cells/transfusion) transfused to enrolled patients.

Steady progress in cell collection and separation soon led to the initiation of several controlled clinical trials, which are summarized in table 3. These trials employed both filtration and centrifugation leukapheresis techniques for the collection of granulocytes. Despite the technological limitations of seven trials (i.e., use of corticosteroids alone for donor stimulation and

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>No. of treated patients</th>
<th>No. of evaluable patients</th>
<th>No. successfully treated (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial septicemia</td>
<td>298</td>
<td>206</td>
<td>127 (62)</td>
</tr>
<tr>
<td>Sepsis organism unspecified</td>
<td>132</td>
<td>55</td>
<td>18 (46)</td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
<td>5</td>
<td>5</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Pneumonia organism unspecified</td>
<td>115</td>
<td>11</td>
<td>7 (64)</td>
</tr>
<tr>
<td>Invasive fungal infectionsa</td>
<td>67</td>
<td>63</td>
<td>18 (29)</td>
</tr>
<tr>
<td>Localized infections</td>
<td>143</td>
<td>47</td>
<td>39 (83)</td>
</tr>
<tr>
<td>Nonspecific fever</td>
<td>184</td>
<td>85</td>
<td>64 (75)</td>
</tr>
</tbody>
</table>

NOTE. Adapted from Strauss [51]. , Not specified.

a All fungal and yeast infections (i.e., sepsis, pneumonia, and sinusitis) were combined.
Insomnia, which is probably an effect of dexamethasone, oc-
common but usually no more than mild to moderate in degree.
ache, which are probably attributable to G-CSF, were relatively
again. Adverse donor side effects, such as bone pain and head-
patients indicated willingness to participate
atives of the transfusion recipients. Sixty percent of the com-
were community donors, whereas only 10 (6%) donors were rel-
hundred sixty-five (94%) of 175 donors providing transfusions
fections. Nineteen patients received a total of 165 transfusions
severe, antibiotic-refractory bacterial or opportunistic fungal in-
tropenic hematopoietic stem cell transplantation patients with
use of granulocyte transfusion therapy exclusively in pediatric
filtration leukapheresis), 3 trials reported clinical efficacy, and
2 reported partial efficacy. No apparent efficacy was observed in
the remaining 2 trials.
Relatives have conventionally been employed as donors in
granulocyte transfusion programs. Recently, the feasibility of a
community blood bank granulocyte transfusion program using
onrelated community donors stimulated with a single-dose reg-
imen of G-CSF (600 μg sc) plus dexamethasone (8 mg orally)
was examined [41]. The recipients of these transfusions were neu-
tropic hemato poetic stem cell transplantation patients with severe, antibiotic-refractory bacterial or opportunistic fungal in-
fec tions. Nineteen patients received a total of 165 transfusions
(mean, 8.6 transfusions/patient; range, 1–25 transfusions). One
hundred sixty-five (94%) of 175 donors providing transfusions were community donors, whereas only 10 (6%) donors were rel-
atives of the transfusion recipients. Sixty percent of the com-
unity donors initially contacted agreed to participate, and 162
(98%) of these 165 donors indicated willingness to participate
again. Adverse donor side effects, such as bone pain and head-
ache, which are probably attributable to G-CSF, were relatively
common but usually no more than mild to moderate in degree.
Insomnia, which is probably an effect of dexamethasone, oc-
urred in 30% of the donors. Transfusion of $81.9 \times 10^9 \pm
2.3 \times 10^8$ PMNL (mean ± SD) resulted in a mean 1-h posttrans-
fusion PMNL increment of $2.6 \times 10^3 \pm 2.6 \times 10^3 /μL$ and re-
stored the peripheral PMNL count to the normal range in 17 of
the 19 patients. The buccal PMNL response, a measure of the
capacity of PMNL to migrate to tissue sites in vivo, was restored
to normal in most patients after transfusion. Chills, fever, and
arterial oxygen desaturation of >3% occurred in 7% of the trans-
fusions, but these changes were not sufficient to limit therapy.
Infection resolved in 8 of 11 patients with invasive bacterial in-
fec tions or candidemia, which suggests that transfusion of PMNL
from G-CSF/dexamethasone–mobilized community donors are of
benefit in this setting.

Efficacy in the treatment of infections by opportunistic fungal pathogens. PMNL represent the most important line of host
defense against opportunistic fungal infections, which remain
particularly problematic for patients with prolonged and severe
neutropenia. In a series of 1186 marrow transplant patients, 187 (10%) developed a noncandidal fungal infection, of whom
32 (17%) survived [59]. To date, only several small series of
patients treated with granulocyte transfusion therapy for fungal
infections have been reported. Bhatia et al. [60] analyzed 30
patients with systemic fungal infection who received granulo-
cyte transfusion therapy, in addition to appropriate antifungal
agents. Although granulocyte transfusion therapy was well tol-
erated, clinical outcome was unchanged in patients with either
invasive noncandidal infection or candidal sepsis. In contrast,
several encouraging case reports and pilot series of granulocyte
transfusion therapy, in which G-CSF–mobilized granulocytes
were used for fungal infections, recently have been published
[61–64]. Currently, the clinical efficacy of granulocyte trans-
fusion therapy in patients with fungal infections remains un-
clear and has yet to be studied systematically. Clearly, controlled
clinical trials of granulocytes obtained from G-CSF–stimulated
donors will be necessary to establish the proper role of gran-
ulocyte transfusion therapy in the management of fungal in-
fec tions in neutropenic patients.

Efficacy in neonatal sepsis and pediatric infections. The neo-
nate is at particular risk because of the rapid depletion of his
or her bone marrow storage pool and associated release of
immature cells, which are functionally less active than mature
PMNL during infection [65]. In 1989, Strauss [65] reviewed 6
controlled trials in which the efficacy of granulocyte transfusion
therapy for the treatment of neonatal sepsis was analyzed. Four
trials reported a significantly better survival for septic neonates
who received granulocyte transfusion therapy plus antibiotics.
In another prospective study by Cairo et al. [66], 35 neonates
with neutropenia and sepsis received either adjuvant granulo-
cyte transfusion therapy or intravenous immune globulin in-
fusions. Survival was significantly higher in the group that re-
ceived granulocyte transfusion therapy, compared with that of
the group that received immune globulin infusions (100% vs.
64%; $P \leq .03$). No serious complications were noted in either
treatment group.
There have been no randomized clinical trials reporting the
use of granulocyte transfusion therapy exclusively in pediatric

<table>
<thead>
<tr>
<th>Table 3. Controlled clinical trials of granulocyte transfusion therapy in neutropenic patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reference, author, year</strong></td>
</tr>
<tr>
<td>[52], Grav, 1972</td>
</tr>
<tr>
<td>[53], Higby, 1975</td>
</tr>
<tr>
<td>[54], Fortunay, 1975</td>
</tr>
<tr>
<td>[55], Vogler, 1977</td>
</tr>
<tr>
<td>[56], Alavi, 1977</td>
</tr>
<tr>
<td>[57], Herzig, 1977</td>
</tr>
<tr>
<td>[58], Winston, 1982</td>
</tr>
</tbody>
</table>

**NOTE.** AA, aplastic anemia; AL, acute leukemia; ANLL, acute nonlymphocytic leukemia; CL, centrifugation leukapheresis; FL, filtration leukapheresis; NI, not indicated. Adapted in part from Strauss [51].

^a Median.
patients. However, in children undergoing high-dose chemotherapy and hematopoietic stem cell transplantation, the efficacy of granulocyte transfusion appears to be comparable to that observed in adult patients. Of the 7 therapeutic trials shown in table 3, 5 included children. In a phase I/II study by Peters et al. [40], 30 patients (mean age, 10 years; range, 2–23 years) received granulocyte transfusion therapy from G-CSF– or prednisolone-stimulated donors for the treatment of life-threatening sepsis during neutropenia. Granulocyte transfusions were well tolerated, and 20 of 30 patients were alive with complete clearance of infection on day 100 after the first granulocyte transfusion. Specifically, 14 (82%) of 17 patients with bacterial infections and 5 (38%) of 13 patients with fungal infections reportedly benefited from granulocyte transfusion therapy.

Adverse Effects Associated with Granulocyte Transfusion Therapy

Mild reactions to granulocyte transfusion therapy are relatively common, especially chills and fever, which can be reduced in incidence and severity by transfusing granulocytes slowly (i.e., at ~10 x 10⁷/h). Routine premedication of patients receiving granulocyte transfusion therapy is not recommended [67]. More severe side effects (after ~1% of transfusions) are hypotension and respiratory distress, with the latter reportedly occurring primarily when granulocytes and amphotericin B are given concomitantly [67]. Transfusion-related acute lung injury is an uncommon condition characterized by the rapid onset of respiratory distress soon after transfusion [68]. The pathogenesis of transfusion-related acute lung injury is not fully understood. It has been reported to occur after the transfusion of blood components from donors with white cell antibodies, but it has been reported only rarely if the patient has these antibodies [69]. This observation suggests that G-CSF mobilization does not promote pulmonary sequestration. Of interest, transfusion-related arterial oxygen desaturation severe enough to limit therapy was not encountered in the recent phase I/II trial of granulocyte transfusion therapy that used community donors stimulated with a single-dose regimen of G-CSF and dexamethasone [41].

The induction of either alloimmunization or graft-versus-host-disease (GVHD) in patients is a potential complication of granulocyte transfusion therapy. However, alloimmunization secondary to granulocyte transfusion therapy appears to be an obstacle to repeated transfusion only in individuals with congenital disorders of PMNL function (e.g., chronic granulomatous disease). Rapid alloimmunization has not been observed to develop in neutropenic patients who are severely immunosuppressed as a result of dose-intensive chemotherapy or transplant conditioning [41, 70]. Granulocyte transfusion products are routinely irradiated with 15–30 Gy to avoid GVHD [44].

Another concern involving the use of granulocyte transfusion therapy is the effect of transfusion-associated leukocyte compatibility on clinical outcome after subsequent hematopoietic stem cell transplantation. This issue was addressed in a recent study of prophylactic granulocyte transfusion therapy, in which leukocyte compatibility was assessed by a lymphocyte toxicity screening assay against a panel of human leukocyte antigen–delayed cells [42]. After stem cell transplantation, patients who had previously received G-CSF–mobilized granulocytes from incompatible donors experienced delayed PMNL engraftment and a greater number of febrile days that required antibiotic therapy. These findings indicate that granulocyte transfusion therapy has the potential to adversely affect the course and outcome of subsequent hematopoietic stem cell transplantation. Thus, granulocyte transfusion therapy should not be considered for routine management of infectious complications in neutropenic patients; instead, it should be reserved for the treatment of severe, potentially life-threatening opportunistic fungal infections and bacterial infections refractory to conventional antimicrobial therapy in this patient population.

Conclusions

Substantial progress has occurred in the field of granulocyte transfusion therapy during the past decade. A number of important observations have rekindled interest in the clinical use of granulocyte transfusion therapy. These observations include (1) the use of G-CSF to elevate blood PMNL counts in normal donors and significantly improve granulocyte yields by centrifugation leukapheresis, (2) the additive, if not synergistic, effects of donor stimulation protocols using G-CSF plus corticosteroids, (3) the feasibility of using community donors for granulocyte transfusion therapy in a blood bank setting, (4) the demonstration of safety and low toxicity of G-CSF–based granulocyte transfusion therapy in both donors and recipients, and (5) the effective storage of granulocyte products obtained from G-CSF–stimulated donors for ≥24 h.

Despite these promising observations, granulocyte transfusion therapy remains an experimental clinical practice. The therapeutic potential of granulocyte transfusion therapy is currently unproven, and controlled clinical trials will be necessary to establish its indications and efficacy in the management of infectious complications in neutropenic patients.

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