Invasive Fusariosis: A Single Pediatric Center 15-Year Experience

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Invasive fungal infection (IFI) is an important cause of mortality in immunocompromised children, particularly after hematopoietic stem cell transplantation. We describe 5 cases of Fusarium IFI in immunocompromised children seen at our institution over a 15-year period. A summary of all published pediatric cases of invasive Fusarium infection is presented. A focus on antifungal management challenges in these patients will be discussed.

Key words. Fusarium; invasive fungal infection; immunocompromised host; hematopoietic stem cell transplantation; children

The improved survival of children with many hematologic malignancies is largely attributable to improved risk stratification, intensification of therapy where appropriate, hematopoietic stem cell transplantation (HSCT), and improvements in supportive care. Intensification of therapy results in profound immunosuppression, predisposing to invasive fungal infections (IFIs), which are an important cause of mortality in children who receive intensive myelo-suppressive chemotherapy and HSCT [1]. Aspergillus and Candida are the most common pathogens responsible for IFI in this population. In children, 2 species of Fusarium, Fusarium solani species complex and Fusarium oxysporum species complex, are the 3rd and 4th most common cause of IFI, as found in a recent American study and in our institution, respectively [1, 2].

Fusarium species are important plant pathogens that are commonly found in soil, water, and organic substrates. Human disease is less common but may include keratitis and onychomycosis in immunocompetent hosts and more invasive disease in immunocompromised individuals. Disease in immunocompromised patients often manifests with fungemia, sinonasal infection, and involvement of the lungs and skin [3]. There are over 50 species of Fusarium described, with F solani species complex and F oxysporum species complex causing 70% of invasive human disease [3]. Fusarium infections have been notoriously difficult to treat, with mortality in adult series ranging from 53% [4] to 66% [5]. There are minimal pediatric data to address evidence-based strategies for treatment. In this report, we describe the cases of invasive Fusarium infection seen at The Hospital for Sick Children (SickKids; Toronto, Canada).

METHODS

We described all culture-proven cases of invasive Fusarium sp infections in immunocompromised children seen at SickKids over a 15-year period from January 1, 1996 to December 31, 2011. The Hospital for Sick Children is a large, tertiary care, pediatric facility in Toronto, Canada with the highest volume of new cancer diagnoses and HSCT procedures in Canada. There are approximately 110 new cases of hematological malignancy diagnosed each year, and 100 HSCT procedures are performed yearly at this center. Specimens for fungal culture were examined by calcifluor stain (Fungi-fluor; Polysciences, Inc, Warrington, PA) and were set up for culture on Inhibitory Mold Agar with 5 mg/L ciprofloxacin (Becton Dickinson, Mississauga, Ontario, Canada) and brain heart infusion agar with 5% sheep blood (Becton Dickinson). Specimens were incubated at 28°C for 3 weeks. Fungal identification was determined by

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microscopic morphology and by internal transcribed spacer (ITS)-2 and elongation factor (EF)-1α polymerase chain reaction (PCR) and sequencing, as required (in-house PCRs). All positive cultures for *Fusarium* were initially identified through review of microbiology records, and charts were subsequently reviewed to determine whether *Fusarium* infections were invasive. Data were extracted for patients with invasive fusariosis and immunocompromised status. We included all cases that met criteria of proven or probable IFI based on the guidelines by the European Organization for Research and Treatment of Cancer (EORTC)/Invasive Fungal Infections Cooperative Group [6]. This study was approved by the Research Ethics Board at SickKids.

## RESULTS

There were 13 children with positive cultures for *Fusarium* species: 8 were noninvasive; there was 1 case each of onychomycosis, keratitis, and tinea pedis; and 5 had positive cultures from superficial surgical or burn wounds. The 5 remaining children were immunocompromised with invasive *Fusarium* infections, and all 5 had lung involvement. Additional sites of involvement included skin (2 of 5), brain (2 of 5), and blood (1 of 5). The 4 fatal cases in our series received HSCT with prolonged neutropenia. Combination therapy with liposomal amphotericin B (Ambisome) and voriconazole was used in 3 of 5 cases. *Fusarium* infection was believed to be a contributing cause of death in all 4 fatal cases (Table 1).

Case 1 is a 3-year-old previously healthy girl, who presented to hospital with fever, hypotension, and pancytopenia. Initial blood films demonstrated the presence of circulating blast cells, and blood cultures were positive for methicillin-susceptible *Staphylococcus aureus*, which were treated with the appropriate antibiotics.

Oncologists diagnosed precursor B cell acute lymphoblastic leukemia (ALL), and chemotherapy was initiated. The oncologist initiated therapy with induction chemotherapy, which included dexamethasone, pegylated L-asparaginase, and vincristine. One week after initial presentation, the patient had improved clinically but remained febrile and neutropenic with negative blood cultures. Results of a computed tomography (CT) scan showed multiple small lung nodules with surrounding halo sign and 1 hypodense liver lesion, all consistent with fungal infection. Caspofungin therapy was added to the patient’s antibiotics; however, a new skin lesion had developed over her elbow, with a central black eschar (Figure 1A). Septate filamentous fungi invading blood vessels were observed on the biopsy (Figure 1B), and fungi grew as *F. solani* species complex. Caspofungin was changed to liposomal amphotericin B and voriconazole. Neutropenia resolved by the 4th week of hospitalization, 1 week after *Fusarium* diagnosis. Over the next few weeks, the patient’s skin lesions resolved and her fever subsided. Initial and repeat trough voriconazole levels were subtherapeutic (<1 mg/L); however, the patient’s dose was not adjusted due to her favorable clinical response (Table 1). Repeat imaging showed resolution of the lung nodules with 2 small liver lesions, 1 of which was not previously seen. The patient was treated with liposomal amphotericin B for a total of 8 weeks combined with voriconazole for 6 weeks, which was stopped due to concerns of potential drug interactions with her chemotherapy. She remained clinically well, off therapy, and had resolution of all imaging findings at 8 weeks after presentation. There was no recurrence in follow-up over the subsequent 12 months.

Case 2 was a previously healthy 9-year-old boy who was diagnosed with Philadelphia chromosome-positive ALL. He relapsed 15 months into therapy and received an HSCT from a matched, unrelated donor. A second relapse resulted in a palliative approach to management. Around the same time, the patient had persisting neutropenia with symptoms of chronic sinusitis, including fever, headache, and sinus pain. The results of imaging studies showed cavitary lung lesions. The patient’s initial sputum culture grew *F. oxysporum* species complex, satisfying EORTC criteria for probable *Fusarium* fungal infection of the lungs and sinuses. Surgical intervention was not considered, and liposomal amphotericin B was stopped after 1 week due to the patient’s palliative care plan. Two months later, the patient presented with severe chest pain and there was evidence of pericardial extension of his fungal pneumonia after imaging was performed. However, 2 subsequent sputum cultures grew only *Aspergillus* species at that time. No pericardial culture was obtained. Several months later, the patient died from his underlying leukemia. Because an autopsy was not performed, it could not be confirmed whether *Fusarium* was the predominant or only cause of his IFI.

Case 3 was an 8-year-old female who initially presented to hospital with respiratory distress, cough, and hepatosplenomegaly on exam. She was diagnosed with juvenile myelomonocytic leukemia. The patient’s past medical history was significant for neurofibromatosis type 1. She was admitted to hospital with diffuse abdominal lymphadenopathy, coagulopathy, anemia, thrombocytopenia, chronic diarrhea, and wasting. Her symptoms persisted despite chemotherapy, and she received an allogeneic HSCT.

The patient had a complicated post-HSCT course with graft-versus-host disease, persistent anemia, thrombocytopenia, chronic renal failure, hemorrhagic cystitis,
# Table 1. Summary of 5 Children With Invasive *Fusarium* Infections From The Hospital for Sick Children

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Gender</th>
<th>Fusarium species</th>
<th>Site(s) of infection</th>
<th>MIC</th>
<th>Underlying condition</th>
<th>Duration of Neutropenia before <em>Fusarium</em> diagnosis (weeks)</th>
<th>Antifungal prophylaxis</th>
<th>Site/method of culture</th>
<th>Treatment and max dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Female</td>
<td>solani</td>
<td>Skin, lung, liver</td>
<td>Am: 4 mcg/mL</td>
<td>ALL</td>
<td>1</td>
<td>No</td>
<td>Skin biopsy</td>
<td>Liposomal amphotericin B (7.5 mg/kg) + voriconazole (14 mg/kg per day)*</td>
</tr>
<tr>
<td>9</td>
<td>Male</td>
<td>oxysporum</td>
<td>Lung, sinuses</td>
<td>Itr: 16 mcg/mL</td>
<td>ALL/HSCT</td>
<td>6</td>
<td>Fluconazole</td>
<td>Sputum</td>
<td>Conventional amphotericin B (1 mg/kg) (for 1 week only)</td>
</tr>
<tr>
<td>8</td>
<td>Female</td>
<td>oxysporum</td>
<td>lung</td>
<td>Flu: &gt;64 mcg/mL</td>
<td>JMML/HSCT</td>
<td>10</td>
<td>No</td>
<td>BAL</td>
<td>Conventional amphotericin B (1 mg/kg)</td>
</tr>
<tr>
<td>1</td>
<td>Female</td>
<td>oxysporum</td>
<td>Skin, lung, blood, brain</td>
<td>Ket: 4 mcg/mL</td>
<td>AA/HSCT</td>
<td>&gt;12</td>
<td>No</td>
<td>Skin biopsy/blood culture</td>
<td>Liposomal amphotericin B (10 mg/kg) + voriconazole (23 mg/kg per day)*</td>
</tr>
<tr>
<td>15</td>
<td>Female</td>
<td>solani</td>
<td>Lung, brain</td>
<td>Vor: 0.5 mcg/mL</td>
<td>AML/HSCT</td>
<td>&gt;12</td>
<td>No</td>
<td>CSF</td>
<td>Liposomal amphotericin B (10 mg/kg) + voriconazole (11.5 mg/kg per day (no levels)</td>
</tr>
</tbody>
</table>

## Abbreviations:
- AA, aplastic anemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BAL, bronchoalveolar lavage; CMV, cytomegalovirus; CSF, cerebral spinal fluid; Flu, fluconazole; HSCT, hematopoietic stem cell transplant; JMML, juvenile myelomonocytic leukemia; Ket, ketoconazole; max, maximum; Itr, itraconazole; MIC, minimum inhibitory concentration; N/A, not applicable; Pos, posaconazole; Vor, voriconazole.

*Voriconazole trough level <0.2 mcg/mL at maximal dose. Not adjusted.

**Voriconazole trough level 0.54 mcg/mL at 18 mg/kg per day. No level done at maximal dose.
cytomegalovirus (CMV) and adenovirus infections, and respiratory failure. Results of a chest radiograph at the time revealed severe bilateral pneumonia, and a bronchoalveolar lavage was positive for *Fusarium* species complex. The patient was started on amphotericin B, but her infection showed no sign of improvement. She died of respiratory failure shortly after treatment was begun. An autopsy was not performed; therefore, it was not possible to differentiate the relative contributions of adenovirus, CMV, and *Fusarium* to her fatal outcome.

Case 4 was a 13-month-old female who initially presented with severe thrombocytopenia and was ultimately diagnosed with severe aplastic anemia. While receiving chemotherapy, the patient developed fever and neutropenia, with progressive black skin lesions over her elbow. A culture from skin biopsy was positive for both *Stenotrophomonas maltophilia* and *Fusarium* species complex. Antibiotics and voriconazole therapy were initiated, but they were changed to liposomal amphotericin B when the patient underwent an allogeneic HSCT. Shortly after transplantation, she developed new skin lesions, which again were positive on culture for *Fusarium* species complex. However, after treatment with appropriate antibiotics and liposomal amphotericin B (7.5 mg/kg) for 2 months, she developed persisting *Fusarium* fungemia despite removal of the central intravenous line and the addition of voriconazole. Topical terbinafine and granulocyte transfusions did not prevent the progression of her disease, multiple organ dysfunction, and death. A limited autopsy was performed, which identified disseminated CMV disease.

Case 5 was a 15-year-old female who presented with a 3-week history of jaw pain on the right side, fatigue, and low-grade fever, accompanied by leukocytosis, neutropenia, and anemia. Results of a bone marrow biopsy showed acute myeloid leukemia. During the patient's first cycle of chemotherapy, she developed prolonged fever and neutropenia and was started on empiric caspofungin. A CT scan at the time suggested right upper lobe consolidation, which resolved on repeat CT scans. On subsequent cycles...
of chemotherapy, she again had prolonged fever and neutropenia with negative cultures despite ground glass opacities on CT scan. She was treated empirically with voriconazole with improvement.

Nine months later, the patient relapsed and underwent an unrelated cord blood HSCT after reinduction chemotherapy. She developed persistent fever with neutropenia, hemoptysis, and progressive hypoxia and respiratory distress. Imaging studies revealed several lesions in the lungs and brain (Figure 1C) that were suggestive of fungal disease. Cultures from cerebral spinal fluid grew *F solani* species complex. The patient was treated with liposomal amphotericin B at 10 mg/kg and voriconazole at 18 mg/kg per day, which increased to 23 mg/kg per day due to subtherapeutic levels of 0.54 mcg/ml (Table 1). Surgical management was believed to be contraindicated due to her rapid clinical deterioration and respiratory instability. The patient died from a catastrophic central nervous system hemorrhage, which was presumed to be secondary to a *Fusarium* lesion in her brain (Figure 1d). An autopsy was not performed.

A review of the literature on invasive *Fusarium* infections in children revealed 33 published cases in immunocompromised children, which are summarized in Table 2. Ages ranged from 5 months to 18 years with a median of 7.5 years. The most common underlying condition was leukemia. Sites of infection were most commonly skin (21), blood (14), lung (11), brain (3), and sinuses (2). A review of the literature also showed that treatment varied: amphotericin B was used in most cases (25); combination therapy was used in 11 cases; granulocyte colony-stimulating factor (GCSF) was used in 6 cases; granulocyte transfusion was used in 4 cases; and surgery was performed in 4 cases. All-cause mortality, including our 5 cases, was 50% [7–35].

**DISCUSSION**

This case series demonstrates the devastating effect of *Fusarium* infections in children with hematologic malignancies, including those requiring HSCT. Case 1 in this series represents a unique scenario of the survival of a child after disseminated fusariosis. The reasons for survival were likely multifactorial. This patient was receiving induction chemotherapy for ALL and, consequently, would be expected to have a shorter and milder duration of neutropenia compared to children with AML and those receiving HSCT. Furthermore, the children undergoing HSCT all had preceding treatments, thus likely rendering them severely immunocompromised. The patient’s duration of neutropenia was relatively short and she did not have documented fungemia, both of which have been suggested as favorable prognostic signs [4, 5].

A functioning immune system is the single most important predictor of survival after acquisition of invasive *Fusarium* infection. Animal models of invasive *Fusarium* infection suggest that innate immune function is pivotal in combating this infection, particularly via well functioning granulocytes and macrophages [3]. Granulocytes inhibit hyphal growth, and macrophages inhibit germination of conidia and growth of hyphae [5]. Prolonged neutropenia and a high fungal burden are the 2 largest risk factors for mortality in animal models [3].

*Fusarium* infections are notoriously difficult to treat, possibly because of their inherently high minimum inhibitory concentrations (MICs) to most available antifungal medications. In vitro susceptibility studies on *Fusarium* species show great variability in MIC range [36–38], which is partly dependent on species designation. In the 3 children in our study who had susceptibility testing done, the MICs ranged from 0.5 to 8 mcg/mL for voriconazole and 1 to 4 mcg/mL for amphotericin B. There is also evidence that *F solani* species complex may be more virulent than other *Fusarium* species, irrespective of susceptibility pattern [36].

Some authors have advocated combination therapy based on case reports of success with such regimens [39, 40]. Despite the theoretical concern that antagonism may occur when combining azoles with polyenes, there are data demonstrating that combination therapy has a synergistic effect “in vitro,” particularly for voriconazole and amphotericin [37] and for voriconazole and terbinafine [41]. Antagonism was not observed in these studies.

In our institution, we consider the use of combination antifungal therapy based on the high mortality of these infections in immunocompromised children, in vitro evidence of synergy, and the inherent resistance of *Fusarium* species to most antifungals. Furthermore, voriconazole levels are commonly subtherapeutic with initial dosing of 4–6 mg/kg. Recent studies suggest that 8–9 mg/kg every 12 hours is a more appropriate regimen for children aged 2–11 years [42, 43]. In studies on *Aspergillus* infections, voriconazole therapeutic drug monitoring (TDM) seems to be an important factor in optimizing treatment [44]. Adverse effects from voriconazole include hepatitis, particularly rising glutamyl transpeptidase, and visual disturbances, which do not seem to be more frequent with the higher dosing [42]. There is also significant interpatient, drug-level variability as well as lower bioavailability upon oral administration in children. For these reasons, TDM monitoring is important in pediatric patients, and drug levels of 1–5 mcg/mL should be targeted [45]. Furthermore,
Table 2. Summary of All Published Cases of Children With Invasive *Fusarium* Infections

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Number of Cases</th>
<th>Age (range)</th>
<th>Underlying Disease</th>
<th>Site(s) of Infection</th>
<th>Species</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mellouli (2010) [8]</td>
<td>1</td>
<td>9 y</td>
<td>leukocyte adhesion deficiency type 1</td>
<td>skin</td>
<td>solani</td>
<td>AB, GCSF, GT</td>
<td>survived</td>
</tr>
<tr>
<td>Cooke (2009) [10]</td>
<td>1</td>
<td>5 y</td>
<td>leukemia</td>
<td>skin</td>
<td>solani</td>
<td>AB, GCSF</td>
<td>survived</td>
</tr>
<tr>
<td>Vagace (2007) [12]</td>
<td>1</td>
<td>11 y</td>
<td>leukemia</td>
<td>blood, lungs</td>
<td>unspecified</td>
<td>AB, caspo, then vori</td>
<td>survived</td>
</tr>
<tr>
<td>Petit (2005) [13]</td>
<td>2</td>
<td>10 y</td>
<td>leukemia (both)</td>
<td>C1: skin, blood</td>
<td>unspecified</td>
<td>C1- AB; C2- AB, vori</td>
<td>C1-died; C2-survived</td>
</tr>
<tr>
<td>Albisetti (2004) [14]</td>
<td>1</td>
<td>2 y</td>
<td>hemophagocytic lymphohistiocytosis</td>
<td>skin</td>
<td>oxysporum</td>
<td>AB, GCSF, then itra</td>
<td>survived</td>
</tr>
<tr>
<td>Kivivuori (2004) [15]</td>
<td>2</td>
<td>5 y, 8 y</td>
<td>leukemia</td>
<td>C1: skin, pharyngeal, fecal blood C2: skin, fecal</td>
<td>C1-solani, unspecified</td>
<td>AB</td>
<td>died (2)</td>
</tr>
<tr>
<td>Yucesoy (2004) [16]</td>
<td>1</td>
<td>7 y</td>
<td>leukemia</td>
<td>blood</td>
<td>unspecified</td>
<td>AB then itra</td>
<td>survived</td>
</tr>
<tr>
<td>Rodriguez (2002) [17]</td>
<td>1</td>
<td>3 y</td>
<td>aplastic anemia</td>
<td>skin, lung</td>
<td>oxysporum</td>
<td>AB, vori, GT, surgery</td>
<td>survived</td>
</tr>
<tr>
<td>Sridhar (2001) [18]</td>
<td>1</td>
<td>NR</td>
<td>leukemia</td>
<td>blood</td>
<td>solani</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Ariffin (1999) [20]</td>
<td>2</td>
<td>5 m–8 y</td>
<td>leukemia</td>
<td>blood (2), lung</td>
<td>unspecified, solani</td>
<td>AB (2), fluc, GCSF</td>
<td>died (2)</td>
</tr>
<tr>
<td>Mangini (1999) [22]</td>
<td>2</td>
<td>NR-9 y</td>
<td>leukemia</td>
<td>skin (2), lung (1)</td>
<td>unspecified (2)</td>
<td>AB</td>
<td>died (2)</td>
</tr>
<tr>
<td>Bleggi-Torres (1996) [23]</td>
<td>1</td>
<td>6 y</td>
<td>NR</td>
<td>brain</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Patterson (1996) [24]</td>
<td>1</td>
<td>2.5 y</td>
<td>leukemia</td>
<td>sinuses, skin</td>
<td>solani</td>
<td>AB, surgery, GCSF</td>
<td>survived</td>
</tr>
<tr>
<td>Repiso (1996) [25]</td>
<td>1</td>
<td>7 y</td>
<td>leukemia</td>
<td>skin, blood</td>
<td>solani</td>
<td>AB, GCSF</td>
<td>survived</td>
</tr>
<tr>
<td>Ammari (1993) [26]</td>
<td>1</td>
<td>13 y</td>
<td>leukemia</td>
<td>lungs, blood</td>
<td>solani</td>
<td>AB, rifampin, fluc</td>
<td>survived</td>
</tr>
<tr>
<td>Alvarez-Franco (1992) [27]</td>
<td>1</td>
<td>18 y</td>
<td>leukemia</td>
<td>skin</td>
<td>unspecified</td>
<td>AB</td>
<td>died</td>
</tr>
<tr>
<td>Neumeister (1992) [28]</td>
<td>1</td>
<td>5 y</td>
<td>Wilms’ tumor</td>
<td>blood</td>
<td>oxysporum</td>
<td>AB</td>
<td>died</td>
</tr>
<tr>
<td>Agamanolis (1991) [29]</td>
<td>1</td>
<td>15 y</td>
<td>leukemia</td>
<td>brain</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Barrios (1990) [30]</td>
<td>1</td>
<td>5 y</td>
<td>leukemia</td>
<td>blood, sinuses, skin</td>
<td>proliferatum</td>
<td>AB, rifampin, 5-FC, GT, surgical drainage of sinuses</td>
<td>survived</td>
</tr>
<tr>
<td>Richardson (1988) [31]</td>
<td>1</td>
<td>7 y</td>
<td>leukemia</td>
<td>skin, blood</td>
<td>unspecified</td>
<td>AB, 5-FC, rifampin</td>
<td>died</td>
</tr>
<tr>
<td>Chaulik (1986) [32]</td>
<td>1</td>
<td>12 y</td>
<td>leukemia</td>
<td>skin, blood</td>
<td>solani</td>
<td>AB, ketoconazole</td>
<td>survived</td>
</tr>
<tr>
<td>Blazar (1984) [33]</td>
<td>1</td>
<td>17 y</td>
<td>leukemia</td>
<td>skin, lung</td>
<td>unspecified</td>
<td>AB</td>
<td>died</td>
</tr>
<tr>
<td>Abramowksy (1974) [34]</td>
<td>1</td>
<td>2 y</td>
<td>burn (60%)</td>
<td>skin, kidney, brain, heart</td>
<td>unspecified</td>
<td>None</td>
<td>died</td>
</tr>
<tr>
<td>Cho (1973) [35]</td>
<td>1</td>
<td>2.5 y</td>
<td>leukemia</td>
<td>skin, eye</td>
<td>solani</td>
<td>AB</td>
<td>died</td>
</tr>
</tbody>
</table>

Abbreviations: NR, not reported or data not found; C1, case 1; C2, case 2; AB, amphotericin B; fluc, fluconazole; GCSF, granulocyte colony-stimulating factor; GT, granulocyte transfusion; itra, itraconazole; vori, voriconazole; 5-FC, 5-flucytosine.
prophylaxis data identified breakthrough infections in 50% and 20% of patients on voriconazole and posaconazole, respectively [5]. For severe infections, it may be prudent to consider a second antifungal agent, such as amphotericin B, until adequate drug levels are achieved and clinical response is observed.

In our review, improvements in mortality over the last 20 years from 92% [31] to 50% are promising and may be related to new antifungal therapies, adjunctive therapies, and aggressive surgical and intravenous catheter management. Granulocyte colony-stimulating factor has been shown to be helpful in cases in which *Fusarium* infections presented in the context of neutropenia. The duration of neutropenia has been inversely correlated with survival [5], and because GCSF may decrease time to neutrophil count recovery, there is a potential role for its use [46]. The same argument has been made for granulocyte transfusions, which may decrease the relative length of neutropenia [27, 30]. Surgical debridement is also another important adjunctive therapy to consider, particularly for sinusitis [9, 30, 46].

CONCLUSION

*Fusarium* species can cause severe disseminated disease in highly immunocompromised children and is associated with high mortality rates, particularly after HSCT. This series supports the need to aggressively pursue specimens for culture in children with suspected invasive fungal disease, to make an etiologic diagnosis and to initiate optimal antifungal therapy. With the advent of newer antifungals combined with aggressive medical and surgical management, it is our hope that outcomes can be improved over time.

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Potential conflicts of interest All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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