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GRANULOCYTE TRANSFUSIONS IN THE MANAGEMENT OF INVASIVE FUNGAL INFECTIONS

Kamille A. West[1], **Juan Gea-Banacloche**[2], **David Stroncek**[1], and **Sameer S. Kadri**[3]

[1]Department of Transfusion Medicine, National Institutes of Health Clinical Center, Bethesda, MD

[2]Experimental Transplantation and Immunology Branch, National Cancer Institute, Bethesda MD

[3]Critical Care Medicine Department, National Institutes of Health Clinical Center, Bethesda, MD

SUMMARY

Granulocyte transfusions have a long history of being used in patients with neutropenia or neutrophil dysfunction to prevent and treat invasive fungal infections. However, there are limited and conflicting data concerning its clinical effectiveness, considerable variations in current granulocyte transfusion practices, and uncertainties about its benefit as an adjunct to modern antifungal therapy. In this review, we provide an overview on granulocyte transfusions and summarize the evidence on their role in the prevention and treatment of invasive fungal infections.

Keywords

granulocytes; transfusions; neutropenia; fungal infection; leukapheresis

RATIONALE FOR GRANULOCYTE TRANSFUSION IN INVASIVE FUNGAL INFECTION

The association between absolute or qualitative deficiency of circulating granulocytes and propensity for bacterial and invasive fungal infections (IFI) has been known for 50 years (Bodey *et al*, 1966). As prompt and effective antibiotic therapy has continued to improve the outcome of bacterial infections, fungal infections have become an increasingly important cause of morbidity and mortality in high risk patients, such as those with leukaemia or undergoing haematopoietic stem cell transplant (HSCT) (Sahin *et al*, 2016). Although late post-transplant fungal infections may occur in non-neutropenic patients on immunosuppressive therapy (Grow *et al*, 2002), prolonged neutropenia is a major risk factor for IFI.

Corresponding author: Kamille West, MD. Department of Transfusion Medicine, National Institutes of Health Clinical Center, 10 Center Drive, Bldg. 10 Room 1C711E, Bethesda, MD 20892. Phone: 301-594-5357. Fax: 301-402-1360. kamille.west@nih.gov.

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Conflicts of Interest

The authors have no relevant conflicts of interest to disclose.

Mortality rates secondary to invasive *Candida albicans* have decreased in HSCT recipients because of the widespread use of fluconazole prophylaxis (Marr *et al*, 2000). However, the spectrum of infections in neutropenic patients has shifted, with multidrug-resistant bacteria and mould infections, such as *Aspergillus, Fusarium, Scedosporium* and *Mucorales*, emerging as major determinants of morbidity and mortality (Marr *et al*, 2002). Without correction of neutropenia, either by recovery of endogenous or graft-related granulocytopoiesis, antimicrobials alone may not resolve infections against which neutrophils form the primary line of defence. Therefore, in cases of delayed neutrophil reconstitution or drug-resistant fungal infection, granulocyte transfusion (GTX) remains a logically attractive solution.

HISTORY OF GRANULOCYTE TRANSFUSION

The introduction of the plastic bag for blood collection (Walter & Murphy, 1952) and refrigerated centrifuge in 1953 allowed for safe and easy preparation of multiple blood components from a single unit of whole blood. This afforded the opportunity to address specific cytopenias by transfusing only the cells of interest. The theoretical potential for leucocyte transfusion was established by early animal studies. Brecher *et al* (1953) showed that granulocytes transfused to neutropenic dogs migrated to areas of infection. Later, animal models of bacterial and fungal infection were supportive of the efficacy of transfused donor granulocytes (Dale *et al*, 1976; Ruthe *et al*, 1978).

Buffy coats prepared from whole blood as a source of granulocytes were limited by the low numbers of neutrophils obtainable from a single healthy donor, about 5×10^8 to 1×10^9 (Reiss *et al*, 1982). Thus granulocytes for transfusion were collected from donors with chronic myeloid leukaemia (CML). This practice, while understandably controversial to modern readers due to the transfusion of malignant cells, was considered a viable option at the time. Neutrophil yields ranged from 2.6×10^9 to 1.8×10^{11} (Freireich *et al*, 1964); transfused cells disappeared from the recipient's circulation with a half-time of one day. Patients were noted to have neutrophil increments (median 1.0×10^9/l) and clinical responses to doses exceeding 1×10^{10} granulocytes.

The development of the automated blood cell separator enabled increased collection efficiency via apheresis, the process of separation of blood components in an extracorporeal circuit. Apheresis allowed selective collection of a larger dose of granulocytes than would be retrieved from a unit of whole blood, with the added advantage of minimal donor red cell loss (Graw *et al*, 1971), eventually obviating the need for donors with CML. Cell kinetics studies showed that transfused granulocytes were of normal appearance and viability (De Fliedner *et al*, 1974) and migrated to sites of inflammation (Dutcher *et al*, 1981). Filtration leukapheresis, due to reduced intravascular recovery and abnormal kinetics of collected granulocytes, as well as adverse reactions in both donors and recipients, was supplanted by centrifugation apheresis (McCullough, 1979; Eckermann and Strauss, 1984).

Granulocytapheresis was further enhanced by the intravenous administration of macromolecule starch solutions (Bearden *et al*, 1977; Iacone *et al*, 1981) to the donor before the procedure, which sediments red cells, separating them from the granulocyte layer and

hence increases the granulocyte yield (Mishler *et al*, 1983). Corticosteroids were administered to donors to increase the circulating white cell count, by both increasing marrow release of granulocytes and decreasing efflux from peripheral blood. However, steroid-stimulated donors yielded granulocyte doses of $2–3 \times 10^{10}$, about half of what is produced daily by normal bone marrow. Functional tests of granulocytes from both steroid-stimulated and unstimulated donors (Glasser & Huestis, 1979) showed statistically significant decreases in chemotaxis, candidacidal activity, and phagocytosis at 24 h of *ex vivo* storage. Randomized controlled trials (RCTs) of both prophylactic and therapeutic GTX were conducted, but the reported benefit ranged from clear to marginal to none in some studies, and some authors reported significant adverse effects. For these reasons, GTX therapy fell out of favour.

In the early 1990s, the availability of recombinant granulocyte colony-stimulating factor (G-CSF), allowing even higher white cell counts to be achieved by marrow stimulation of healthy donors (Inaba *et al*, 1992), led to renewed interest in GTX. A single injection of G-CSF alone or combined with an oral dose of steroids enabled the collection of up to $6 – 8 \times 10^{10}$ granulocytes (Stroncek *et al*, 2001). Co-administration with systemic steroids enabled reduction in G-CSF dose, ameliorating associated side effects, including bone pain, headache and fever (Heuft *et al*, 2002). Donor granulocyte count elevations were sustained longer when G-CSF was administered subcutaneously rather than intravenously (Stroncek *et al*, 2002). The therapeutic efficacy of G-CSF given directly to patients for prevention or as adjunctive treatment of severe refractory infections is not well-defined. Therefore, transfusion of granulocyte concentrates still holds clinical and research interest.

ANTIFUNGAL THERAPY IN IFI: EVOLUTION AND CURRENT PRACTICE

The management of IFI has changed over the past 15 years due to the availability of two new classes of drugs (echinocandins and mould-active azoles), the increased use of computed tomography and the development of new biomarkers (galactomannan antigen in serum and bronchoalveolar lavage for aspergillosis and serum β-D-glucan for several fungal infections) to aid with diagnosis (Lehrnbecher *et al*, 2016). Systemic antifungal agents have three applications in clinical practice: prophylaxis (i.e., administration of antifungal agents to prevent infection), treatment of a documented specific fungal infection, and treatment of a suspected fungal infection (triggered by a particular constellation of signs and symptoms, but in the absence of definite proof of fungal infection).

Candida species occur as part of normal human flora of the gastrointestinal tract and, often, the skin. Consequently, invasive candidiasis and candidaemia occur due to endogenous organisms in the setting of neutropenia and/or mucosal damage caused by chemotherapy, radiation and/or instrumentation in critically ill patients in concert with disruption of bacterial flora by broad-spectrum antibiotics. Moulds, on the other hand, are not part of the normal flora of the human respiratory tract; mould infections usually follow systemic corticosteroid use or periods of prolonged neutropenia. Fluconazole (Goodman *et al*, 1992) or micafungin (van Burik *et al*, 2004) are recommended for targeted prophylaxis against invasive candidiasis. Meta-analyses of prophylaxis trials conclude that second-generation azoles [posaconazole (Ullmann *et al*, 2007; Cornely *et al*, 2007a) and voriconazole (Wingard

et al, 2010)] are more effective than fluconazole to prevent invasive aspergillosis (IA) (Bow *et al*, 2015; Ping *et al*, 2013; Ethier *et al*, 2012).

Professional societies, such as the Infectious Diseases Society of America (IDSA), the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and the European Confederation of Medical Mycology (ECCM), issue guidelines that provide evidence-based recommendations for the treatment of established infections with the most common fungal agents, *i.e.* candidiasis (Pappas *et al*, 2016) and aspergillosis (Patterson *et al*, 2016). Echinocandins, azoles and lipid formulations of amphotericin B are considered acceptable treatment for of invasive candidiasis in neutropenic patients. Randomized trials have provided evidence to optimize antifungal therapy for aspergillosis. Specifically, voriconazole is superior to amphotericin B (Herbrecht *et al*, 2002); 10 mg/kg/day of liposomal amphotericin B is not superior to 3 mg/kg/day (Cornely *et al*, 2007b); the combination of voriconazole with an echinocandin may be superior to voriconazole in a subgroup of higher-risk patients (Marr *et al*, 2015); and isavuconazole is non-inferior to voriconazole and has less hepatotoxicity (Maertens *et al*, 2016). The role of therapeutic drug monitoring and pharmacogenetics for voriconazole and posaconazole remain controversial (Lee *et al*, 2013; Hamada *et al*, 2013; Chau *et al*, 2014; Ashbee *et al*, 2014; Laverdiere *et al*, 2014; Moriyama *et al*, 2015), but most experts agree it should be considered in high-risk patients.

Due to low overall incidence, the evidence for management of established infection due to uncommon fungal organisms, such as mucormycosis (Cornely *et al*, 2014), dematiaceous fungi (Chowdary *et al*, 2014), rare yeasts (Arendrup *et al*, 2014) and hyalohyphomycoses (Tortorano *et al*, 2014), is sparse and limited to case series and expert opinion. Invasive mucormycosis, the third most frequent cause of IFI, is still associated with high mortality. Surgical resection is life saving in many cases. There are no biomarkers for the disease, and only liposomal amphotericin B and posaconazole are effective (Ruping *et al*, 2010). Recovery of neutrophil counts is shown to improve outcomes (Pagano *et al*, 2004); thus, GTX may play an important therapeutic role. *Fusarium* is a refractory mould in which granulocytes might be the primary driver of a clinical response (Kadri *et al*, 2015).

The approach to suspected IFI is evolving. The decades-old practice of adding amphotericin B after 4–7 days of persistent fever during neutropenia (Pizzo *et al*, 1982), which resulted in many patients without fungal infection being exposed to the toxic agent, is being superseded by approaches that attempt to identify those patients who truly have IFI by intensive use of computed tomography, biomarker tests and PCR (Cordonnier *et al*, 2009; Maertens *et al*, 2011; Maschmeyer *et al*, 2013; Morrissey *et al*, 2013).

The most common clinical presentation of a suspected or “possible” invasive fungal infection is of dense, well-circumscribed pulmonary nodules or infiltrates in patients with prolonged neutropenia in the absence of microbiological confirmation (De Pauw *et al*, 2008). Evidence-based recommendations that can guide the practitioner in this setting are currently lacking. However, prompt empiric therapy upon suspicion of IFI seems prudent, given that withholding treatment when infection truly exists can be catastrophic. The available evidence suggests that the most common breakthrough fungal infection is

Aspergillus in those on fluconazole prophylaxis, and non-*Aspergillus* mould among those on micafungin prophylaxis (van Burik *et al*, 2004). Some case series have suggested increased frequency of mucormycosis in patients on voriconazole prophylaxis (Imhof *et al*, 2004; Chamilos *et al*, 2005). These data serve to guide empiric therapy choices especially in the absence of microbiological or biomarker data. A fundamental concept in the management of IFIs is that host factors, such as neutropenia, that render the patient susceptible to the infection should be corrected whenever possible, as antifungal agents alone have a significant failure rate (Maertens *et al*, 2016).

IMPACT OF NEUTROPHILS ON FUNGAL PATHOGENESIS

Neutrophils recognize and respond to fungal pathogens using pattern recognition receptors, including toll-like receptors and dectin-1 (Kennedy *et al*, 2007). After phagocytosis of the pathogen, the contents of the cytoplasmic granules are released into the vacuole and expressed onto the surface of the organism (Cohn & Hirsch, 1960). The azurophil (primary) granules contain myeloperoxidase (MPO) and three predominant neutral proteases; cathepsin G, elastase and proteinase 3. NADPH oxidase pumps electrons into the phagocytic vacuole, thereby inducing a charge across the membrane. The movement of compensating potassium ions produces conditions in the vacuole conducive to microbial killing and digestion by the enzymes released from the cytoplasmic granules (Reeves *et al*, 2002).

When fungal elements are too large to be phagocytosed, neutrophils release granule proteins and chromatin that together form extracellular fibres, dubbed neutrophil extracellular traps or NETs (see Fig. 1) that degrade conidia and hyphae (McCormick *et al*, 2010). Neutrophil-induced hyphal damage to *A. fumigatus* and resistant filamentous fungi, such as *Scedosporium*, is enhanced synergistically in the presence of newer triazole agents (voriconazole and posaconazole) (Walsh *et al*, 2002; Gil-Lamaignere *et al*, 2002).

DONOR SELECTION AND COMPONENT PREPARATION

Identifying a suitable donor may take some time depending on the size of donor pool, and the requirements of the patient. Using community donors is more readily feasible than relying on related donors only (Hübel *et al*, 2002). Because granulocyte concentrates contain between 20 and 50 ml of red blood cells (RBCs) per product, ABO compatibility is ideal to prevent haemolytic transfusion reactions. Human leucocyte antigen (HLA) compatible donors may be indicated if the patient has a history of alloimmunization. For patients who are awaiting HSCT, prospectively avoiding transplant donor antigens is crucial to avoid the formation of donor-specific antibodies targeting the graft (O' Donghaile *et al*, 2012). Cytomegalovirus (CMV) seronegative donors are generally recommended for seronegative recipients.

It usually takes at least a day to prepare a donor for granulocytapheresis, with subcutaneous G-CSF injection 12–18 h prior, and/or oral dexamethasone 8–12 h prior to collection. The apheresis procedure takes about 4 h. Alternatively, granulocytes derived from whole blood buffy coats may be used; a dose of ten buffy coats for adults and 10–20 ml/kg for children weighing less than 50 kg is recommended. A pooled granulocyte component is also

available in the UK (Bashir *et al*, 2008); 10 buffy coats are pooled into a final volume of 200–250 ml, each pack containing approximately 1×10^{10} granulocytes. In the blood bank, a sample from the granulocyte donor undergoes a full RBC cross-match with the recipient. Red cell depletion by sedimentation may be required if there is major ABO incompatibility between donor and recipient (Bryant *et al*, 2010), adding a further 4 h to the process. Finally, the granulocyte concentrate must be irradiated before release to the patient to prevent graft-versus-host disease.

CLINICAL EFFICACY

We performed a structured narrative review of the existing literature on GTX to prevent or treat IFI. The details of the literature search are described in the supplement. Previous reviews have described the limited data on the use of GTX for the prevention or treatment of infections in general (Price, 2007; Strauss, 2012). The published literature largely comprises case reports and uncontrolled case series, with heterogeneous patient populations, intervention parameters and outcome measures. Obstacles to conducting RCTs include cost, logistical factors, and low enrolment partly due to the unwillingness of patients and physicians to potentially forfeit what they believe to be a life-saving intervention (Seidel *et al*, 2008; Price *et al*, 2015). Patients with IFI represent a fraction of cases in most studies; extracting a precise estimate of benefit from GTX in overall or species-specific fungal subgroups in mixed study populations remains challenging. Finally, advances in antifungal agents and supportive care may have diminished the role of GTX, making it difficult to show its benefit in recent randomized controlled studies. Notwithstanding, we provide a categorical summary of the existing evidence for GTX in IFIs from individual case reports, case series, matched cohort studies and clinical trials and, where possible, report on adults and paediatric populations separately.

Case Reports

We summarized the outcomes of 97 patients with fungal infection treated with GTX from individual case reports and small series (Table I). The most common underlying illnesses were acute leukaemia (45%), chronic granulomatous disease (26%) and aplastic anaemia (12%). Granulocyte dose and transfusion course varied considerably and were often not specified. In a third of the cases, patients also underwent surgical debridement or excision of locoregional disease. Overall, 77% reported clinical, radiological or microbiological improvement with GTX therapy; 2% reported stable disease. Adverse events, including febrile and pulmonary reactions, cytomegalovirus (CMV) transmission and HLA alloimmunization were described in 16%. These findings must be interpreted with caution, given the known propensity for positive publication bias.

Case Series of IFIs in the G-CSF Era

Seven case series specifically reported on the treatment or prevention of fungal infections using G-CSF mobilized granulocytes (Table II). Hester *et al* (1995) and Dignani *et al* (1997) described a group of 15 adult patients with haematological malignancies and refractory fungal infections. Eleven patients were determined to have favourable responses (9

improved, 2 stable) and 4 had progression of infection; 8 patients remained free of infection 3 weeks after therapy.

Hermann *et al* (2001) reported 4 older patients (median age 62 years) with leukaemia who had fungal infections at the time of HSCT. A combination of reduced intensity conditioning, GTX and G-CSF was employed to reduce the period of neutropenia. Three of four patients had documented regression of fungal lesions, and all four patients survived without relapse of leukaemia over a year post-transplant. Kerr *et al* (2003) reported favourable clinical outcomes of GTX in 9 HSCT patients at high risk for IFI (due to existing or previous IA, or prolonged neutropenia) compared to a control group, although there was no survival difference. Four of seven patients with radiological abnormalities prior to transplant showed improvement on imaging. Yenicesu *et al* (2011) reported full clinical and radiological recovery in 3 of 5 patients with active IFI who had undergone HSCT with GTX support.

Kadri *et al* (2015) published a series of 11 neutropenic patients with invasive *Fusarium* infections. Ten of 11 (91%) patients had objective clinical, radiological or microbiological responses within the first few days of GTX, and survived 30 days post-GTX. The authors compared their results to those of 23 prior published cases of *Fusarium* infection treated with GTX, with clinical response in only 30%. Higher clinical response rates in this recent series might reflect wider use of voriconazole, G-CSF and dexamethasone stimulated donors, improvements in primary disease management and supportive care. Locally invasive sinus infections, which may carry a lower risk of mortality than disseminated fungaemia, were more common in the case series. Notably, there was a five-fold greater use of surgical debridement (100% vs. 17%) in patients with invasive *Fusarium* sinusitis compared to cases in the systematic review.

Safdar *et al* (2004) performed a single institution retrospective analysis of 491 patients with candidaemia, 29 of whom received GTX. The criteria for treatment with GTX included a positive blood culture for *Candida* species for > 72 h after appropriate systemic antifungal therapy was initiated, or when neutrophil count recovery was expected to be delayed for > 3–4 weeks after diagnosis of infection, or both. There was no difference in overall attributable mortality (48% in the transfused group, 45% in the control group, $p = 0.5$) but because various risk factors for higher mortality were more common in the transfused group, the authors interpreted their results to suggest that GTX had been beneficial.

Raad *et al* (2013) performed a single institution retrospective review of 128 patients with haematological malignancies and prolonged neutropenia with proven or probable IA. Fifty-three patients received GTX and 75 did not. Multivariate logistic regression analyses showed no significant association between GTX and response. Patients with invasive pulmonary aspergillosis (IPA) who received GTX were less likely to respond to antifungal therapy ($p = 0.03$), and more likely to die of IA ($p = 0.009$) when compared with the non-GTX group. In retrospective comparative effectiveness studies, however, it is difficult to account for confounding by indication for GTX (which may have been administered to sicker patients) in the absence of randomization or matching of cases (e.g. using propensity scores), and as such outcomes are difficult to interpret.

Case Series and Matched-cohort Studies Collectively Reporting Bacterial and Fungal Infections in Adult Patients

In many case series of infections treated with GTX, patients with bacterial infections had better outcomes than those with IFI (Table III and IV). Grigg *et al* (1996) reported a series of 8 patients with refractory infections. All three patients with bacterial infection cleared the infection and survived; all five patients with fungal infection, four of whom had *Aspergillus* pneumonia, died. Rutella *et al* (2003) administered granulocytes from HLA-matched siblings to 18 patients with haematological malignancies and refractory infections. Responses were seen in 6 of 9 patients with bacterial isolates, all 4 patients with fungaemia, but none of 3 with focal fungal infections. In a prospective cohort study, Mousset *et al* (2005) reported a 30-day overall response rate of 82%, which included 93% response in bacterial and 78% for fungal infections; infection-related mortality was very low. Infection did not recrudesce in any of the 23 patients in the secondary prophylaxis arm.

Conversely, in a series of 25 patients with malignancies and severe refractory neutropenia-related infections, Lee *et al* (2001) reported that patients with fungal or gram-negative organisms isolated showed a more favourable response to GTX than those infected with gram-positive organisms (73%, 60%, and 31% respectively). In a single-centre retrospective study, Kim *et al* (2011) similarly reported better outcomes in fungal infections (60%) and gram-negative bacterial infections than in gram-positive infections (30%) in 128 patients with haematological disease. For gram-positive infections, antibiotics are usually highly efficacious and extensive drug resistance limiting antibiotic options is less common compared to gram-negative counterparts, such that appropriate initial therapy, and in turn, outcomes are likely to be better even in neutropenia, making GTX relatively more relevant in IFI and gram-negative compared to gram-positive bacterial infections.

Illerhaus *et al* (2002) reviewed 18 patients who received GTX to treat severe infection with an overall response rate of 67%, including a 55% response rate in patients with *Aspergillus* pneumonia. GTX was also administered to 8 high-risk patients with a history of serious infection, all of whom had a stable clinical course without severe infections until neutrophil recovery.

Safdar *et al* (2006) retrospectively evaluated 20 recipients of high-dose donor GTX (≈5.5 × 10^{10} neutrophils per transfusion) who had received concurrent rIFN-γ1b. Four weeks after therapy started, 9 patients (45%) had complete or partial resolution of infection; and, in another 3 patients (15%), progression of infection was halted.

Ofran *et al* (2007) reported a single centre retrospective analysis of 47 neutropenic patients treated with GTX for life-threatening infections. Patients with fungal infections (n=28) received more GTX than those with bacterial infections (median 8 vs. 4, $p < 0.001$), and 18 (64%) of GTX recipients with fungal infections survived. This study found no association between fungal infection and infection-related survival among recipients of GTX; the authors acknowledge the sample was probably underpowered to show this effect.

In a series of patients with severe aplastic anaemia treated with GTX (Quillen *et al*, 2009a), of 18 patients with IFI, 44% survived to hospital discharge, compared to 58% overall. Al

Tanbal *et al* (2010) described 22 patients receiving at least three continuous days of GTX, most of whom had disseminated fungal infection (73%). Fifteen (68·2%) patients showed clinical improvement. Safdar *et al* (2014) reported 74 patients, 45 of whom had IFI with a 46% overall response with use of GTX. Wang *et al* (2014) treated 56 patients with SAA and severe infections with GTX combined with G-CSF. Among 31 patients who had IFI, survival at 30 days, 90 days and 180 days was 87%, 58% and 52% respectively.

Although still susceptible to the effect of unmeasured confounders, matching of cases in non-randomized studies offers a fairer assessment of clinical effectiveness of an intervention compared to case series. Hübel *et al* (2002) prospectively examined the effect of GTX therapy on survival and microbial response in 74 patients undergoing marrow transplantation with active infection compared to 74 matched concurrent or historic controls receiving antibiotics alone. The number of fatal or progressive fungal infections and survival was comparable in both groups.

Case Series Collectively Reporting Bacterial and Fungal Infections in Paediatric Patients

A number of series of paediatric patients in diverse countries have emerged in recent years (Table IV). In a retrospective review of 32 children transfused for proven or suspected infection, Grigull *et al* (2006) reported 73% survival for bacterial infection and 57% for fungal infection.

Kikuta *et al* (2006) conducted a pilot study of GTX collected from G-CSF-stimulated blood relatives without apheresis. Only 2 of 13 patients had fungal infections (one with disseminated *C. albicans*, who died on day 3, and one with oral *A. flavus*, who survived to day 30). Eight of 11 children with bacterial infections survived to day 30.

Sachs *et al* (2006) conducted an open, single-centre, prospective Phase II clinical trial to assess the feasibility, safety and efficacy of early-onset G-CSF mobilized GTX in neutropenic children with severe infections. Overall, 25 of 27 (93%) were able to clear the infection being treated with GTX. All six patients with invasive aspergillosis showed clinical and radiological improvement, one patient with disseminated *C. krusei* cleared blood cultures. This study boasts a remarkable response rate, but this may have been due to the lower proportion (7/27) of cases with fungal infection, and/or as claimed by the authors, attributed to the early initiation of GTX, i.e., after a median infection period of 6 days, compared with 8 days (Peters *et al*, 1999) and 12 days (Hester *et al*, 1995; Cesaro *et al*, 2003) in other studies.

Drewniak *et al* (2008) reported the outcomes of 16 severely ill children treated with GTX. Eight of 11 patients (73%) with proven *Aspergillus* infection showed clinical recovery and negative galactomannan levels within 10 days of starting GTX. Four additional children received pre-emptive GTX during HSCT due to chronic infections. All four survived transplantation without evidence of disseminated infection; three of these had chronic mould infections.

Seidel *et al* (2009) conducted a prospective study of 49 children and 10 young adults suffering from bacterial (n=55) and/or fungal (n=31) infections during neutropenia. The first

30 patients were reported in a prior publication (Peters *et al*, 1999). The 28-day and 100-day survival probability for patients with fungal infections was 0.51 ± 0.12 and 0.40 ± 0.11 respectively, compared to 0.89 ± 0.06 and 0.65 ± 0.09 for bacterial infections (p = 0.039).

In a retrospective analysis, Graham *et al* (2009) reported the outcomes of 13 paediatric oncology patients with proven or suspected serious infection. Eight of the 13 patients had fungal infections, four of who died prior to discharge; however the dose of granulocytes per transfusion was not specified. Atay *et al* (2011) reported 35 paediatric patients with high-risk febrile neutropenia or defective granulocyte functions who received GTX for 3 consecutive days during refractory infections. Ten of 18 (56%) patients with fungal infections responded favourably. Oztürkmen *et al* (2013) retrospectively reported 10 children with haematological disorders who developed 13 episodes of febrile neutropenia with or without microbiologically documented infection treated with GTX. During 7 of 13 of episodes (53.8%), patients received G-CSF as well as GTX. The overall clinical response and infection-related mortality rates were 69% and 31%, respectively. Two of three children with IFI responded, and one patient with candidaemia did not.

Diaz *et al* (2014) retrospectively reviewed 18 children with granulocyte dysfunction or severe neutropenia who received GTX. Four of five (80%) cases that received GTX for IFI demonstrated response and one case of invasive fusariosis progressed. Nikolajeva *et al* (2015) performed a retrospective analysis on 28 consecutive paediatric HSCT recipients treated with GTX. Seven of 14 patients with IFI showed radiological improvement, with 79% 100-day survival.

Randomized Controlled Trials of Prophylactic Granulocyte Transfusion

We identified 8 prospective controlled trials of prophylactic GTX, in which at least one patient in either the control group or the GTX group developed a fungal infection (Table V). Two of these studies (Clift *et al*, 1978; Gomez-Villagran *et al*, 1984) concluded that prophylactic GTX was protective; there were no breakthrough fungal infections in the prophylactic group. The other six (Schiffer *et al*, 1979; Winston *et al*, 1980; Winston *et al*, 1981; Strauss *et al*, 1981; Buckner *et al*, 1983; Petersen *et al*, 1986) reported little to no benefit, but an increased risk of complications, such as CMV infection and pulmonary complications. Notably, all of these studies employed unstimulated, low-dose granulocyte transfusions; none of the studies included patients with neutrophil dysfunction. No RCTs of prophylactic GTX have been conducted since the start of the G-CSF era.

Data on prophylactic GTX in patients with neutropenia or neutrophil dysfunction has been reviewed extensively in a recent Cochrane database systematic review (Estcourt *et al*, 2015). The authors concluded that this intervention did not improve overall or infection-related mortality or incidence of localized breakthrough fungal infection; but in a subgroup analysis, there were fewer people with infections in the group receiving prophylactic transfusions at a dose of 1.0 to 4.0 × 10^{10} granulocytes per day. The suggestion of lower incidence of fungaemia among cases that received prophylactic GTX was supported by low quality evidence.

Randomized Controlled Trials of Therapeutic Granulocyte Transfusion

We identified 5 RCTs of therapeutic GTX including patients with proven or probable fungal infection (Table VI). Three early studies (Higby *et al*, 1975; Alavi *et al*, 1977; Vogler & Winton, 1977) reported some benefit of GTX; however, fungal infections represented a minority of cases in these studies. Two recent controlled trials failed to confirm or refute the benefit of therapeutic GTX. Seidel *et al* (2008) found that the probability of 28-day survival after randomization was > 80% in both groups, and no effect of GTX on survival until day 100 could be detected in patients with fungal, bacterial or unknown infection, but this study was underpowered due to low enrolment. Price *et al* (2015) conducted a multicentre RCT, the RING (Resolving Infection in Neutropenia with Granulocytes) study. Initially, only patients with chemotherapy-related neutropenia and documented infection were enrolled. Due to poor recruitment, the eligibility criteria were changed to include patients with presumed infection and patients with underlying marrow disease. The primary end-point of this study was a composite of survival plus microbial response at 42 days. For invasive infections, response was defined as resolution or evidence demonstrating clinical improvement; stable infection was considered to be a failure. Invasive fungal infections and fungaemia comprised 36% and 11% respectively. Differences in primary end-point success rates for granulocyte and control arms were not statistically significantly different for any infection type whether analysed by intention-to-treat or per protocol. However, this study was underpowered due to low accrual rates and may have missed a clinically positive effect. The granulocyte dose was also lower than anticipated; the target of $\geq 4.0 \times 10^{10}$ granulocytes per transfusion was only achieved in 70% of subjects. In a post-hoc analysis, subjects who received an average dose per transfusion of $\geq 0.6 \times 10^{9}$ granulocytes/kg tended to have better outcomes than those receiving a lower dose.

A recent update of a Cochrane review on therapeutic granulocyte transfusion (Estcourt *et al*, 2016) concluded that in patients who are neutropenic due to myelosuppressive chemotherapy or HSCT, there is insufficient evidence to determine whether granulocyte transfusions affect all-cause mortality. There were no differences between the granulocyte dose subgroups ($< 1 \times 10^{10}$ per day versus $\geq 1 \times 10^{10}$ per day); however there may be a reduction in all-cause mortality in participants receiving granulocyte transfusions compared to those that did not in studies published before the year 2000. There is low-grade evidence that therapeutic granulocyte transfusions may not increase the number of patients with clinical resolution of an infection. Notably, the Cochrane review did not offer specific recommendations on the subgroup with IFI.

ADVERSE EFFECTS

The collection process entails minimal risk to donors. The short-term side effects of G-CSF, such as bone pain, headache and myalgia are generally mild and treatable. Axdorph Nygell *et al* (2015) reported no serious short-term adverse events in 18 years of granulocytapheresis; long-term follow-up of granulocyte donors stimulated with G-CSF and dexamethasone after 10 years (Quillen *et al*, 2009b), suggests that granulocyte donation is safe.

Febrile transfusion reactions and pulmonary complications, including transfusion-related acute lung injury (TRALI) (Sachs & Bux, 2003), are well-recognized complications of GTX, and are more likely to occur in patients with pre-existing granulocyte-reactive (HLA or human neutrophil antigen, HNA) antibodies (Dutcher *et al*, 1990; Heim *et al*, 2011). Neutrophil antibodies decrease the localization of transfused granulocytes to sites of inflammation (Stroncek *et al*, 1996). Lee *et al* (2004) demonstrated pulmonary localization of technetium-99m–labelled granulocytes in patients with pneumonia; cells accumulated at the area of infection in responders but not in the non-responders, suggesting that efficacy depends on the cells' ability to migrate to the site of infection. By selecting HLA-compatible granulocyte donors, appropriate increments can be obtained and adverse reactions minimized (Quillen *et al*, 2009a). GTX can also cause alloimmunization to HLA and HNA (Stroncek *et al*, 1996), resulting in subsequent platelet and leucocyte transfusion refractoriness (Heim *et al*, 2011). One group described massive haemoptysis (3.5%) and respiratory failure (5.9%) in GTX recipients (Kim *et al*, 2011). Pulmonary toxicity associated with co-infusion with Amphotericin B was reported in one publication (Wright *et al*, 1981). However, other authors (Bow *et al*, 1984; Dutcher *et al*, 1989) failed to prove any specific detrimental interaction, concluding that the relationship was a function of tropism of the transfused neutrophils for pulmonary sites of IFI.

Granulocyte transfusion poses many of the same infectious risks as other blood products, and increased risk of infection with intracellular pathogens, such as CMV (Hersman *et al*, 1982); transmission of West Nile Virus (Meny *et al*, 2011) has also been reported. Due to the presence of viable lymphocytes in the granulocyte product, patients are at risk of transfusion-associated graft-versus-host disease (TA-GVHD) (Rosen *et al*, 1978; Nikoskelainen *et al*, 1983), a rare but highly fatal complication that results when transfused T-lymphocytes engraft, proliferate and attack host tissue antigens in a recipient who is unable to reject the allogeneic cells, either due to immune compromise or HLA-similarity to the donor. To prevent this complication, granulocyte concentrates must be irradiated before transfusion.

Perhaps in the future, functionally mature neutrophils generated from induced pluripotent stem cells (iPSCs) (Morishima *et al*, 2011; Sweeney *et al*, 2014) may resolve the problems of supply, adverse reactions and burdens on donors.

EVIDENCE SUMMARY AND CONCLUSIONS

Morbidity and mortality from IFIs remains substantial. Transfusion of granulocytes from stimulated healthy donors is often accompanied by a significant increase in the patient's neutrophil count; the cells are capable of localization to areas of infection and appear to function normally. The process of granulocyte collection is relatively safe for donors.

While there is low-grade evidence that GTX may reduce the incidence of fungaemia, non-selective prophylaxis for all neutropenic patients does not prevent mortality due to localized fungal infection, and is accompanied by significant risks to recipients; as such, we do not recommend this practice. GTX may have a role in preventing progression of existing fungal

infection during HSCT-induced neutropenia (Borge *et al*, 2010; Hermann *et al*, 2001; Drewniak *et al*, 2008, Diaz *et al*, 2014).

Recipients of GTX with IFI tend to be quite ill with several competing risk factors for mortality; therefore clinical response might be a more realistic marker of benefit than survival. Studies of GTX in the post-G-CSF era generally reported higher response rates, even for some refractory mould species. Unfortunately, the quality of the data suggesting response to therapeutic GTX in IFI is low, and predominantly limited to individual cases and uncontrolled case series. It remains unclear whether the RING trial was truly a negative study or whether it was unable to demonstrate the benefit of GTX due to low sample size. No RCTs to date have reported specifically on comparative effectiveness of GTX by fungal species. Nevertheless, in light of the evidence and its limitations, the authors would still recommend use of GTX in IFI if rapidly available at sufficient cell doses (at least 1.0×10^{10} or $\geq 0.6 \times 10^{9}$ granulocytes/kg) in select circumstances, such as salvageable patients with anticipated recovery of neutropenia. The risks and benefits must be weighed on a case-by-case basis. Treatment schedules may vary, but responses have been reported using intervals of up to 3 days between transfusions, with criteria for discontinuation including neutrophil recovery or clinical resolution of infection. The GRANITE (Transfusion of granulocytes for patients with febrile neutropenia) study, an ongoing multicentre RCT based in Germany (German Clinical Trials Register number DRKS00000218), may yet offer helpful results. Future studies should evaluate high-dose GTX and aim to compare homogenous groups of patients to controls, evaluating clearly defined parameters of response to GTX.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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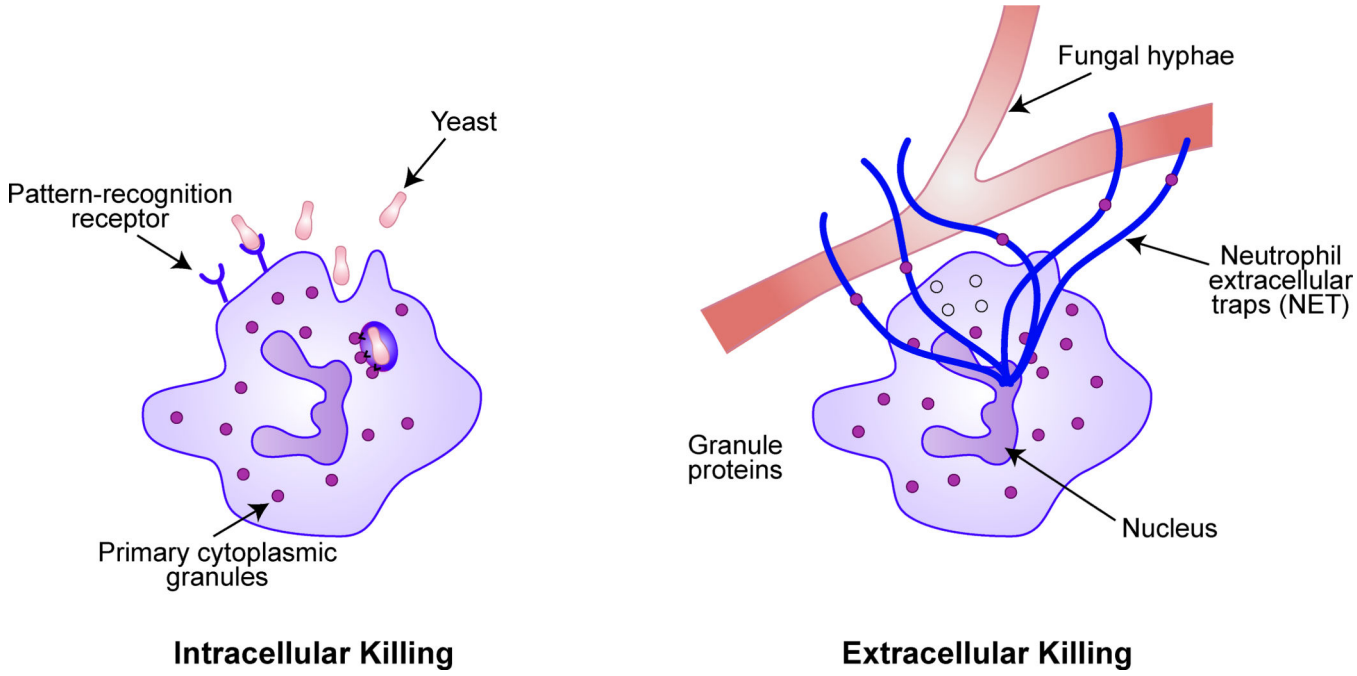

Figure 1.

Neutrophil-mediated intracellular and extracellular killing of fungal pathogens. During phagocytosis, neutrophil azurophilic granules fuse with the phagosome and release contents (cathepsin G, elastase, proteinase 3, and myeloperoxidase) into the phagocytic vacuole. For larger structures like fungal hyphae, the neutrophil releases web-like extracellular traps (NETs) composed of decondensed chromatin in complex with antimicrobial proteins that trap and neutralize pathogens. Adapted with permission from Macmillan Publishers Ltd: (Wheeler, M.L. & Underhill, D. M. Time to cast a larger net. *Nature Immunology*, 11, 1000–1001), copyright (2014).

Table I

Summary of case reports and small series of therapeutic granulocyte transfusions in invasive fungal infections.

	Number of Cases	Disseminated Infection	Clinical Response	Radiological Response	Microbiological Response	Overall response
Pre-G-CSF Era (1973 – 1992)	**16**	**5 (31%)**	**14 (87%)**	**4 (25%)**	**3 (19%)**	**14/16 (87%)**
Aspergillus	11	2 (18%)	9 (82%)	3 (27%)	2 (18 %)	9/11 (82%)
Fusarium	4	3 (75%)	4 (100%)	1 (25%)	1 (25%)	4/4 (100%)
Candida	1	0 (0%)	1 (100%)	NS	NS	1/1 (100%)
G-CSF Era (1993 – 2015)	**81**	**33 (41%)**	**54 (67%)**	**16 (20%)**	**10 (12%)**	**61/81 (75%)**
Aspergillus	46	10 (22%)	27 (59%)	11 (24%)	3 (7%)	32/46 (70%)
Mucorales	12	3 (25%)	8 (67%)	1 (8%)	1 (8%)	10/12 (83%)
Fusarium	10	9 (90%)	9 (90%)	1 (10%)	4 (40%)	9/10 (90%)
Candida	9	9 (100%)	8 (88%)	1 (11%)	2 (22%)	8/9 (88%)
Other fungi[a]	4	2 (50%)	2 (50%)	2 (50%)	0 (0%)	2/4 (50%)
Total	**97**	**38 (39%)**	**68 (70%)**	**20 (20%)**	**13 (13%)**	**75/97 (77%)**

Invasive fungal infections were classified according to the Revised European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group definitions (De Pauw *et al*, 2008).

Outcomes of therapeutic granulocyte transfusion, where specified, were classified as: (1) clinical response (defervescence, reduction or disappearance of local symptoms of infection, or decrease in size or appearance of visible lesions), (2) radiological response (decreased size or disappearance of lesions on imaging) or (3) microbiological response (clearance of previously positive cultures or antigen tests).

[a] *Trichosporon*, and *Scedosporium* spp.

G-CSF, granulocyte colony-stimulating factor; NS, not specified.

Table II

Case series of specific IFIs treated with G-CSF-stimulated granulocyte transfusions.

Study	N (controls)	Underlying Condition	Study Design	Infections	Average GTX Dose	Intervention	Outcomes	Adverse Events
Hester *et al* (1995)	15	HM	Uncontrolled	11 moulds, 4 yeast	4.1×10^{10}	Therapeutic	73% stable or improved, 20% 3 month survival	Pulmonary reactions (30%)
Hermann *et al* (2001)	4	HSCT, HM	Uncontrolled	IA, Mucor	4.6×10^{10}	Pre-emptive[a]	75% regression of fungal lesions, 100% survival > 1 year	No serious side effects
Kerr *et al* (2003)	9 (18)	HSCT, HM/AA	Controls matched for conditioning regimen	IA	6.4×10^{10}	Pre-emptive[b]	57% showed radiological improvement, GTX group less likely to become febrile ($p < 0.05$), fewer days of fever ($p < 0.05$), no survival benefit	Fever, bronchospasm (11%)
Safdar *et al* (2004)	29 (462)	HSCT, HM	Controls, unmatched	Candidaemia	5.6×10^{10}	Therapeutic	Fewer CR in GTX group ($p < 0.001$), no difference in attributable mortality ($p = 0.5$)	NS
Yenicesu *et al* (2011)	5	HSCT, HM/AA	Uncontrolled	IPA, Invasive Candidiasis	3.49×10^{10}	Therapeutic	60% full clinical recovery	
Raad *et al* (2013)	53 (75)	HM	Controls, unmatched	Proven and probable IA	5.5×10^{10}	Therapeutic	IPA less likely to respond to antifungal therapy ($p = 0.03$), more likely to die of IA ($p = 0.009$) in GTX group	Pulmonary reactions (53%)
Kadri *et al* (2015)	11	HSCT, HM/AA	Uncontrolled	Invasive Fusariosis	6.84×10^{10}	Therapeutic	91% 30-day survival, 73% 90-day survival	Pulmonary reactions (18%), HLA alloimmunization (9%)

AA, aplastic anaemia; CR, complete response; G-CSF, granulocyte colony-stimulating factor; GTX, granulocyte transfusion; HLA, human leucocyte antigen; HM, haematological malignancy; HSCT, haematopoietic stem cell transplant; IA, invasive aspergillosis; IFI, invasive fungal infection; IPA, invasive pulmonary aspergillosis; NS, not specified.

[a]Patients had existing fungal infection at the time of HSCT.

[b]Patients were considered at high risk due to history of IA or because of prolonged neutropenia. Many patients had evidence of disease at the time of the study.

Table III

Case series reporting bacterial and fungal infections in adult patients treated with GTX in the G-CSF era.

Study	N (fungal /total)	Underlying Condition	Average GTX Dose	Intervention	Outcome (Fungal)	Outcome (Bacterial)	Adverse Events
Grigg *et al* (1996)	9/11	BMT, HM, AA	$5{\cdot}9 \times 10^{10}$	Therapeutic (8) Prophylactic (3)	0% resolved, 67% successful prophylaxis (recent infection)	100% resolved	No pulmonary reactions
Lee *et al* (2001)	11/25	HM	6.6×10^{10}	Therapeutic	73% favourable response	45% favourable response	Pulmonary oedema (8%), hypoxia (4%), SVT (4%)
Illerhaus *et al* (2002)	10/18	HM	2.6×10^{10} 3.2×10^{10}	Therapeutic (18), Prophylactic (16)	55% IPA responded, no benefit of prophylactic GTX	78% septicaemia responded	CMV transmission, alloimmunization
Hübel *et al* (2002)	57/74	HM	$4{\cdot}6–8{\cdot}1 \times 10^{10}$	Therapeutic (paired controls)	Non-progression in 18% mould, 55% yeast, no difference vs controls	Fewer progressive bacterial infections in control group (p = 0.04)	Fever (17.5%), chills (30%), desaturation and pulmonary oedema (1%)
Rutella *et al* (2003)	7/20	HM	1.7×10^{10}	Therapeutic	57% response, 100% fungaemia, 0% IFI	54% response rate	Fever, chills, bronchospasm
Mousset *et al* (2005)	31/44, 20/23	HSCT, HM	4.3×10^{10}	Therapeutic (44), Prophylactic (23)	78% response at 30 days, 58% survival at 100 days	92% response at 30 days, 77% survival at 100 days	NS
Safdar *et al* (2006)	19/20	HSCT, HM,	5.6×10^{10}	Therapeutic	45% CR or PR, 15% stable	NS	Transient dyspnoea (5%)
Ofran *et al* (2007)	28/47	HM, AA	3.6×10^{10}	Therapeutic	64% infection-related survival	53% infection-related survival	Pulmonary reactions (13%)
Quillen *et al* (2009a)	18/32	SAA	6.8×10^{10}	Therapeutic	44% survival, 33% CR, 22% PR, 17% stable, 28% progress	58% overall survival to discharge	HLA alloimmunization (17%), pulmonary (15%)
Al-Tanbal *et al* (2010)	16/22	SAA, HM, CGD	2.8×10^{10}/L	Therapeutic	75% survival	68% clinical improvement	TRALI (4.5%)
Ang & Linn (2011)	13/15	HM	5.0×10^{10}	Therapeutic	31% cleared	63% cleared	NS
Kim *et al* (2011)	37/128	HM, AA	0.96×10^{9}/kg	Therapeutic	47% control of proven or probable IFI	Overall control of infection 53%	Fever (19%), hypotension (6.5%), respiratory (9%)
Safdar *et al* (2014)	33/74	HSCT, HM, other	5.6×10^{10}	Therapeutic	45% patients had IFI	46% overall response	Fever (3%), respiratory (8%)
Wang *et al* (2014)	31/56	SAA	0.92×10^{10}	Therapeutic	87% 30-day, 58% 90-day, 52% 180-day survival	92% 30-day, 84% 90-day, 84% 180-day survival	Fever, chills, allergy, dyspnoea

AA, aplastic anaemia; BMT, bone marrow transplantation; CGD, chronic granulomatous disease; CMV, cytomegalovirus; G-CSF, granulocyte colony-stimulating factor; GTX, granulocyte transfusion; HM, haematological malignancy; HSCT, haematopoietic stem cell transplant; IFI, invasive fungal infection; IPA, invasive pulmonary aspergillosis; NS, not specified; PR, partial response; SAA, severe aplastic anaemia; TRALI, transfusion associated acute lung injury.

Table IV

Case series reporting bacterial and fungal infections in paediatric patients treated with GTX in the G-CSF era.

Study	N (fungal /total)	Underlying Condition	Average GTX Dose	Intervention	Outcome (Fungal)	Outcome (Bacterial)	Adverse Events
Grigull *et al* (2006)	6/32	HSCT, HM	6.35×10^{10}	Therapeutic	67% survival	81% survival	Fever (9.6%), respiratory distress (5.3%)
Kikuta *et al* (2006)	2/13	HO	6.4×10^{8}/kg	Therapeutic	50% response	73% response	Hypoxia (8%)
Sachs *et al* (2006)	7 /27	HO, AA	2.0×10^{10}	Therapeutic	100% response	93% overall response	Mild fever, chills (7%), no pulmonary reactions
Drewniak *et al* (2008)	13/16, 3/4	HO, HSCT	2×10^{9}/kg	Therapeutic (16), Pre-emptive[a] (4)	73% response (IA), no progression with pre-emptive GTX	Overall 68% response	NS
Seidel *et al* (2009)	31/69	HO, HSCT	6×10^{9}/kg in first 5 days	Therapeutic	28-day, 100-day survival probability 0.51 ± 0.12 and 0.40 ± 0.11	28-day, 100-day survival probability 0.89 ± 0.06 and 0.65 ± 0.09	Fever (14%), chills (3%), airway obstruction (3%)
Graham *et al* (2009)	8/13	HO	NS	Therapeutic	50% survived to discharge	100% survived to discharge	Fever (15%)
Atay *et al* (2011)	18/35	HO, CGD	2.7×10^{10}	Therapeutic	55% clinical response, 78% infection-related survival	65% clinical response, 88% infection-related survival	No serious reactions
Oztürkmen *et al* (2013)	4/10	HM	2.9×10^{10} 0.6×10^{9}/kg	Therapeutic	50% response	80% response	Oliguria and/or mild respiratory distress (23%)
Diaz *et al* (2014)	5/18	HM, CGD	6.7×10^{10}	Therapeutic (13), Pre-emptive[a] (5)	80% complete or partial response	100% in non-fungal infection	Respiratory (46%)
Nikolajeva *et al* (2015)	14/28	HM, AA, CGD	3.6×10^{10}	Therapeutic	50% radiological improvement, 43% stable disease, 79% 100-day survival	50% 100-day survival	Fever (18%), mild respiratory symptoms (11%)

[a]GTX was used pre-emptively to prevent exacerbation of existing infection during HSCT.

AA, aplastic anaemia; CGD, chronic granulomatous disease; G-CSF, granulocyte colony-stimulating factor; GTX, granulocyte transfusion; HM, haematological malignancy; HO, haematology/oncology; HSCT, haematopoietic stem cell transplant; IA, invasive aspergillosis; NS, not specified.

Table V

Randomized controlled trials of prophylactic granulocyte transfusion in non-infected patients.

Study	N	Indication for GTX	Stimulation average GTX Dose	GTX Course	Overall Outcomes	Fungal Outcomes	Adverse Events
Clift *et al* (1978)[a]	69	BMT (HM/AA), ANC < 0.2×10^9/l	US, 2.22×10^{10} (FL), 1.57×10^{10} (CFC)	Daily, mean 12.4 (6–25)	Fewer infections (2/29) in GTX group vs control group (17/40) 21-days post-HSCT	Fewer deaths from fungal infection in GTX group (0/29) vs controls (2/40)	NS
Schiffer *et al* (1979)[a]	19	AML ANC < 0.5×10^9/l	D, 1.15×10^{10}	Alternate days, mean 11 (3-19)	No severe infection in GTX group, 3/9 in control group	3/9 fungal infections in control group	Fevers, pulmonary reactions alloimmunization
Winston *et al* (1980)[a]	38	BMT (HM/AA), ANC < 0.5×10^9/l	US, 1.2×10^{10}	Daily, mean 23.4 (13–34)	No significant difference	1/19 fungal pneumonia each in GTX and control group	NS
Strauss *et al* (1981)	102	AML ANC < 0.5×10^9/l	US, 3.4.x $10^9/m^2$	Daily, mean 18.5 (3–28)	No significant difference	5/54 IFI (GTX) vs 3/48 (controls)	Transfusion reactions (72%), pulmonary infiltrates (57%)
Winston *et al* (1981)[a]	46	AML ANC < 0.5×10^9/l	US, 0.56×10^{10}	Daily, median 24 (7–28)	No significant difference ($p = 0.48$)	1/21 IFI (controls)	68% had reactions, CMV, pneumonitis
Buckner *et al* (1983)[b]	182	BMT (HM/AA), ANC < 0.2×10^9/l	NS	Daily, median 13 (2–31)	No significant difference in infection or mortality at 100 days	3 IFI (GTX) vs 8 (controls)	Severe pulmonary reaction, CMV, pneumonitis
Gomez-Villagran *et al* (1984)	35	AML ANC < 0.5×10^9/l	D, 1.24×10^{10}	Daily, mean 6.16 (5–11)	Fewer life-threatening infections ($p < 0.01$), fewer infectious deaths ($p < 0.05$) in GTX group vs controls	No fungal infections in GTX group, 2 oral candidiasis in control group	Pulmonary (2.3%), febrile (57.1%) and allergic (1.5%) reactions, passive haemolysis
Petersen *et al* (1986)[a]	112	BMT (HM), ANC < 0.2×10^9/l	NS	Daily, median 12 (6–27)	No significant difference in 100-day mortality post-HSCT, death from infection	1/67 IFI (GTX) vs 5/45 (controls)	7% transfusion reactions, mostly pulmonary

AA, aplastic anaemia; AML, acute myeloid leukaemia; ANC, absolute neutrophil count; BMT, bone marrow transplantation; CFC, continuous flow centrifugation; CMV, cytomegalovirus; D, dexamethasone; FL, filtration leukapheresis; GTX, granulocyte transfusion; HM, haematological malignancy; HSCT, haematopoietic stem cell transplant; IFI, invasive fungal infection; NS, not specified; US, unstimulated.

[a]Patients were eligible to receive therapeutic GTX during the study if they developed infection.

[b]Partially randomized: if only one intervention option was available, patients were allocated to that modality.

Table VI

Randomized controlled trials of therapeutic GTX for documented or suspected infection.

Study	N	Underlying condition	Stimulation average GTX Dose	GTX Course	Outcome Measures	Outcome of GTX	Fungal outcomes	Adverse Events
Pre-G-CSF Era								
Higby *et al* (1975)	36	HM, ANC < 0.5 × 10^9/l	D, 2–5 × 10^{10}	Daily, 4 days	20-day survival	20-day survival 88% 15/17 (GTX), 5/19, 26% (controls)	2 candida infections in GTX group, 1 in control group[a]	NS
Alavi *et al* (1977)	31	AML/ALL, ANC < 0.25 × 10^9/l	HC, 5 × 10^{10} (3.3 × 10^{10} in children, 5.9 × 10^{10} in adults)	Daily, 7 per episode (3–18)	21-day survival	No significant difference overall; with persistent marrow failure, 21-day survival 75 % in GTX, 20 % controls,(p = 0.03)	1 candida infection each in GTX and control groups	Fever (16%) chills (7%), laryngospasm (1), urticaria (2)
Vogler & Winton (1977)	30	HM, AA, DIG ANC < 0.3 × 10^9/l	US, HC or D, 2.68 ×10^{10}	NS	Microbiological or clinical resolution of infection, survival	Response in 10/17 GTX group vs 2/13 controls (p < 0.05) Median survival 22.5 days (GTX), vs 7.7 days (controls) p < 0.01	1 candida infection in control group	No reactions
G-CSF Era								
Seidel *et al* (2008)	79	HM/AA/ST	G-CSF, 6.6 × 10^8/kg	> 3 per week, median 3 (1–13)	28-day survival after randomization	No statistically significant difference in survival	Fungal infections in 55 patients	Pulmonary (4), other reactions (7)
Price *et al* (2015)	97	HM/AA, ANC < 0.5 × 10^9/l	G-CSF+D, 5.49×10^{10}	Median 5 GTX	Microbiological or clinical resolution of infection, survival at 42 days	No difference in overall success rates for GTX (42%) vs controls (43%) by MITT (p> 0.99) or per protocol (49% and 41%, p=0.64)	36% IFI, 11% fungaemia No difference in outcomes by infection type	Mild fever, chills (41%), hypoxia, tachycardia, hypotension, allergic reactions (20%)

AA, aplastic anaemia; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; ANC, absolute neutrophil count; D, dexamethasone; DIG, drug-induced granulocytopenia; G-CSF, granulocyte colony-stimulating factor; GTX, granulocyte transfusion; HC, hydrocortisone; HM, haematological malignancy; IFI, invasive fungal infection; MITT, modified intent-to-treat analysis; NS, not specified; ST, solid tumour; US, unstimulated.

[a]Organisms only specified for patients < 45 years old.