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Role of Granulocyte Transfusions in Invasive Fusariosis: Systematic Review and Single Center Experience

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Abstract

Background—Invasive *Fusarium* infection is relatively refractory to available antifungal agents (AFAs). Invasive fusariosis (IF) occurs almost exclusively in the setting of profound neutropenia and/or systemic corticosteroid use. Treatment guidelines for IF are not well established, including the role of granulocyte transfusions (GTs) to counter neutropenia.

Study Design and Methods—We conducted a systematic review, identifying IF cases where GTs were used as adjunctive therapy to AFAs and also report a single-center case-series detailing our experience (1996-2012) of all IF cases treated with AFAs and GTs. In the systematic review cases, GTs were predominantly collected from non-stimulated donors, whereas, in the case-series, they were universally derived from dexamethasone/G-CSF-stimulated donors.

Results—Twenty-three patients met inclusion criteria for the systematic review and 11 for the case-series. Response rates post-GTs were 30% and 91% in the review and case-series, respectively. Survival to hospital discharge remained low at 30% and 45%, respectively. Ten patients in the systematic review and 3 in the case-series failed to achieve hematopoietic recovery and none of these survived. In the case-series, donor-stimulated GTs generated mean 'same-day' neutrophil increments of 3.35 ±1.24 $\times 10^9$/L and mean overall posttransfusion neutrophil increments of 2.46 ± 0.85 $\times 10^9$/L. Progressive decrements in neutrophil response to GTs in 2 cases were attributed to GT-related HLA alloimmunization.

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KER contributed to the case-series and manuscript.
JRS conducted the systematic review and contributed to the manuscript.
JG conceptualized the study and critically revised the manuscript.
SFL oversaw the systematic review and case-series and critically revised the manuscript.

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Conclusion—In patients with IF, donor-stimulated GTs may contribute to high response rates by effectively bridging periods of neutropenia/marrow suppression. However, their utility in the absence of neutrophil recovery remains questionable.

Keywords

fusarium; fusariosis; granulocyte transfusion; neutropenia

Introduction

Fusarium has emerged over the last 4 decades as a serious human pathogen whose pathogenicity is intimately linked to host immune factors.[1-4] While this plant fungus is known to cause superficial disease such as keratitis and onychomycosis in the immune competent host, unregulated proliferation in the setting of profound neutropenia results in locally invasive and disseminated (collectively termed invasive) disease.[2,5] At many centers, it ranks second only to *Aspergillus* as the cause of invasive mold infections.[5] Evidence for improvement in the outcome of invasive aspergillosis is well established with the use of newer antifungal agents.[6] Whereas some improvement has recently been observed in the outcome of invasive fusariosis (IF), it remains largely a refractory disease.

Fusarium sporulates *in vivo*, facilitating hematogenous dissemination and resulting in fungemia in as many as 70% of cases; the highest among molds seen in hematopoietic transplant recipients.[7] While there is considerable interspecies variability in susceptibility, most *Fusarium* species remain relatively resistant to all available antifungal agents.[4] *Fusarium* growth often breaks through empiric antifungal prophylaxis in neutropenic patients,[8] and definitive diagnosis is often delayed as the organisms are frequently misidentified on histopathology.[9] Even in the presence of apparent *in vitro* susceptibility, minimum inhibitory concentrations (MIC) correlate poorly with clinical outcomes. Optimum management is not well defined, with observational evidence of comparable but low efficacy for liposomal amphotericin (46-53%),[7,10] voriconazole (47-60%),[7,11] and posaconazole (48%).[12] These factors make IF more difficult to treat than other pathogenic molds.

Among host factors, persistent neutropenia remains the single most important prognostic factor in IF.[3] Despite antifungal therapy, mortality is high when neutropenia is severe and prolonged. In contrast, up to 70% of cases resolve when neutrophils promptly return to normal.[13] Granulocyte transfusions (GTs) have been used as an adjunct to antimicrobial agents with varying success for patients with persistent neutropenia and life-threatening infections.[14,15] Initial experience with GTs in the treatment of invasive mold infections was tempered by the occurrence of adverse pulmonary reactions to transfusion, unimpressive neutrophil increments, and the availability of newer, more potent antifungal agents.[15,16] A resurgence of interest in GTs occurred following the introduction of donor preparative regimens incorporating granulocyte-colony stimulating factor (G-CSF) and dexamethasone, leading to the collection of higher-yield components and greater neutrophil increments in the recipient.[17,18]

The use of GTs may serve as a bridge to clinical stability until definitive marrow recovery occurs. However, the low incidence of IF and the even lower incidence of GT therapy in IF have resulted in a reliance on uncontrolled outcome data limited to individual case reports or small series to guide management.[19,20] Results from the single randomized clinical trial designed to address this question have not yet been reported.[21]

In this investigation, we systematically review the literature for cases of IF treated with GTs and present our experience in a consecutive series of such cases treated at the NIH Clinical Center in the past 16 years.

Materials and Methods

Systematic Review

PubMed, Scopus, EMBASE and Web of Science databases were searched by JRS and SSK for all publications up to May 2013 using keywords and strategies described in supplemental data. Searches were not limited by publication date or language. Inclusion criteria included cases with culture and/or biopsy evidence of IF in which at least one GT was administered following the diagnosis, and which provided sufficient detail to determine subject age, underlying diagnoses, site of infection, antifungal treatments, and outcome. Manuscripts meeting these minimum criteria were then evaluated for inclusion into the study series. The articles comprised randomized controlled and uncontrolled trials, observational studies, case series and individual reports.[22-37]

NIH Case-Series

Case Identification—Cases were identified among subjects admitted to the NIH Clinical Center, the inpatient facility at the National Institutes of Health (NIH, Bethesda, MD), between September 1996 and September 2012. The Biomedical Translational Research Information System (BTRIS) database (intramural data repository for the NIH) was queried to identify all cases with at least one culture growing *Fusarium* species from any site. Among these, cases in which at least two GTs derived from a dexamethasone/G-CSF-stimulated donor were administered at the time of treatment of the *Fusarium* infection were included. Independent queries were conducted within departmental databases and crosschecked. Infections were classified as proven, probable or possible based on standard definitions laid out by an international consensus committee.[38] NIH Office of Human Subjects Research Protection (OHSRP) approved the study protocol and relevant principal investigators approved the use of their patient data for this study.

Outcome Measures—The primary outcome was response as assessed within 14 days of starting a course of GTs. For the systematic review, response was defined as clinical improvement as reported in the original publication or clearance of microbiologic evidence of *Fusarium* infection. If neither was stated in the original publication, episodes were classified as “no response”. Similarly, for the case-series, response included clinical, microbiologic, or radiologic outcomes. Clinical response was defined as evidence of defervescence, hemodynamic stabilization and/or resolution of symptoms related to site involved. Microbiological response was defined as absence of *Fusarium* growth on

subsequent cultures obtained from the same site that had previously grown *Fusarium* spp. Radiological response was defined as evidence of decrease in size of nodules and/or area of infiltration.

Secondary endpoints included survival to hospital discharge, mean overall and 'same-day' increments in absolute neutrophil counts (ANC) following transfusion, and percent of subjects who developed HLA alloimmunization. Subjects who had their pretransfusion counts, granulocyte transfusion, and posttransfusion counts all accomplished within a 24 hour period were defined as having 'same day' ANC assessments. In the absence of a controlled clinical trial, substantial variability existed in the timing of pre- and posttransfusion sampling for ANC, necessitating this definition. Values are given as mean ± standard deviation, unless otherwise stated.

Human leukocyte antigen (HLA) typing and HLA antibody screening were routinely performed prior to initiation of granulocyte transfusions, and HLA antibody screening was repeated every 3 to 4 weeks in patients who underwent an extended course of transfusions. Methods used for detecting these antibodies included a microlymphocytotoxicity assay, a flow cytometric panel reactive assay (flow-PRA®; OneLambda, Canoga Park, CA), and an enzyme-linked immunosorbent assay (ELISA Lambda Antigen Tray; OneLambda, Canoga Park, CA). An attempt was made to find partially HLA-matched granulocyte donors for patients who were alloimmunized.

Granulocyte Collection and Processing—Granulocyte donors were enrolled in an IRB-approved protocol and received a single subcutaneous injection of G-CSF (filgrastim, Amgen, Thousand Oaks, CA) 12-18 hr prior to leukapheresis and 8 mg of dexamethasone orally 12 hr prior to leukapheresis. The dose of G-CSF was 5 ug/kg until July 2005 and 480 ug as a standard dose thereafter. Less than 2% of donors were family members who had previously donated a hematopoietic stem cell graft, the remainder were unrelated community members. Granulocyte concentrates were collected with a blood cell separator (Spectra, Terumo Inc., Lakewood, CO, or CS3000-Plus, Fenwal Inc., Deerfield, IL), processing 7 liters of whole blood to which a 6% hetastarch solution (Hespan 500 mL, Braun Medical, Irvine, CA) containing 30 mL of trisodium citrate (Tricitrasol 46.7%, Citra Labs, Braintree, MA) was added at a 12:1 ratio. Granulocyte products were sedimented by gravity following collection to remove red cells if they were not ABO-compatible with the recipient. All granulocyte concentrates were irradiated to 25 Gy and transfused within 8-10 hr of collection. Amphotericin therapy was avoided for 4 hr before and 4 hr after transfusion. Once a course of granulocyte therapy was initiated, the goal was to provide granulocyte concentrates daily or on alternate days.

Results

Systematic Review

Patient characteristics—The initial literature search generated 469 unique citations with 17 articles meeting all inclusion criteria. These results identified 23 patients across 3 series and 14 case reports published between 1984-2012, involving patients who had *Fusarium* infection and also received GTs (Table 1). Mean patient age was 26.3 (range 1-59) years.

All of the affected patients had an underlying disease process or associated therapy that resulted in profound neutropenia (ANC < 0.2×10^9/L) or neutrophil dysfunction. Species-level *Fusarium* identification was reported only in 10 of 23 episodes. Blood cultures were positive in 15/23 (65%) episodes of *Fusarium* infection and all cases with fungemia were reported to demonstrate necrotic cutaneous lesions. Other manifestations included pulmonary nodular infiltrates, endophthalmitis, retinitis, meningoencephalitis, sinus infection, splenic and renal necrosis, and osteomyelitis.

Granulocyte transfusions and outcomes of therapy—Only two patients received granulocytes derived from donors stimulated with G-CSF,[33,37] one of these two survived to hospital discharge. Disease resolution was defined as either clearance of blood cultures, resolution of cutaneous lesions, or nonspecifically as resolved. In 2 cases, resolution occurred concomitant with ANC recovery, but *Fusarium* relapse occurred when neutropenia returned (Table 1). Seven of 23 (30%) of cases had a response (clinical, radiographic, and/or microbiologic) in association with GTs prior to ANC recovery and the infection ultimately resolved in 6 of 7 cases that demonstrated response. Fifteen of 23 had at least transient ANC recovery, and 7 of these (30%) survived to hospital discharge. All 10 patients without sustained marrow recovery failed to clear the infection and died. Among the more recent cases (1998-2012), 4 of 5 (80%) patients cleared the infection and 3 of 5 (60%) survived to discharge, compared to only 9 of 18 (50%) episodes of *Fusarium* clearance described prior to 1998, with only 4 of 18 (22%) cases surviving to discharge.

NIH Case-Series

Patient characteristics—Between 1996 and 2012, there were 113 unique subjects admitted to the NIH Clinical Center with evidence of at least one tissue or blood culture growing *Fusarium* species. During the same period, 155 unique subjects, including 101 patients with severe neutropenia and 54 patients with chronic granulomatous disease, were administered at least one course of dexamethasone/G-CSF-mobilized GTs. Among these 101 subjects were 11 patients who received GTs as adjunctive therapy subsequent to the diagnosis of invasive *Fusarium* infection. In all 11 cases, the diagnosis of IF was proven by either culture or molecular identification of the fungus in samples from blood, skin, nasal/sinus, synovial or bone sites. The median time from initial positive *Fusarium* diagnosis to first GT was 4 days (range 1-8 days).

Among the 11 patients with IF who received a course of GTs, mean age was 46 (range 17-58) years and all but one were male. Eight of the cases (73%) occurred in or after 2008. The most common underlying diagnosis was severe aplastic anemia (5/11), followed by myelodysplastic syndrome (2/11), non-Hodgkin lymphoma (2/11) and one case each of acute lymphocytic and chronic myelocytic leukemia (Table 2). All 11 patients had experienced at least 30 consecutive days of neutropenia (ANC < 0.5×10^9 cells/L) and all had an ANC < 0.1×10^9 cells/L immediately prior to the diagnosis of IF. None had a prior history of *Fusarium* infection. Seven (64%) had one or more concomitant infections. Three (27%) had undergone allogeneic hematopoietic stem cell transplantation (HSCT). Three were known to have received systemic corticosteroids prior to diagnosis of fusariosis.

Clinical presentation, marrow suppressive regimens, and concomitant infections are provided in supplemental data.

Characteristics of *Fusarium* infection—Six cases had evidence of fungemia (positive *Fusarium* blood cultures) and/or hematogenous seeding in the form of multiple culture-positive lesions in the skin and/or joints. Five cases involved the paranasal sinuses, all of which were found to be invasive, 3 based on radiologic and 2 on histologic criteria. Five patients had lung infiltrates or nodules consistent with pulmonary involvement, but lung involvement was possible or probable, but not proven, in these cases. One patient each had retinal involvement (probable) and bone involvement (proven).

The species of *Fusarium* was identified in 9/11 cases: 5 *F. solani* and one each of *F. proliferatum*, *F. moniliforme*, *F. falciforme* and *F. verticillioides*. The remainder was reported as *Fusarium* species. Susceptibility testing performed at a reference laboratory showed the expected pattern of generalized resistance, with just the single *F. moniliforme* showing susceptibility to amphotericin, posaconazole and voriconazole (Table 3).

Following the microbiologic diagnosis of *Fusarium*, 6 patients received a combination of liposomal amphotericin and voriconazole, 3 received voriconazole alone and 2 received liposomal amphotericin alone (prior to availability of voriconazole). After US Food and Drug Administration approval of voriconazole as salvage therapy for fusariosis in 2002, 100% (9/9) of the cases received voriconazole as monotherapy or as part of combination therapy. Only locally invasive cases (sinusitis) received voriconazole as monotherapy. The mean Sequential Organ Failure Assessment (SOFA) score,[39] measured on the day of the first granulocyte transfusion, was 8.9 (SEM 0.21, range 8-10, n=11).

Hematologic response to granulocyte transfusions—A total of 133 granulocyte components were administered to 11 patients, for a median of 7 transfusions per patient (range 2-39). The mean granulocyte content per component was $6.84 \pm 2.34 \times 10^{10}$ cells in a volume of 320 ± 33 mL. The overall mean ANC increment per transfusion across all 11 cases was 2.46 ± 0.85 (range 0.03-8.78) $\times 10^9$ cells/L and ‘same day’ ANC increment was 3.35 ± 1.24 (range 0.42-10.88) $\times 10^9$ cells/L. ANC's remained greater than 0.5×10^9/L for at least 36 hours following transfusion in 61% of the transfusion events (n=41) in which data were available (Table 4).

Two patients (18%) showed unequivocal evidence of HLA alloimmunization related to GTs, with concomitant decrement in ANC response. Mean ANC increment declined from 1.65 ± 0.94 (first 16 GTs) to 0.59 ± 0.51 (last 10 GTs) ($p=0.003$) in patient #10 and from 2.24 ± 1.14 (first 8 GTs) to 0.21 ± 0.69 (last 4 GTs) $\times 10^9$ cells/L ($p<0.011$) in patient #11. A cord blood transplant performed in patient #10 eight weeks after the start of GTs did not engraft; the patient was found to have developed HLA alloimmunization to an antigen expressed on the cord blood unit.

Clinical responses and survival—Ten of 11 patients (91%) had objective clinical, radiographic, or microbiologic responses in IF within the first several days after the start of GTs; in 8 of these 10, progression of infection had been evident on maximized antifungal

regimens prior to the addition of GTs (Table 2). Following the first transfusion, blood cultures rapidly became negative in all 4 patients who presented with positive blood cultures. Brisk responses were also seen in the skin, with cessation of the appearance of new skin lesions and resolution or stabilization of existing lesions in 5 of 6 patients. All 5 patients with invasive *Fusarium* sinusitis showed a clinical and/or microbiologic response; however, all 5 also underwent surgical debridement. The single patient with progressive *Fusarium* infection showed new joint involvement and progression to osteomyelitis despite repeated joint debridement.

Ten of 11 patients (91%) survived for at least 30 days after and 8 of 11 (73%) survived for at least 90 days after initiation of GTs. Five of 11 (45%) survived to hospital discharge and remained alive for 1-10 years. Survival to discharge was strongly correlated with hematopoietic recovery. None of 3 (0%) without neutrophil recovery versus 5 of 8 (62%) with neutrophil recovery survived to discharge. Three of 8 succumbed to refractory underlying disease or treatment complications despite marrow recovery. Only one of 3 patients who underwent allogeneic HSCT within 2 months of the diagnosis of IFI engrafted and survived until discharge.

Respiratory insufficiency occurred in Patients #2 and #4 after 20 and 11 GTs, respectively (Table 2). Both patients developed pulmonary failure and death, and the GTs were considered contributors to this outcome, possibly through volume overload.

Discussion

This study describes the largest clinical experience to date with granulocyte therapy as part of a multimodality approach to the treatment of invasive *Fusarium* infections in patients with neutropenia. It is also the largest study in which granulocyte concentrates derived exclusively from G-CSF and dexamethasone-stimulated donors were used to treat IF. These products have markedly increased granulocyte content resulting in dramatically higher neutrophil increments in recipients and may have enhanced clinical efficacy compared to components prepared from non-G-CSF-stimulated donors.[14,40]

In one retrospective review of patients with IF and neutropenia who were treated with high-dose lipid formulations of amphotericin-B and newer broad-spectrum triazoles without GTs, initial clinical response rates of 45 to 70% and survival rates of 30% were reported.[13] Our systematic review of clinical response rates in 23 patients who received GTs and appropriate antifungal agents revealed an overall response rate of 30%, with 30% of patients surviving to discharge. Thus, our review did not suggest that GTs conferred greater efficacy than use of modern antifungal agents alone. This may be secondary to considerable variability in the pattern of use of GTs across patients. Specifically, only two of the 23 IF cases received granulocyte components derived from G-CSF-stimulated donors, and ANC increments following transfusion were largely not reported. This likely resulted from the absence of published evidence-based guidelines, an evaluation period spanning 3 decades, and varying institutional policies regarding donor stimulation, product acquisition, and duration and frequency of administration. Contrastingly, a recent observational study [7] on IF cases pooled from 4 databases reported a 21% improvement in survival in the last decade (compared to

1985-2000). Although 28 (12%) of IF cases in the study received GT, outcomes and type of GTs were not reported for that subgroup.

The initial clinical response rate in our NIH case series was higher than previously reported, with 10 of 11 (91%) demonstrating objective and often rapid responses. Blood cultures cleared after the first GT in all patients and skin lesions stabilized or improved within 2 days of initiating transfusions in all but one patient. Ten of 11 (91%) patients survived for at least 30 days and 8 of 11 (73%) for at least 90 days after starting the transfusions. Lastly, 5 of 11 (45%) survived to hospital discharge, including 5 of 8 (62%) with neutrophil recovery. Lack of long-term survival in 6 patients was associated with failure of marrow recovery or refractory underlying disease. In retrospect, these 6 cases constituted futile efforts at treatment. Granulocyte transfusions are resource-intensive and costly (range $2,000-4,800/GT) and may be difficult to justify when the risk of futility is high. However, neutrophil counts exceeded 0.5×10^9/L for greater than 36 hours following more than half of the transfusions in our case series, such that GTs could be given on an alternate date regimen, thus decreasing costs. The appropriateness of continuing to provide GTs should be reviewed at frequent intervals, as decisions to terminate this therapy in the absence of ANC recovery may be difficult, even when justified.

Higher clinical response rates in our patients might reflect greater efficacy of GTs, wider use of voriconazole, improvements over time in supportive care, or improvements in allogeneic HSCT outcomes and management of primary disease. There were more locally invasive sinus infections in the NIH case series, which may carry a lower risk of mortality than cases with fungemic dissemination. There was also a 5-fold greater use of surgical debridement (100% vs. 17%) in patients with invasive *Fusarium* sinusitis compared to cases in the systematic review. Although it is possible that locally invasive cases would do well even without GTs, SOFA scores revealed that even these cases were profoundly ill. Consistent with prior studies, MIC values for all *Fusarium* isolates except a single *F. moniliforme* sinus isolate in our series demonstrated relative *in vitro* resistance to amphotericin-B, posaconazole and voriconazole. ANC increments in our patients receiving GTs were similar to those in prior studies.[14,19]

GTs were not without risk. Respiratory distress was a contributing factor in two patient deaths and volume overload or other factors associated with GTs may have contributed to pulmonary insufficiency in these cases. In one patient, HLA alloimmunization due to the transfusions resulted in the rejection of a cord blood graft to which the patient had become sensitized.

There were limitations to this study. The systematic review lacked prospective, randomized trials or even large observational studies. In addition, the case series was not powered to generate comparative inferences between GTs from stimulated versus non-stimulated donors using published IF cases that were matched for illness severity as historical controls. Heterogeneity in time and type of response assessment across cases in the literature review also precluded such comparisons in response and at least partially explain the remarkable differences observed. However, our series does offer a descriptive evaluation of all cases of

IF that received the same type of GTs at a single center over a 16-year period, eliminating the publishing bias associated with individual case reports.

Our study suggests that prompt initiation of GTs derived from G-CSF and dexamethasone-stimulated donors can act in synergy with antifungal drugs to arrest or reverse *Fusarium* infection until neutrophil recovery occurs. While every patient in our literature review and case-series that failed to recover their neutrophils died, our study is underpowered to definitively conclude that death is universal in the absence of neutrophil recovery. In those patients whose neutrophil counts ultimately recovered, the role played by G-CSF-mobilized GTs in providing a sustained granulocyte boost during the neutropenic period was uncertain. The relatively high survival rate in this series suggests that transfusions may influence survival. Further studies, including the recently concluded randomized trial of G-CSF-mobilized granulocyte transfusions in neutropenic infections may provide a more definitive conclusion regarding the role of GTs in IF.[21]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Published Case Series/Reports of Invasive Fusariosis in which Granulocyte Transfusions were Administered (1984-2010)

No. (Ref)	Age Sex	Illness	Fusarium Species	Site	Treatment	Days of GTs	Response to GTs	ANC Recovery	Fusarium Resolved	Outcome
1 (22)	12 M	ALL	*Solani*	Blood, skin	AmB, Keto	3	No	Yes	Yes	Response after ANC recovery. Alive at 19 months, *Fusarium* free
2 (23)	40 M	ANLL	*Moniliforme*	Blood, skin, lung	AmB, Rif	3	No	No	No	Died of disseminated *Fusarium* 15 days post IF diagnosis
3 (24)	44 F	ALL	*Fusarium spp.*	Blood, skin	AmB, Keto, 5FC	10	No	No	No	Died of disseminated *Fusarium* 62 days post IF diagnosis
4 (25)	55 M	AML	*Solani*	Blood, skin, eyes	AmB, 5FC	13	No	No	No	Died of disseminated *Fusarium* 98 days post IF diagnosis
5 (25)	15 M	AML	*Solani*	Blood, skin, eye	AmB	7 (CML donor)	No	No	No	Died of disseminated *Fusarium* 86 days post IF diagnosis
6 (26)	54 F	AML	*Solani*	Blood, lung	AmB, 5FC	3	No	Yes	Yes	Response after ANC recovery. Alive at 29 months, *Fusarium* free
7 (27)	24 M	ALL	*Fusarium spp.*	Skin, muscle abscess	AmB, Rif, Keto	38	No	Yes	No	Response after ANC recovery. Died of VOD 36 days post IF diagnosis, fusarial abscesses on autopsy
8 (27)	24 F	MDS	*Fusarium spp.*	Skin	AmB, Rif, Keto	7	No	Yes	Yes	Response after ANC recovery. Died of VOD 60 days post IF diagnosis, no

No. (Ref)	Age Sex	Illness	Fusarium Species	Site	Treatment	Days of GTs	Response to GTs	ANC Recovery	Fusarium Resolved	Outcome
										Fusarium on autopsy on autopsy
9 (28)	20 F	TCL	*Fusarium spp.*	Skin	AmB, Keto	NS	No	No	No	Died of multi-system organ failure, *Fusarium* present.
10 (29)	59 M	ALL	*Proliferatum*	Blood, skin	AmB, Keto, griseofulvin	NS	Yes	Yes	Yes	Discharged but died of ALL 3 months post IF diagnosis
11 (30)	15 M	ALL	*Oxysporum*	CNS, skin, spleen kidney	AmB, 5FC, miconazole	NS	No	Yes	No	Response after ANC recovery. Died of fusarial leptomeningitis 4 months post IF diagnosis
12 (31)	44 M	CML	*Fusarium spp.*	Blood, nasal septum	AmB, 5FC, septotomy	10	No	Yes	Yes	Response after ANC recovery. Died of CMV pneumonitis 58 days post IF diagnosis
13 (31)	24 F	AML	*Fusarium spp.*	Skin, sputum	AmB	NS	No	No	No	Died of disseminated *Fusarium* 6 days post IFI diagnosis
14 (31)	25 M	CML	*Fusarium spp.*	Blood, skin, sinus	AmB, 5FC, turbinectomy	NS	No	No	No	Died with disseminated *Fusarium* 22 days post IF diagnosis
15 (31)	2 F	AML	*Fusarium spp.*	Blood, skin	AmB, 5FC, Rif	NS	NS	Yes	Yes	Alive at 9 months, *Fusarium* free
16 (31)	18 M	CML	*Fusarium spp.*	Skin	AmB, toe amputation	NS	NS	Yes	Yes	*Fusarium* cleared with ANC recovery but recurred 2 months later with graft failure. Died 117 days post IF diagnosis

No. (Ref)	Age Sex	Illness	Fusarium Species	Site	Treatment	Days of GTs	Response to GTs	ANC Recovery	Fusarium Resolved	Outcome
17 (31)	11 M	AML	*Moniliforme*	Blood, skin, sputum	AmB, 5FC, Rif, SCH-39304	NS	NS	Yes	Yes	*Fusarium* cleared with ANC recovery but recurred 2 weeks later with graft failure. Died 48 days post IF diagnosis
18 (31)	53 M	AML	*Fusarium spp.*	Blood, skin	AmB, 5FC, GM-CSF	15	Yes	Yes	Yes	Died of AML and bacterial sepsis several months post IF diagnosis
19 (33)	3 F	SAA	*Fusarium spp.*	Skin	AmB	39*	Yes	No	No	Despite initial response, died of dissem-inated *Fusarium* 40 days post CBT
20 (34)	3 F	SAA	*Oxysporum*	Skin, spleen, chest wall	AmB, Vori, knee/chest debridement	19	Yes	Yes	Yes	Died of CMV pneumonia and GVHD 213d after IF diagnosis (not discharged)
21 (35)	50 M	AML	*Fusarium spp.*	Blood, skin	AmB, Vori, GM-CSF	6	Yes	Yes	Yes	*Fusarium* free 23 days post IF diagnosis, AML in remission
22 (36)	9 F	LAD-1	*Solani*	Blood, knee joint	AmB, 5FC	>40	Yes	Yes	Yes	*Fusarium* free 5 months post IF diagnosis
23 (37)	1 M	SAA	*Fusarium spp.*	Blood, skin, bone	AmB	12*	Yes	Yes	Yes	*Fusarium* free 230 days post IF diagnosis

AML = acute myelogenous leukemia, CML = chronic myelogenous leukemia, ALL = acute lymphoblastic leukemia, ANLL = acute non-lymphocytic leukemia, MDS = myelodysplastic syndrome, SAA = severe aplastic anemia, LAD-1 = leukocyte adhesion deficiency type 1, TCL = T-cell lymphoma, CNS = central nervous system, AmB = Amphotericin B (including plain and lipid formulations), Keto = ketoconazole, Rif = Rifampin, 5-FC = 5-Fluocytosine, Vori = voriconazole, GM-CSF = granulocyte/monocyte colony-stimulating factor, SCH-39304 = experimental imidazole, GTs = granulocyte transfusions, NS = not stated, VOD = veno-occlusive disease of the liver, CMV = cytomegalovirus, HSCT = hematopoietic stem cell transplantation. IF = invasive fusariosis, CBT = cord blood transplant.

*GTs derived from G-CSF-stimulated donors.

Table 2

Single Center Case Series of Invasive Fusariosis Treated with Granulocyte Transfusions (NIH Clinical Center 1996-2012)

Pt	Year	Age Sex	Illness	Fusarium Species	Sites*	Relevant Radiology	SOFA Score	Treat-ment	Surgical Debridement	Allo-HSCT†	No. GTs‡ (wks)	Response to GTs§	ANC Recovery	Outcome
1	1996	46 M	CML	*Fusarium spp.*	Skin	Lung nodules	8	L-AmB	None	1 mo. prior	7 (1)	Clinical	Yes	Alive. Disease remission.
2	1998	17 M	SAA	*Solani*	Blood, skin	None	8	L-AmB	None	No	20 (3)	Clinical Microbiologic	No	Died 1 day after last GTs; ARDS, MSOF.
3	2002	51M	SAA	*Moniliforme*	Sinus	ES opacification, MS thickening	8	Vori, L-AmB	Middle turbinectomy, ethmoidectomy	No	7 (1)	Clinical Radiologic Microbiologic	Yes	Alive. Disease remission.
4	2008	17 F	SAA	*Solani*	Sinus	MS opacification, lung nodules	9	Vori	Antrostomy MS debridement	10 d prior; 5 wks post	11 (3)	Clinical Radiologic	Yes	Died 10 wks after last GTs; ARDS, DAH (comfort measures instituted) Autopsy: no fusarium
5	2008	68 M	MDS	*Fusarium spp.*	Sinus	MS opacification, RLL nodule	10	Vori	Bilat middle turbinectomy	1 wk prior	2 (2 d)	Clinical Radiologic	Yes	Alive, cGVHD. Disease remission.
6	2010	21 M	Pre-B ALL	*Solani*	Sinus	Complex sinus opacification	8	Vori	Middle meatotomy, ethmoidectomy	No	8 (2)	Clinical Microbiologic	No	Died 2 wks after last GTs; refractory ALL.
7	2010	58 M	MDS	*Falciforme*	Blood, skin	Retina, lung nodules	9	Vori, L-AmB	None	No	6 (1.5)	Clinical; microbiologic	Yes	Died 1 mo. after last GTs; encephalopathy (comfort measures instituted)
8	2010	65 M	MDS/CMML	*Solani*	Skin	None	10	Vori, L-AmB	None	7 mo. post	5 (1.5)	Clinical Microbiologic	Yes	Discharged. Died 17 mos later. Autopsy: no fusarium
9	2011	50 M	DLBCL	*Proliferatum*	Blood, skin	Lung nodules	9	Vori, L-AmB	None	5 mo. prior	6 (2)	Clinical Microbiologic	Yes	Died 1 mo. after last GTs; relapsed DLBCL (comfort measures instituted)
10	2012	9 M	SAA	*Solani*	Blood, skin,joints, bone	None	9	Vori, L-AmB	Multiple bones (osteomyelitis)	2 mo. post	39 (12)	None; progression	No	Died 6 wks after last GTs; rejected HSCT due to HLA alloimmunization.

Pt	Year	Age Sex	Illness	Fusarium Species	Sites*	Relevant Radiology	SOFA Score	Treat-ment	Surgical Debridement	Allo-HSCT†	No. GTs‡ (wks)	Response to GTs§	ANC Recovery	Outcome
11	2012	17M	SAA	*Solani*	Sinus	ES thickening	8	Vori, L-AmB	Nasal septum, MT debridement	11 d post	12 (5)	Clinical Radiologic	Yes	Alive. HLA alloimmunized. Disease remission.

In all 11 cases, neutropenia (ANC < 0.5×10^9/L) was present for > 30 days preceding fusarium diagnosis.

*Sites from which *Fusarium* was isolated and identified.

†Time relative to start (pre) or end (post) of granulocyte transfusions.

‡GTs = granulocyte transfusions.

§prior to ANC recovery.

SAA = severe aplastic anemia, MDS = myelodysplastic syndrome, ALL = acute lymphoblastic leukemia, DLBCL = diffuse large B-cell lymphoma, CML = chronic myelogenous leukemia, ES = ethmoidal sinus, MS = maxillary sinus, SOFA = sequential organ failure assessment score, Vori = voriconazole, L-AmB = liposomal amphotericin B, Caspo = caspofungin, Itra= itraconazole, HSCT = hematopoietic stem cell transplant, ARDS = acute respiratory distress syndrome, DAH = diffuse alveolar hemorrhage, MSOF = multisystem organ failure.

Table 3
In-Vitro Antifungal Susceptibilities for *Fusarium* Isolates in NIH Case Series

Patient	Fusarium Species	Minimum Inhibitory Concentration (MIC) ug/mL*		
		Amphotericin B	Voriconazole	Posaconazole
3	*Moniliforme*	1	1	0.25
4	*Solani*	2	8	>16
6	*Solani*	16	8	>16
7	*Falciforme*	4	16	>16
8	*Solani*	2	16	>16
9	*Proliferatum*	4	8	>16
10	*Solani*	2	>16	>16
11	*Solani*	2	16	>16

*Determined by Fungal Testing Laboratory, San Antonio, Texas (http://pathology.uthscsa.edu/strl/fungus/s_testing.shtml) and performed following current Clinical and Laboratory Standards Institute document for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi; currently CLSI M38-A2. Species could not be determined for patients #1 and #5 and susceptibility testing was not attempted for *F. Solani* isolate from Patient #2. Among the other antifungal agents tested, MIC for itraconazole from Patient #3 was 1, for terbinafine from Patient #7 was >2, and for flucytosine from Patients #9 and 10 was >64.

Table 4

Increments in ANC[a] following Granulocyte Transfusions in NIH Case Series

Patient	No. of Granulocyte Transfusions (No. with Same Day Posttransfusion ANC)	Mean Time from Pre-ANC[b] to Transfusion (hr)	Mean Time Transfusion to Post-ANC[c] (hr)	Mean Overall ANC Increment ($\times 10^9$/L)	Mean Same-day[d] ANC Increment ($\times 10^9$/L)
1	7 (3)	13:38	2:06	1.86	1.92
2	20 (7)	NA[e]	NA	0.44	0.93
3	7 (4)	15:54	1:59	0.13	0.42
4	11 (2)	13:02	2:54	0.97	2.52
5	2 (1)	17:14	1:55	6.67	10.27
6	8 (2)	6:24	1:55	3.1	3.21
7	6 (1)	10:31	5:05	2.85	0.84
8	5 (1)	15:21	0:25	0.03	0.82
9	6 (2)	6:14	7:12	8.78	10.88
10[f]	39 (2)	6:35	6:44	1.09	1.67
11[f]	12 (0)	NA	NA	1.17	NA
Series Mean		**13:39**	**3:32**	**2.46**	**3.35**

[a] ANC= Absolute neutrophil count

[b] Pre-ANC = ANC sample drawn prior to starting granulocyte transfusion.

[c] Post-ANC = ANC sample drawn following granulocyte transfusion.

[d] Same-day ANC represents those cases in which pre- and posttransfusion counts were obtained on the same calendar day (before midnight).

[e] NA = not available.

[f] HLA-alloimmunization occurred during the course of transfusions in Patients #10 and 11, and was associated with a decrease in ANC increments (see text).