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REVIEW ARTICLE

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Granulocyte transfusion *vs.* neutropenia — is there a chance to win this battle?

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ABSTRACT

Bacterial and fungal infections remain a significant cause of morbidity and mortality in patients with prolonged severe neutropenia that results from the treatment of an underlying haematological malignancy. Granulocyte transfusions have been broadly used to prevent and/or treat life-threatening infections in these patients. The purpose of this review was to answer the question, "Are granulocyte transfusions effective in combating hazardous infections in haematology/oncology patients with neutropenia?".

Key words: haematological malignancy, neutropenia, bacterial infection, fungal infection, leukapheresis, granulocyte transfusion

Introduction

In patients with haematological malignancies (HM), plenty of factors, including dose-intensive chemotherapy and haematopoietic stem cell transplantation (HSCT), may cause severe and persistent neutropenia, resulting in the risk of a compromised immune system and increased susceptibility to opportunistic and life-threatening bacterial and fungal infections. Granulocyte transfusions (GTx), which have been in use for more than 50 years, seem to be a sensible therapeutic approach to this problem [1, 2]. The theoretical potential for granulocyte transfusion was established by early animal studies, which showed that granulocytes transfused to neutropenic dogs were of normal appearance and viability and migrated to the sites of infection [3]. Later, animal models of bacterial and fungal infections supported the efficacy of GTx therapy [4, 5]. In the 1960s, granulocytes were collected from patients with chronic myeloid leukaemia (CML) who had high white blood cell (WBC) counts, using filtration techniques and without blood group compatibility and infectious agent testing. This was the first known use of GTx in humans [6]. Due to the transfusion of malignant cells, this method is contentious to readers today, yet it was thought to be a realistic choice at the time [2, 7]. The increased granulocyte collection efficiency was achieved by the introduction of automated blood cell separators. Apheresis enabled the selective collection of higher doses of granulocytes than would be possible from a unit of whole blood, with the added benefit of less donor red cell loss, ultimately eliminating the need for CML donors [8]. To further enhance leukapheresis, before the procedure, donors were injected with macromolecule starch solutions, which sediment red blood cells (RBC), separating them from the granulocyte layer and increasing the granulocyte yield [9–11]. Donors were also given corticosteroids to increase the amount of WBC in the bloodstream by both stimulating granulocyte release from the bone marrow and limiting their efflux from the peripheral blood. The functional tests carried out on granulocytes collected from both steroid-stimulated and unstimulated donors revealed that their chemotaxis, candidacidal activity, and phagocytosis significantly decreased at 24 hours of *ex vivo* storage [12]. Granulocyte transfusions were eventually reduced to a minor role because of the difficulties in cell collection, GTx-related toxicity, and low clinical efficacy [13]. Early in the 1990s, interest in the therapeutic use of GTx to strengthen host defences was revived by the development of leukapheresis and the clinical use of granulocyte colony-stimulating factor (G-CSF)

[14]. All things considered, there have been significant improvements in the collecting and administration methods since the launch of GTx therapy. Nowadays, granulocytes are collected from related or unrelated donors after priming them with a combination of G-CSF and corticosteroids [15]. Furthermore, even though the therapeutic efficacy of GTx is not well-defined, granulocyte transfusion still holds clinical and research interest. As the results of the latest studies on the efficacy of GTx therapy in neutropenic patients with haematological malignancies have now been published, it seems to be a good idea to review the existing data.

Neutrophils — first responders to a "crime scene"

Neutrophils are the most numerous innate immune cells in the peripheral blood of healthy adults and represent 50–70% of circulating leukocytes. Under physiological conditions, neutrophils are produced in the bone marrow at a rate of 10^9 cells/kilogram of body weight/day [16]. An emergency granulopoiesis takes place in cases of inflammation or infection, enhancing daily neutrophil production [17]. The differentiation of haematopoietic cells into myeloblasts, promyelocytes, myelocytes, metamyelocytes, band cells, and ultimately granulocytes is regulated by a wide range of stimuli [18]. Because of their short life span, neutrophils need to be regularly replenished by the bone marrow precursor cells [19]. Neutrophils die by spontaneous apoptosis, and the liver, the spleen, and the bone marrow are the places in the body where blood is cleansed of dead cells [20]. Neutrophils contain a characteristic segmented nucleus that is made up of 3–5 lobes connected through a thin strip of nuclear material [21]. Their cytoplasm is filled with many little granules, which are a crucial feature of these cells and contain different types of proteins. Based on that, they can be classified as azurophilic, specific, or gelatinase granules. Azurophilic granules' main component is myeloperoxidase (MPO) — the enzyme that triggers the oxidative burst [22–24]. Specific granules mainly include lactoferrin. Gelatinase granules serve as a reservoir for metalloproteases–gelatinase and leukolysin. Thus, the collection of antimicrobial agents, which are necessary for most neutrophils' activities and impact both innate and adaptive immunity, is covered by the granules [25]. Neutrophils are the first leukocytes to reach the sites of inflammation or infection to fight off invading microorganisms [26]. The activation of neutrophils involves endothelial cell adhesion, chemotaxis (migration to inflamed tissues), phagocytosis, degranulation, reactive oxygen species (ROS) generation, and cytokine production. The cytokines released to contribute to the inflammatory process by drawing more leukocytes to the sites of inflammation [27]. As soon as they are activated, neutrophils migrate following the gradient of cytokines and other compounds, adhere to the endothelial cells and pass to the tissues. Then, in the process of chemotaxis, they move towards the sites of inflammation, where they phagocytose and digest pathogens and release ROS [28]. Besides that, neutrophils release several cytokines, such as IL-1, IL-6, and tumour necrosis factor α (TNF-α), and chemical mediators [29]. Neutrophils participate in both efferent (phagocytosis and degranulation) and afferent (release of immunomodulatory molecules) processes that are related to inflammatory and immune responses [30]. Neutrophils quickly perish after performing specific actions in damaged or infected tissues, releasing toxic granular proteins and DNA genomic strands to capture and eliminate invading microorganisms [31, 32].

Granulocyte concentrates in a nutshell

Granulocyte concentrates (GC) are plasma-suspended granulocytes (especially neutrophils) mainly prepared from the whole blood of healthy donors by automatic apheresis using a cell separator. Granulocyte products may also be obtained by pooling up to 12 ABO-matched buffy coats within 18 hours of donation with platelet additive solution added before recentrifugation, which results in the development of a purer pooled granulocyte component. The red cell residue, supernatant, and granulocyte-rich layer (buffy coat) are separated. The buffy coat is then mixed with 70 mL of ABO-matched plasma from one of the donations [33]. To ensure a sufficient number of granulocytes and prolong their survival time, blood donors are pretreated with corticosteroids and/or G-CSF [34–36]. However, the exposure of healthy donors to any form of premedication is controversial from a safety and ethical point of view. Most of the side effects associated with the use of stimulating factors are mild and short-term (headache, muscle pain, or bone pain). Although, there are reports that repeated administration of stimulating factors may cause thrombosis (possibly as a result of the increased number of WBC in the blood), rupture of the spleen, allergic reactions, or bone marrow expansion that leads to flu-like symptoms [37–41]. During apheresis, the collected blood is supplemented by hydroxyethyl starch (HES), which is a sedimenting agent, to improve the separation of granulocytes from erythrocytes. Granulocyte donations are limited to four per blood donor per year due to the possibility of severe itching after HES infusion [37, 42]. Neutrophils that are morphologically and functionally intact are the key elements of GC. The presence of platelets, which are

frequently abundant in GC, helps lessen the recipient's thrombocytopenia. Residual amounts of erythrocytes, plasma, anticoagulants, or sedimentation accelerators are said to have no clinical impact on the GC's recipient. However, due to the relatively high content of erythrocytes, a serological compatibility test must be done before transfusion [43]. Every GC should be irradiated before storage, which does not worsen the function of granulocytes but protects against transfusion-associated graft-versus-host disease (TA-GvHD). GC can be stored without agitation at room temperature for up to 24 hours. After this time, there is a gradual impairment of neutrophil function–from chemotaxis to bactericidal capacity. Because of that, granulocyte transfusion should be done as soon as possible after preparation [44–46]. The therapeutic dose of granulocytes ranges from 1.5 to 3 x 10^8 granulocytes/kilogram of body weight for adults and children and should be over 1 x 10^9 granulocytes/kilogram of body weight for newborns [47, 48]. GC should be administered at least once a day until the expected clinical effect is achieved, meaning fever and/or other symptoms of infection are resolved, or the number of granulocytes increases as a result of the patient's production. However, an increase of fewer than 500 granulocytes/μL up to 4 hours after transfusion is considered unsatisfactory and not promising [49, 50]. Before transfusion, every GC must be subjected to visual quality control. Bag integrity, coagulation, aggregate formation, discolouration, and haemolysis must be checked. Additionally, the product's expiration date, proper assignment to the patient, and complete labelling must all be verified. Any questionable GC should not be transfused [43].

Indications and contraindications for GTx therapy

As mentioned before, neutrophils play a key role in the body's defence responses against microorganisms. Therefore, any quantitative and/or qualitative disorder of these cells significantly increases the risk of life-threatening infections [51]. Neutropenia is a condition in which the absolute number of neutrophils circulating in the peripheral blood is lower than 1500/μL. It can be caused by excessive destruction (chemotherapy, radiotherapy, or autoimmune diseases–Felty's syndrome), decreased production (aplastic anaemia, acute leukaemias, or myelodysplastic syndromes) and inappropriate distribution (splenomegaly) [52]. Neutrophil dysfunction, on the other hand, underlies such conditions as chronic granulomatous disease and Chediak-Higashi syndrome [53, 54]. Therefore, it is believed that GTx should be used in cases of severe infections in the absence of effective antibacterial and/or antifungal drugs, such as 1) infection in a neutropenic patient with a neutrophil count < 500/μL, 2) sepsis in newborns with a neutrophil count < 3000/μL (due to the high mortality rate in this group of patients), 3) recurrent infections in patients with certain congenital neutrophil dysfunction, and 4) bone marrow hypoplasia. In contrast, GTx is contraindicated in patients with no prognosis for the recovery of granulopoiesis, or patients in whom post-transfusion adverse reactions have occurred [49, 50, 55–57]. Patients treated concurrently with amphotericin B also should not receive GTx. It is recommended to maintain an interval of 4–8 hours between the administration of amphotericin B and the GTx therapy. This is because reports are indicating that concomitant therapy with amphotericin B and GTx may increase the risk of severe pulmonary post-transfusion reactions [58, 59]. However, this relationship has not been sufficiently well documented. It should be remembered that post-transfusion complications are observed quite often after granulocyte transfusion. Moreover, it has been suggested that the increased frequency of observed pulmonary complications may be the result of the increased tropism of the transfused neutrophils to the inflammation sites in the lungs [60].

Chronic granulomatous disease

Chronic granulomatous disease (CGD) is a hereditary primary immunodeficiency resulting in recurrent and severe infections, dysregulated inflammation, and autoimmunity. It is caused by the dysfunction of the NADH oxidase complex in phagocytes. The NADPH oxidase complex is made up of membrane-bound and

Table 1. Estimated risks of selected post-transfusion complications [64]

Adverse effect	Risk per blood products transfused
Febrile nonhemolytic transfusion reaction	1 in 900
Acute haemolytic transfusion reaction	1 in 200 000
Delayed haemolytic transfusion reaction	1 in 22 000
Transfusion-associated circulatory overload	1 in 9 000
Transfusion-related acute lung injury	1 in 60 000
Transfusion-associated graft-versus-host disease	1 in 13 000 000

cytosolic proteins that take part in ROS production after neutrophils and monocytes are activated. Genetic mutation in any of the structural subunits of the NADH oxidase complex causes irregularities in the production of ROS that are essential for killing invading microorganisms [61].

Chediak-Higashi syndrome

Chediak-Higashi syndrome (CHS) is a rare autosomal recessive immune disease that is characterized by partial oculocutaneous albinism, bleeding tendency, recurrent and severe infections, and neurological symptoms, such as ataxia or neuropathies. It is caused by the mutation in the lysosomal trafficking regulator (LYST) gene that regulates the synthesis, fusion, and transport of cytoplasmic granules. The mutation disrupts these processes, resulting in enlarged vesicles and non-functional lysosomes, which lead to impaired bactericidal activity [62].

Adverse effects of GTx

After years of clinical practice, it is believed that treatment with blood and its components is irreplaceable and generally safe. However, despite the introduction of best collection methods, testing of donors and recipients, and the blood safety vigilance system, there is still a risk of various post-transfusion complications, from mild to severe, that are life-threatening. Post-transfusion complications constitute a diverse group of adverse reactions to the transfusion of blood products that occur during or shortly after transfusion. Some of them may take months or even years to appear. Hence, it is extremely important to observe the patients before, during, and after the transfusion [63].

Febrile nonhemolytic transfusion reaction

Febrile nonhemolytic transfusion reaction (FNTR) occurs in about 1% of transfusion cases [65–68]. It manifests as a temperature increase of 1°C or greater, chills, hypertension, rigours, tachycardia, and tachypnoea. It is caused by a binding reaction between the recipient's antibodies and the donor's granulocytes, which are the main components of GC. The presence of proinflammatory cytokines in the transfused product may also be the cause [67].

Haemolytic transfusion reaction

A haemolytic transfusion reaction (HTR) is a life-threatening reaction that is triggered by the recipient's antibodies destroying the donor's RBC which may be found in small amounts in the granulocyte concentrate. HTR occurs in cases of donor-recipient ABO mismatch [65–67]. It can be acute (occurring within 24 hours) or delayed (occurring at 24 hours or more). It can result in haemolysis (intravascular or extravascular), fever, chills, jaundice, acute kidney injury, pain, shock, disseminated intravascular coagulation, and death [67, 68].

Septic reaction

Septic reaction is linked to involuntary bacterial infection of blood products, most commonly with *Staphylococcus spp.* and *Streptococcus spp.* — bacteria from the skin microbiome [68, 69]. It occurs in 1 out of every 100 000 units of the transfused product [68, 70]. Symptoms, which include fever, chills, increased heart rate, a drop in blood pressure, and sudden changes in consciousness, usually develop within 24 hours of the transfusion. It is imperative to rapidly isolate the bacteria from the transfused product and/or the patient's blood, identify it, and initiate antimicrobial therapy with broad-spectrum antibiotics [71].

Transfusion-transmitted infection

A transfusion-transmitted infection (TTI) is a virus, parasite, or other pathogens that can be transmitted in donated blood products through a transfusion to a recipient. Preventing the spread of these microorganisms by transfusion is essential. Before each blood donation, donors are screened for signs and symptoms of infectious disease and for activities that might put them at risk for infection. Blood samples taken from them are also tested each time for the presence of infectious agents. Yet, despite careful donor selection and performing screening tests, there is a small but real risk of transfusion-transmitted infection (Tab. 2) [70].

Transfusion-associated circulatory overload

Transfusion-associated circulatory overload (TACO) is one of the most serious risks in transfusion medicine

Table 2. Estimated risks of transfusion-transmitted infections [70]

Pathogen	TTI risk per unit of the transfused product
human immunodeficiency virus (HIV)	1 in 2 000 000
hepatitis C virus (HCV)	1 in 2 000 000
hepatitis B virus (HBV)	1 in 2 000 000
cytomegalovirus (CMV)	1 in 3 000 000 or less
Plasmodium spp.	1 in 3 000 000 or less
Treponema pallidum	none

[72]. It develops during or shortly after (within 6 hours) the transfusion. It is caused by an increase in hydrostatic blood pressure as a result of fluid volume overload. It leads to fluid leakage into the alveolar space, which imitates congestive cardiac failure [73]. It is distinguished by dyspnoea, orthopnoea, tachycardia, hypertension, and elevated central venous pressure. These symptoms can progress to acute pulmonary oedema, which can be seen on chest X-rays and is sometimes accompanied by cardiomegaly [74, 75]. Treatment options for TACO include oxygen therapy, diuretics, continuous positive airway pressure (CPAP), and therapeutic phlebotomy [76].

Transfusion-related acute lung injury

Transfusion-related acute lung injury (TRALI) is non-cardiac pulmonary oedema that occurs within 6 hours after the transfusion. It manifests with sudden dyspnoea, hypoxia, a respiratory failure that often requires mechanical ventilation, and bilateral infiltrates in the lungs visible on chest X-rays. Its symptoms usually disappear after 48–96 hours, with a mortality rate ranging between 5–10%. It is believed that the presence of anti-leukocyte antibodies (anti-HLA) in the recipient's blood is the cause of this condition [40].

Transfusion-associated graft-versus-host disease

TA-GvHD is a rare disease with a very high mortality rate (90–100%). It is caused by the reaction between the transfused immunologically competent and proliferating donor's T cells and the recipient's cells [65–68]. Patients at the highest risk of TA-GvHD are typically severely immunocompromised (bone marrow transplant recipients and patients with severe lymphopenia or inherited deficiencies in cellular immunity). Symptoms that appear 4–30 days after the transfusion include fever, skin rash, nausea, vomiting, diarrhoea, liver and kidney failure, and bone marrow damage with pancytopenia. To prevent TA-GvHD, the blood product intended for the transfusion should be irradiated [67, 68].

The efficiency of GTx in neutropenic patients — clinical evidence

Despite widespread clinical use, there are limited studies on neutropenic patients that examine the efficiency of GTx in combating life-threatening infections with pathogens resistant to appropriate pharmacological treatment. A literature search on granulocyte transfusions in haematology/oncology patients with neutropenia was performed, using PubMed, ScienceDirect, and Wiley Online Library databases. The medical search terms included "granulocyte transfusion," "haematological malignancy," "neutropenia," and "infection," resulting in 166 citations. The exclusion criteria were: 1) articles without open access, 2) articles published in a language other than English, 3) review articles, case studies, editorials, abstracts, and conference presentations, 4) studies conducted on animals, paediatric patients, and non-oncological patients, 5) studies in which the outcome results of GTx therapy were not the primary outcome measure, 6) articles published before 2011 (to ensure the latest results). Eight studies met all established criteria. Table 3 summarizes the results obtained from these studies.

Kim et al. [77] performed an efficiency analysis which included 979 GTx for 138 episodes of febrile neutropenia in 128 patients who received at least three GTx per episode. The most common underlying diseases were acute leukaemia (70.3%), lymphoma (12.3%) and aplastic anaemia (9.4%). At the time of GTx, the underlying disease was rather relapsed or refractory (50%) or newly diagnosed (31.2%) than in complete remission (18.8%). The most common cause of neutropenia was dose-intensive chemotherapy (78.3%), followed by underlying disease (13%). In almost half of the cases, patients suffered from various comorbidities, such as diabetes mellitus (21.7%), cardiovascular disease (8.7%) or liver disease (8%). The presence of microorganisms in the blood cultures was found in 78 episodes (56.5%). Gram-negative bacteria (23.9%), Gram-positive bacteria (14.5%) and fungi (7.2%) were isolated from the blood cultures. In 10.9% of episodes, patients were infected with multiple species of bacteria. Patients received a median of 5 GTx per episode (range: 3–38), with a median granulocyte dose of 0.96 x 10^9/kg/transfusion (range: 0.47–1.8 x 10^9/kg/transfusion). Adverse reactions, such as fever (18.8%), hypotension (6.5%), rigour (5.9%), rash (4.7%), massive haemoptysis (3.5%) and respiratory failure (5.9%), were observed and generally well tolerated. The authors noted that the control of infection was achieved in 73 of the 138 episodes (52.9%) with a 28-day infection-related survival rate of 64.7 ± 4.1% and that the granulocyte dose had no relationship with both infection control and infection-related survival rate. They also showed that patients with fungal infections and Gram-negative bacterial infections had better infection control than patients with Gram-positive bacteriemia and multiple species bacteriemia. It led them to the conclusion that GTx could be a viable adjunctive treatment for febrile neutropenia in patients with haematologic diseases.

Raad et al. [78] came to the opposite conclusion. Their study included 128 patients with HM and prolonged neutropenia with a proven or probable invasive aspergillosis (IA) infection, of whom 53 patients received one or more GTx and 75 none. The vast majority of patients suffered from leukaemia (89% in the GTx group

Table 3. Overview of results from studies of granulocyte transfusions in neutropenic patients

Study	Patients	Average GTx dose	Adverse effects	Results
Kim et al. (2011) [77]	N = 128 median age: 45 (range: 18–90) underlying conditions: acute leukaemia (70.3%), lymphoma (12.3%), aplastic anaemia (9.4%), myelodysplastic syndrome (5.8%), multiple myeloma (2.2%) indications for GTx: Gram-negative bacterial infection (23.9%), Gram-positive bacterial infection (14.5%), fungal infection (7.2%)	0.96 x 10^9/kg/ transfusion (range: 0.47–1.8 x 10^9/ kg/transfusion)	fever (18.8%), hypotension (6.5%), rigour (5.9%), rash (4.7%), massive haemoptysis (3.5%), respiratory failure (5.9%)	infection control rate: 52.9% survival at 28 days: 64.7 ± 4.1%
Raad et al. (2013) [78]	N = 53 (GTx group), 75 (non-GTx group) median age: 44 (range: 9–75, GTx group), 54 (range: 7–83, non-GTx group) underlying conditions: leukaemia (89% in the GTx group, 84% in the non-GTx group), lymphoma (8% in the GTx group, 13% in the non-GTx group), myeloma (2% in the GTx group, 1% in the non-GTx group) indications for GTx: proven or probable invasive *Aspergillus spp.* infection	5.5 x 10^{10} neutrophils/ transfusion	fever (45%), skin rash (2%), pulmonary reactions (53%)	favourable response at the end of therapy: 15% (GTx group) *vs.* 31% (non-GTx group) IA-related mortality rate: 60% (GTx group) *vs.* 40% (non-GTx group)
Safdar et al. (2014) [79]	N = 74 median age: 56 (range: 12–81) underlying conditions: acute leukaemia (76%), chronic leukaemia (14%), lymphoma (1%), other (9%) indications for GTx: neutropenic infection (49%), progressive severe neutropenia (38%), persistent febrile neutropenia (11%), neutropenia without fever (2%)	5.6 x 10^{10} cells/ transfusion (range: 4–10 x 10^{10} cells/transfusion)	respiratory complications (8%), fever (3%)	GTx therapy was discontinued in 34 patients (46%) due to clinical response and neutrophil count recovery 22 patients (30%) died of advanced refractory leukaemia infection alone was considered the cause of death in 17 patients (23%)
Wang et al. (2014) [80]	N = 56 median age: 29 (6–65) underlying conditions: aplastic anaemia indications for GTx: fungal infection (55%), bacterial infection (45%)	9.2 ± 4.7 x 10^9 cells/ component transfused	chills and fever (8.3%), dyspnoea (1.9%), allergic reactions (3.4%) and acute heart failure (0.2%)	overall survival rate at 30 days, 90 days and 180 days: 89%, 70% and 66%, respectively survival rate at 30 days, 90 days and 180 days for bacterial infections: 92%, 84% and 84%, respectively survival rate at 30 days, 90 days and 180 days for fungal infections: 87%, 58% and 52%, respectively
Kadri et al. (2015) [81]	N = 11 median age: 46 (range: 17-58) underlying conditions: severe aplastic anaemia (46%), myelodysplastic syndrome (18%), non-Hodgkin's lymphoma (18%), acute lymphocytic leukaemia (9%), chronic myelocytic leukaemia (9%) indications for GTx: invasive *Fusarium spp.* infection	6.84 ± 2.34 x 10^{10} granulocytes/ component transfused	respiratory complications (18%) and HLA immunization (18%)	10 patients (91%) had objective clinical, radiographic and/or microbial responses 10 patients (91%) survived for at least 30 days and 8 patients (73%) survived for at least 90 days after the initiation of GTx therapy

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Table 3. cont. Overview of results from studies of granulocyte transfusions in neutropenic patients

Study	Patients	Average GTx dose	Adverse effects	Results
Price et al. (2015) [82]	N = 48 (GTx group), 49 (non-GTx group) median age: 47 (± 20, GTx group), 55 (± 17, non-GTx group) underlying conditions: acute nonlymphocytic leukaemia (65%), acute lymphocytic leukaemia (12%), non-Hodgkin's lymphoma (7%), myelodysplasia (3%), other (13%) indications for GTx: proven fungal infection (27%), invasive bacterial infection (22%), bacteriemia alone (24%)	54.9 x 10^9 granulocytes/ transfusion	fever, chills and/or modest changes in blood pressure (41%), hypoxia, tachycardia, hypotension and/or allergic reactions (20%)	overall success rates were 42% and 43% for the GTx group and the non-GTx group, respectively
Teofili et al. (2016) [83]	N = 96 median age: 46 (range: 20–74) underlying conditions: acute myeloid leukaemia (77.2%), lymphoma (13.2%), acute lymphoblastic leukaemia (6.1%), myelodysplastic syndrome (1.7%), chronic lymphatic leukaemia (0.9%), multiple myeloma (0.9%) indications for GTx: infections with *Klebsiella pneumoniae* (35%), *Candida spp.* (20%), *Aspergillus spp.* (19%) and *Escherichia coli* (16%) located in the bloodstream (60.5%) or the lungs (29.8%)	2.16 x 10^8/kg/ transfusion (range: 0.46–7.34 x 10^9/kg/transfusion)	no serious GTx-related adverse effects were observed	overall IRM: 30.7% dose-dependent IRM values: 44.4% in the low-dose group, 18.4% in the standard-dose group, and 48.4% in the high-dose group
Garg et al. (2018) [84]	N = 60 median age: 21 (range: 16–45) underlying conditions: acute myeloid leukaemia (40%), severe aplastic anaemia (25%), acute lymphoblastic leukaemia (15%), non-Hodgkin's lymphoma (5%), other (15%) indications for GTx: bacterial infection proved by positive bacterial blood cultures (73%), proven or probable fungal infection (13.5%), an infection that was difficult to define due to negative blood cultures combined with the typical symptoms of infection (13.5%)	10.4 x 10^8 cells/kg/IE (range: 8.8–14.4 x 10^8 cells/kg/IE)	TRALI (10%), hypercalcaemic tetany (2%)	infection resolution rate: 68.2% survival at 30 days: 67.7%

and 84% in the non-GTx group). The median number of GTx received was 7 (range: 1–44). The median duration between antifungal therapy initiation and the first GTx received was 7 days (range: 0–69 days). Among patients who received GTx, 45% experienced fever, 2% experienced skin rash and 53% experienced pulmonary reactions, such as worsening shortness of breath or pulmonary infiltrates. Ultimately, 70% of these patients died within 84 days of antifungal therapy initiation, and the median duration between their last GTx and death was 5 days (range: 0–52 days). The authors observed that patients with IA who received GTx were less likely to respond to antifungal therapy (15% *vs.* 31%) and more likely to die of IA (60% *vs.* 40%) when compared with the non-GTx group of patients. They also noted that IA-related death was associated with both the number of GTx received and the early initiation of GTx after starting antifungal therapy. In other words, patients who received GTx were more likely to die of IA than patients who did not receive GTx. Because of the data gathered, the authors concluded that GTx does not improve response to antifungal therapy and is associated with worse outcomes of IA infection in HM patients.

Safdar et al. [79] published a study of 74 neutropenic patients with various infections who received GTx. The most common underlying malignancies were acute leukaemia (75%) and chronic leukaemia (14%). The malignancy status was defined as relapsed or refractory in as many as 84% of the patients. Thirty-one per cent of the patients were diagnosed with comorbidities. The most common ones turned out to be diabetes mellitus (16%) and renal failure (4%). Of all the patients, 57% had bacteraemia (mostly caused by *Staphylococcus spp.*, *Enterococcus spp.*, and *Pseudomonas aeruginosa*), 45% were infected with fungi (*Aspergillus spp.*, *Candida spp.*, and *Fusarium spp.*), and 14% had a viral infection (herpes simplex virus, human parainfluenza virus, and cytomegalovirus). GTx were given to 36 patients (49%) with non-severe infection, 28 patients (38%) with progressive severe infection, 8 patients (11%) with persistent febrile neutropenia, and 1 patient (2%) with neutropenia without fever. The patients received a median of 4 (range: 1–50) GTx. Eight patients (11%) experienced GTx-related adverse effects, such as respiratory complications (8%) and fever (3%). The authors pointed out that GTx therapy was discontinued in 34 patients (46%) due to clinical response and neutrophil count recovery and that 22 patients (30%) died of advanced refractory leukaemia, whereas infection alone was considered the cause of death in 17 patients (23%). It also did not escape their attention that patients with confirmed severe infections had noticeably better survival rates when they received GTx than those who did not have severe infections. All things considered, the authors concluded that the benefits of GTx therapy require further assessment.

Wang et al. [80] investigated the efficacy of GTx in 56 severely infected patients with aplastic anaemia (AA). Among these patients, 51 cases (91%) were very severe aplastic anaemia (VSAA) and 5 cases (9%) were severe aplastic anaemia (SAA). Fungal and bacterial infections accounted for 55% and 45% of all cases, respectively. The majority of infections were polymicrobial, meaning they involved more than one bacterial strain, more than one mould, or mixed bacterial-fungal infections. The most common pathogens isolated from the sites of infection were *Candida albicans*, *Aspergillus spp.*, *Stenotrophomonas maltophilia*, and *Pseudomonas aeruginosa*. The median number of granulocyte concentrates transfused was 18 (range: 3–75), with a total number of transfusions of 1078. Chills and fever (8.3%), dyspnoea (1.9%), allergic reactions (3.4%) and acute heart failure (0.2%) were the most common adverse effects observed, but in all cases, they were mild or moderate and successfully treated. The survival rate at 30 days, 90 days, and 180 days from the first GTx was considered an indicator of the efficacy of GTx therapy. Ignoring the aetiology of infection, the survival rate at 30 days, 90 days, and 180 days was 89%, 70%, and 66%, respectively. For patients with bacterial infections, this rate was 92%, 84%, and 84%, respectively. For patients who had fungal infections, it was 87%, 58%, and 52%, respectively. Therefore, the authors found that granulocyte transfusions could be an adjunctive therapy for treating severe infections in patients with AA.

Kadri et al. [81] conducted a study on 11 patients who received GTx as an adjunctive therapy after being diagnosed with invasive *Fusarium spp.* infection (IFI). In all cases, the diagnosis was proven by culture and/or molecular identification of the fungus in the samples from the infection sites. The most common underlying disease was SAA (46%), followed by myelodysplastic syndrome (18%), and non-Hodgkin's lymphoma (18%). The median number of transfusions per patient was 7 (range: 2–39), with a total number of transfusions of 133. The mean granulocyte content per component transfused was $6.84 \pm 2.34 \times 10^{10}$. GTx-related toxicity was observed in 4 patients (36%): respiratory complications in 2 patients (18%) and HLA immunization in 2 patients (18%). As it turned out, 10 patients (91%) had objective clinical, radiographic, and/or microbial responses within the first several days after the first GTx. Moreover, 10 patients (91%) survived for at least 30 days and 8 patients (73%) survived for at least 90 days after the initiation of GTx. Thus, the authors stated that GTx therapy may contribute to high response rates by effectively bridging periods of neutropenia/marrow suppression in patients with IFI.

Price et al. [82] enrolled 97 neutropenic patients with infections in their study. Of them all, 48 patients received GTx and 49 did not. The most common underlying haematologic malignancy was acute nonlymphocytic leukaemia (65%), followed by acute lymphocytic leukaemia (12%). The most common causes of neutropenia were chemotherapy (75%) and HSCT (17%). Most of the patients had proven fungal infections (27%), invasive bacterial infections (22%), or bacteraemia alone (24%). The median number of GTx received was 5 (range: 1–20), with a total number of transfusions of 316. The median granulocyte content per transfusion was 54.9 x 10^9. Among patients who received GTx, 41% developed mild to moderate transfusion reactions, such as fever, chills, and/or modest changes in blood pressure. More severe reactions (hypoxia, tachycardia, hypotension, and/or allergic reactions) were observed in 20% of the patients. The authors examined that overall success rates were 42% and 43% for the GTx group and the non-GTx group, respectively. Furthermore, these rates did not differ within any infection type. Overall, Price et al. did not observe any benefit of granulocyte transfusion therapy.

Teofili et al. [83] assessed the efficiency of GTx therapy based on the results of 96 patients who received a total of 491 granulocyte transfusions during 114 infectious episodes (IE). Most of the patients suffered from acute myeloid leukaemia (77.2%) or lymphoma (13.2%). The most common microorganisms isolated from the sites of infection were *Klebsiella pneumoniae* (35%), *Candida spp.* (20%), *Aspergillus spp.* (19%), and *Escherichia coli* (16%). Infections were mainly located in the bloodstream (60.5%) or the lungs (29.8%). The first GTx was given after a median number of 5 days of antimicrobial therapy (range: 2–33). The median number of GTx received was 4 (range: 1–14), with a median granulocyte dose of 2.16 x 10^8/kg/transfusion (range: 0.46–7.34 x 10^9/kg/transfusion). Luckily, no serious GTx-related adverse effects were recorded. Based on the median dose of granulocytes transfused, all the patients were divided into three groups: 1) the low-dose group (< 1.5 x 10^8 cells/kg), 2) the standard-dose group (1.5–3 x 10^8 cells/kg), and 3) the high-dose group (> 3 x 10^8 cells/kg). The conclusions were drawn based on the assessment of the impact of clinical, microbiological, and GTx-related variables on infection-related mortality (IRM). Overall, the authors recorded 35 deaths due to infections, with an overall IRM of 30.7%. More specifically, the IRM values differed depending on the median dose of granulocytes transfused as follows: 44.4% in the low-dose group, 18.4% in the standard-dose group, and 48.4% in the high-dose group, meaning the patients of the low- and high-dose groups were more likely to die of IE than the patients of the standard-dose group. The increased mortality among these patients was observed since the first days of GTx therapy. Of the 7 patients dead within that period, 2 patients were in the low-dose group, 5 patients were in the high-dose group, and no deaths were detectable in the standard-dose group. Additionally, Teofili et al. checked if GTx therapy was similarly effective against bacterial and fungal infections, determining that fungal infections may necessitate very high doses of granulocytes while lower doses may be sufficient to overcome bacterial infections. Altogether, they concluded that GTx therapy could constitute a valuable tool to improve the outcomes of infections in neutropenic patients.

Garg et al. [84] reviewed 60 patients who received 143 granulocyte transfusions for 66 IE. The most common diagnoses were acute myeloid leukaemia (40%), severe aplastic anaemia (25%), and acute lymphoblastic leukaemia (15%). Out of all 66 IE, 73% were bacterial infections proved by positive bacterial blood cultures, 13.5% were proven or probable fungal infections, and another 13.5% were difficult to define due to negative blood cultures combined with the typical symptoms of infection. In all cases of bacterial infections, multidrug-resistant organisms (MDRO) were isolated from the sites of infection. The most common of these were *Klebsiella pneumoniae* and *Staphylococcus aureus*. The median duration of fever before giving GTx was 7 days (range: 5–12 days). The median number of GTx given was 2 (range: 1–3), with a median granulocyte dose of 10.4 x 10^8 granulocytes/kg/IE (range: 8.8–14.4 x 10^8 granulocytes/kg/IE). Of all patients, 7 (12%) experienced GTx-related side effects: 1 patient (2%) developed hypercalcaemic tetany and 6 patients (10%) developed TRALI, which did not require ventilator support. The resolution of infection was seen in 68.2% of all cases, and the survival at 30 days was 67.7%. This prompted the authors to reflect that GTx may play a vital role, especially when other antimicrobial therapies are unsuccessful.

Conclusions

In conclusion, this review failed to provide a definitive answer as to whether granulocyte transfusions are effective in combating life-threatening bacterial and fungal infections in neutropenic patients with haematological malignancies or not. There are plenty of reasons why the authors of the reviewed studies found it difficult to draw unequivocal conclusions. The following factors may have contributed to the ambiguity of the obtained results: 1) a lack of an appropriate control group, 2) a small number of patients included in the study, 3) the status of the underlying haematological malignancy (complete remission, relapsed or refractory, newly diagnosed), 4) not all the patients suffered from co-

morbidities, 5) indications for GTx therapy (established bacterial and/or fungal infection, febrile neutropenia, persistent non-neutropenic fever, or fever of unknown aetiology), 6) donor availability, 7) donor stimulation scheme (e.g., corticosteroids alone, G-CSF alone, or G-CSF with corticosteroids), 8) GTx type (granulocytes collected from related donor or HLA-matched unrelated donor), 9) differences in granulocyte collection methods, 10) time from the onset of symptoms of infection to the first GTx, 11) differences in granulocyte doses used, 12) previous alloimmunization of the patient (i.e. already existing anti-leukocyte antibodies), and finally 13) preferences of treating physicians. The therapeutic efficacy of granulocyte concentrates collected from G-CSF- and corticosteroid-stimulated donors will only be reliably determined if randomized clinical trials on a sufficiently large number of patients in both study and control groups are performed.

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