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Invasive *Aspergillus* infections in a pediatric hospital: a ten-year review

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Aspergillus, a ubiquitous saprophytic mold, is found in multiple environmental sites throughout the world. The fungus grows well on a variety of organic substrates including soil, decaying vegetation and stored hay. It may contaminate a number of sites in hospitals and has been isolated from hospital air.[1–4] Infection with the organism is usually initiated by inhalation of air-borne spores. Invasive disease occurs predominantly in hosts with compromised immune systems, particularly those with prolonged and profound granulocytopenia.[5] *Aspergillus* is second only to *Candida* in the frequency of opportunistic mycosis among compromised hosts.[6]

Invasive *Aspergillus* infections have been well characterized in adult patient populations[7–9] but the reported series in children are small.[10–12] We report the results of a 10-year retrospective review of 39 cases of invasive aspergillosis at the Hospital for Sick Children in Toronto, Ontario, Canada. Our purpose was to describe the clinical, epidemiologic and microbiologic features and to determine whether there were any unique aspects to invasive *Aspergillus* infection in the pediatric population.

MATERIALS AND METHODS

Patient population. The Hospital for Sick Children is a 535-bed university-affiliated pediatric hospital in Toronto, Ontario, Canada, providing primary, secondary and tertiary care. An active oncology department manages patients with acute leukemia and other hematologic disorders and malignancies. Kidney, bone marrow and liver transplantations have been performed at this center since 1970, 1984 and 1986, respectively.

During the study period immunocompromised patients were admitted primarily to three medical wards. Bone marrow transplant patients were cared for in naturally ventilated private rooms. Other transplant patients and those with malignancies were cared for in private or in two-bed rooms. The outpatient hematology-oncology clinic is located on the top floor immediately below the hospital heliport.

Infection control policies. Invasive *Aspergillus* infections were first noted at the Hospital for Sick Children in 1982, coincident with a period of major renovation and construction. Since 1983 a policy of precautions to be taken during construction and ceiling tile removal in patient care areas has been in effect. This includes a planning meeting with the participation of plant and operations, infection control, nursing and environmental services before the initiation of work. Air-tight plastic and/or drywall barriers are erected around the construction area to contain dust and surfaces are decontaminated with a 0.5% solution of sodium hypochlorite. All immunocompromised patients are to be transferred from affected areas during construction periods and traffic restricted where possible.

Identification and case definition. Cases of invasive aspergillosis were identified through nosocomial infection surveillance, pathology, health and microbiologic records between January 1, 1979, and December 31, 1988. Patients were included if they had evidence of invasive *Aspergillus* infection as determined by biopsy, autopsy or other diagnostic procedure (see below). Patients were excluded if the isolate was obtained from a nonsterile site in the absence of histopathologic evidence for invasion. A case is considered definite if there was histopathologic evidence for invasive fungal infection on tissue biopsy and an *Aspergillus* species was grown in culture. A case is considered probable if either (1) there was histopathologic evidence for invasive fungal infection with septate hyphae, but cultures either failed to grow or were not performed or (2) there was a positive culture for *Aspergillus* from an aspirate of a suspected lesion of a normally sterile site in the absence of histologic confirmation.

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The medical records of identified cases were reviewed for details concerning patient demographics, underlying medical condition and its treatment, preceding antimicrobial therapy, degree and duration of neutropenia, concomitant infections, diagnostic procedures, extent of disease, therapy and outcome.

Microbiology. Sputum or biopsy specimens of patients with suspected *Aspergillus* infection were plated on blood agar and Sabouraud's media with and without cycloheximide and incubated at 30°C for 21 days. Nasal swabs were planted on Sabouraud's media and incubated at 30°C for 14 days. Slide cultures were made of suspicious colonies and species were confirmed morphologically by standard methods.[13]

RESULTS

Patient demographics. Over this 10-year period 39 cases of invasive *Aspergillus* infection (24 definite, 15 probable) were identified (Table 1). No cases were identified in the five years preceding 1981. The initial cluster of cases in 1982 corresponded to a period of renovation in the areas housing the patients. Over the subsequent years the number of cases has remained constant (3 to 7/year) despite implementation of specific infection control policies during construction and the increased activity of the transplant programs. There were 18 males and 21 females with ages ranging from 22 days to 18 years (median, 10 years).

Confirmation of diagnosis. There were 24 definite cases with histopathologic evidence for invasive fungal infection on biopsy (skin, 10 cases; lung, 3 cases; eosphagus, 1 case; bowel, 1 case) or autopsy (lung, 2 cases; disseminated, 7 cases) and a positive culture for an *Aspergillus* species. There were 15 probable cases, including 13 with invasive septate fungal hyphae on biopsy (skin, 4 cases; lung, 3 cases; trachea, 1 case) or autopsy (brain, 1 case; lung, 2 cases; disseminated, 2 cases) but cultures were either negative (9 cases) or not performed (4 cases). In the other 2 probable cases there was a positive culture for *Aspergillus* (skin lesion aspirate, 1 case; brain abscess, 1 case) but histopathology was not available. The former responded to therapy with systemic amphotericin B, the latter died and no autopsy was performed (Table 1).

Mycologic studies. Multiple *Aspergillus* species were implicated as causative agents including *Aspergillus flavus* (17 cases), *Aspergillus fumigatus* (4 cases), *Aspergillus niger* (1 case), *Aspergillus nidulans* (1 case) and *Aspergillus terreus* (3 cases).

Associated medical conditions and therapy. Except for one patient all had an underlying disease that compromised immune function (Table 1). In most cases this underlying illness resulted in neutropenia. Thirty-three patients (85%) had a neutrophil count of less than 1000×10^6/liter at the time the *Aspergillus* infection was first suspected. In 19 of 39 patients (49%) the neutrophil count was $<100 \times 10^6$/liter and in 12 of 39 patients (31%) the count was between 101 and 499×10^6/liter. Six cases (15%) had neutrophil counts greater than 1000×10^6/liter. In 5 of these cases other immune abnormalities possibly contributory were identified. Patient 1 with severe combined immunodeficiency had been treated with bone marrow transplant but had only 15% normal T cell function and required replacement therapy for hypogammaglobulinemia. Two patients were posttransplant. Patient 29 was being treated with steroids for graft *vs.* host disease and Patient 23 had chronic rejection of a renal transplant and was on treatment with azathioprine, steroids and cyclosporin. Patient 8, a 22-day-old neonate, was on high dose corticosteroid therapy for an overwhelming congenitally acquired viral myopericarditis. Although Patient 20 had an absolute granulocyte count $>1000 \times 10^6$/liter he was in leukemic blast crisis. Only Patient 39 had presumed normal B and T cell function. Nine months before infection he had repair of a complex congenital heart lesion with insertion of a Gortex® graft. This was the initial site of the *Aspergillus* infection, which was presumably nosocomially acquired.

Thirty patients (76%) had received chemotherapy and 20 (51%) had received corticosteroids during the admission when their *Aspergillus* infection was documented. Four patients (Patients 9, 18, 26 and 36) had received total body irradiation. Immunomodulating agents used in other cases included cyclosporin (Patients 9, 22, 23, 26 and 36), azathioprine (Patients 23 and 36), antithymocyte globulin (Patient 22), gammaglobulin (Patients 1, 5 and 12) or interferon (Patient 35).

The patients had been hospitalized for a median of 47 days (range, 0 to 180 days) in the 6 months preceding the suspicion of their *Aspergillus* infection. Thirty-seven patients (95%) had received broad spectrum antibiotics for a median of 20 days (range, 5 to 225 days) before the clinical suspicion of their fungal infection.

Clinical presentation and outcome. *Cutaneous.* In 16 cases (41%) *Aspergillus* infection was first suspected as a result of a skin lesion (Table 1). These were described as tender, erythematous macules or vesicles (Fig. 1*A*) which frequently progressed to necrotic eschars (Fig. 1*B*). The skin lesions typically presented at sites of trauma commonly related to armboards or intravenous sites (11 of 16; 69%) and were first identified on the palm (6 cases), dorsum of the hand (2 cases), forearm (3 cases), back (2 cases), ankle (1 case) or thigh (1 case). One patient presented with multiple lesions on the scapula, knee, elbow and forearm. On histopathology septate hyphae were found invading deep and superficial vessels with evidence of thrombosis and focal necrosis of vessel walls and invasion into the dermis. Various species were

TABLE 1. Invasive *Aspergillus* Infections at the Hospital for Sick Children, Toronto, 1979 to 1988

Patient	Sex	Age (years)	Underlying Disease	*Aspergillus* Species	Presenting Site	Postmortem Site	Therapy Amphotericin B (mg/kg)	Other Therapy	Outcome
1	F	2	SCID BMT	Unknown	None	Tracheal ulceration	None		Died
2	M	9	ALL	Unknown	Skin (arm-board)		15	Topical Ampho B	Alive, no recurrence at 5 months
3	F	2	AA BMT	*Aspergillus terreus*	Skin (arm-board)	Not done	20	Debridement Rifampin	Died, clinical evidence for dissemination to new skin sites and lung
4	F	17	ALL Diabetes	*Aspergillus flavus*	Esophagus larnyx, lungs	Not done	1		Died
5	M	2	SCID BMT GVH	*Aspergillus fumigatus*	Skin	Disseminated	6	Debridement Topical Ampho B	Died
6	F	15	ALL	*Aspergillus flavus*	Lung, trachea	Disseminated	8		Died
7	M	10	ALL BMT	*Aspergillus flavus*	Skin (arm-board)	None	32	Debridement Topical Ampho B	Died (unrelated)
8	F	22 days	Viral myocarditis	*Aspergillus flavus*	Skin	Skin only	6		Died
9	F	10	AA BMT	*Aspergillus flavus*	Lung	Lung, heart	None		Died
10	M	17	ALL	*Aspergillus flavus*	Lung	Disseminated	8		Died
11	F	16	AML	*Aspergillus flavus*	Skin (arm-board)	Not done	25	5-Flucytosine Granulocytes	Resolved, recurred later at new skin sites
12	M	18	ALL Diabetes	*Aspergillus nidulans*	Skin (arm-board)	Not done	31		Died, progressive skin lesions
13	F	7	Lymphoma	Unknown	Skin (arm-board)	Not done	0.5		Died
14	M	3	FEP	*Aspergillus fumigatus*	None	Disseminated	18		Died
15	F	16	Hodgkin's lymphoma	*Aspergillus flavus*	Lung, trachea	Not done	14		Died
16	F	4	Lymphoma	*Aspergillus fumigatus*	Skin (arm-board)	Not done	10	Debridement	Resolved, then recurred 1 month later which resolved Died later, other causes
17	M	11	Rhabdomyosarcoma	Unknown	Skin (arm-board)	Not done	15	5-Flucytosine	Resolved, died 2 months later of other causes
18	F	18	AA BMT	*Aspergillus terreus*	Skin (arm-board)	Not done	17	5-Flucytosine Debridement	Survived to discharge Died 40 days later
19	F	13	AML Sarcoma	Unknown	Lung	Lung	4.2		Died
20	M	11	AML	*Aspergillus fumigatus*	Brain	Not done	None		Died
21	M	5	AA BMT GVH	*Aspergillus flavus*	Lung	Disseminated	2		Died
22	F	10	AA	*Aspergillus flavus*	Lung Sinuses	Disseminated	19		Died

TABLE *continued*

TABLE 1. —*continued*

Patient	Sex	Age (years)	Underlying Disease	*Aspergillus* Species	Presenting Site	Postmortem Site	Therapy Amphotericin B (mg/kg)	Other Therapy	Outcome
23	F	16	Renal transplant	Unknown	Brain	Brain	<1		Died
24	M	8	ALL BMT	*Aspergillus flavus*	Skin	Disseminated	7	5-Flucytosine Rifampin Granulocytes	Died
25	F	7	ALL	Unknown	Skin	Not done	30	Debridement	Survived to discharge Clinical dissemination to eye, kidney, liver
26	F	2	AA, AML BMT	*Aspergillus flavus*	Lung	Disseminated	<1		Died
27	M	6	AML BMT	*Aspergillus flavus*	Lung	Disseminated	<1		Died
28	F	16	ALL	Unknown	Lung		33	5-Flucytosine	Survived Alive at 3 months
29	F	7	ALL BMT GVH	Unknown	Lung	Disseminated	None		Died
30	F	16	AML	*Aspergillus flavus*	Skin (armboard)	None	43	Debridement Topical Ampho B	Resolved Died 16 months later
31	M	15	AA	*Aspergillus flavus*	Lip, nose Lung	Disseminated	None		Died
32	M	6	ALL BMT	*Aspergillus niger*	Skin (armboard)	Not done	17	Debridement Topical Ampho B	Resolved, no recurrence at 3 months
33	M	6	ALL Down's	Unknown	Lung	Lung	<1		Died
34	F	2	T cell deficiency	*Aspergillus terreus*	Small bowel	Liver (restricted)	2	5-Flucytosine	Died
35	M	7	ALL	Unknown	None	Lung	7		Died
36	F	17	ALL BMT GVH	*Aspergillus flavus*	Lung	Disseminated	4		Died
37	M	2	AA BMT	Unknown	Lung	Disseminated	4		Died
38	M	8	ALL	*Aspergillus flavus*	Skin	Skin, lung	8	Debridement	Died
39	M	11	Congenital cardiac disease	Unknown	None	Endocarditis Lung			Died

AA, aplastic anemia; GVH, graft *vs.* host disease; AML, acute myelogenous leukemia; FEP, familial erythrophagocytic syndrome; SCID, severe combined immunodeficiency; BMT, bone marrow transplant; ALL, acute lymphocytic leukemia; 5-FC, 5-flucytosine; Ampho B, amphotericin B.

isolated by culture of the biopsy specimen: *A. flavus* (6 cases); *A. fumigatus* (2 cases); *A. niger* (1 case); *A. terreus* (2 cases); *A. nidulans* (1 case). All patients received systemic treatment with intravenous amphotericin B at a mean of 15 days of neutropenia and 16 days of broad spectrum antibiotics. Nine patients had local debridement of the skin lesion and 5 patients had topical application of amphotericin B soaks to the affected areas several times per day (to make the solution one vial of amphotericin B powder was mixed with 10 ml of mineral oil and 5 ml of the mixture were added to 45 g of Vaseline® petroleum jelly).

The skin lesions resolved in 9 cases (56%) but failed to resolve or progressed on treatment in the other 7 cases (44%). In Patient 3 the skin lesion resolved on therapy; however, there was clinical and radiologic evidence for dissemination to the eye, kidney and liver. Despite initial resolution Patients 11 and 16 developed recurrent skin lesions with subsequent episodes of neutropenia. These new lesions resolved in Patient 16; Patient 11 died and no autopsy was obtained. Five of six patients whose skin lesions resolved and did not recur did not have clinical evidence for *Aspergillus* infection at the time of their death, which was thought to be attributable to unrelated causes. This was confirmed on autopsy in Patients 7 and 30. Patient 2 was lost to follow-up but had no clinical evidence of recurrence 5 months after antifungal therapy was discontinued. In all cases that responded to therapy, resolution of the skin lesions was coincident with recovery from neutropenia.

All seven cases whose skin lesion failed to respond to therapy died with their infection. At autopsy three of the seven cases had evidence of disseminated aspergillosis to lung (Patients 5 and 24) or extensively to multiple sites (Patient 24), and one had the infection confined to the skin (Patient 8). The other three patients (Patients 3, 12 and 13) died and no autopsy

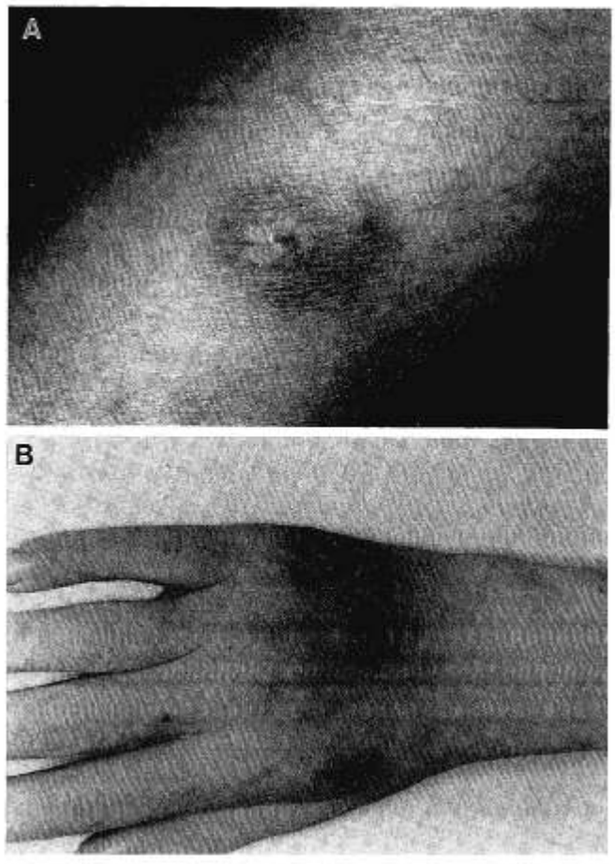

FIG. 1. *a*, early primary cutaneous *Aspergillus* infection. Erythematous macule with central pustule at site of intravenous catheter insertion. *b*, late primary cutaneous *Aspergillus* infection with central necrotic area and surrounding erythema.

was obtained. There was clinical evidence for dissemination in two patients, to lungs (Patient 3) or brain (Patient 13). Recovery from neutropenia did not occur in any of these patients.

The average dose of systemic amphotericin B in patients whose skin lesions resolved was 22.6 mg/kg, higher than that in those who died of their infection (10.1 mg/kg) but this most likely reflects the difference in duration of therapy (average of 30 *vs.* 13 days, respectively), which related to survival. Adjunctive local debridement was used in 6 of 9 (67%) who had resolution of their skin lesion and 3 of 7 (43%) in whom the lesion progressed. Amphotericin B soaks were used in 4 of 9 (44%) cases in whom the skin lesions resolved and 1 of 7 (14%) in whom they progressed.

Respiratory. In 16 cases (41%), *Aspergillus* infection was first suspected in the respiratory tract on the basis of fever and an abnormal chest x-ray (15 cases) or pleuritic chest pain (1 case) despite broad spectrum antibiotics. No patient had respiratory symptoms or abnormal chest x-ray on hospital admission. Further presumptive evidence for *Aspergillus* was available premortem in 14 patients (88%) on the basis of positive cultures from a sinus aspirate (1 case), sputum (5 cases), endotracheal tube aspirate (1 case), bronchoalveolar lavage fluid (2 cases), pleural fluid (1 case) or open lung biopsy (5 cases). In 6 patients subsequently confirmed to have invasive pulmonary disease at autopsy, a premortem biopsy of radiologically involved lung was negative.

Amphotericin B was initiated after a mean of 22 days of fever and neutropenia, after a mean of 31 days of broad spectrum antibiotics and after a mean of 5 days after the first abnormal chest x-ray. Fifteen patients (94%) died of their infection after receiving a mean dose of 3.8 mg/kg amphotericin. An autopsy was performed in 13 patients. The infection was disseminated widely in 11 cases but was confined to the lungs in the other 2 cases. The 3 patients in whom an autopsy was not performed had their *Aspergillus* infection confirmed pathologically by lung biopsy (2 cases) or esophageal biopsy (1 case). The 1 surviving case (Patient 28) received 33 mg/kg of amphotericin B with improvement of the chest x-ray infiltrates coincident with resolution of neutropenia. Although the course of antifungal treatment was thought to be suboptimal, the drugs were discontinued at her family's request. She was subsequently discharged to another hospital for palliative care and was alive 2 months after the amphotericin was discontinued.

Presentation at other sites and outcome. *Gastrointestinal.* Patient 34 with a T cell deficiency (atrophic thymus gland with lymphocyte depletion) was hospitalized with fever and pancytopenia. An acute abdomen developed and at surgery a bowel infarction from midduodenum to midjejunum was found. Histopathologic examination of the resected bowel demonstrated invasive aspergillosis. Liver involvement found at surgery was confirmed on biopsy. Despite intravenous amphotericin B and oral 5-flucytosine she died 1 week later.

Cerebral. Patient 23 on immunosuppressive therapy for failed renal transplant developed cytomegalovirus pneumonia. Just before death, there was a change in her level of consciousness, and a computer-assisted tomographic scan showed a small right parietal hemorrhage with surrounding edema and midline shift. Postmortem examination revealed multiple cerebral abscesses and leptomeningitis secondary to *Aspergillus*.

Patient 20 with relapsed acute myelogenous leukemia presented with new neurologic symptoms. A brain biopsy was positive for *Aspergillus*. Treatment was withheld.

Cases not clinically suspected: autopsy diagnosis. The other four cases of aspergillosis (Patients 1, 35, 39 and 14) were not clinically suspected before death but were confirmed at autopsy to invade trachea, lung or heart or was disseminated. Patients 14 and 35

had received an average of 12 mg/kg amphotericin B for treatment of suspected candidiasis.

DISCUSSION

This retrospective study reviewed invasive *Aspergillus* infections in a pediatric hospital. Environmental exposure to this fungus is common but invasive disease uncommon as reflected by our documentation of only 39 cases over a 10-year period. Many findings in this study are similar to those described in adult series.[7-9] Specific aspects we wish to highlight include (1) the underlying medical conditions, (2) the high frequency of cutaneous presentation, (3) the difficulty in confirming the diagnosis and late initiation of specific antifungal therapy and (4) the poor outcome and the need for preventative strategies.

Demographics. As in previous reports[7, 8] certain host characteristics were associated with invasive aspergillosis. All patients in our series had an underlying medical condition which may have predisposed them to infection, and in most cases this underlying illness or its treatment had effects on the immune system. Granulocytes have a specific role in resistance to invasive infection by *Aspergillus* and together with tissue macrophages comprise the main cellular immune defense.[14] The majority of our cases (74%) occurred in patients with hematologic malignancies or bone marrow transplant recipients. Most patients were neutropenic at the time of documentation of the fungal infection. T cell function also appears to contribute to the host defense. Six (15%) of our patients had normal levels of circulating granulocytes, but in 5 defects in cell-mediated immunity could be attributed to the underlying disease or its treatment. There were some differences in the specific underlying disorders in our series compared to previous reports including familial erythrophagocytic syndrome, Fanconi's aplastic anemia, subacute combined immunodeficiency, etc., reflecting the pediatric nature of these conditions and the fact that many of those affected do not survive into their adult years.

Previous studies have shown the duration of granulocytopenia[5] rather than its presence is the major risk factor for invasive aspergillosis. Although lacking a control group for comparison, the mean duration of the granulocytopenia ($<1000 \times 10^6$/liter) before clinical suspicion of the *Aspergillus* infection was 20 days. As in previous reports[5, 8, 9] concurrent chemotherapy (76%) and corticosteroid therapy (51%) were also associated with invasive *Aspergillus* infection. Broad spectrum antibiotic therapy has also been considered a major risk factor in adult patients[7, 8] and in our series 95% cases had received these drugs an average of 37 days before the clinical suspicion and institution of specific antifungal therapy. Thirteen patients (33%) had all of neutropenia, antibiotics, chemotherapy and steroids.

Cutaneous presentation. A major feature distinguishing our patients is the high frequency of cutaneous presentation (16 of 39; 41%). In previous series of invasive aspergillosis[7, 9] the lung was the most common initial site of involvement. In a standard pediatric infectious diseases textbook, primary cutaneous infection is discussed only briefly.[15]

A primary cutaneous form of aspergillosis was first described by Meyers and Dunn[16] in 1930. Other small series and case reports[17-43] describe similar lesions in both normal and compromised hosts (Table 2). These cutaneous lesions present as erythematous or edematous plaques which may progress to necrotic ulcers with central black eschars or hemorrhagic bullae. The lesions may develop from direct inoculation of the fungus from an environmental source as a result of trauma or may result from the localization of *Aspergillus* to areas of stasis during fungemia. In hospitalized patients they have been described at sites of insertion of peripheral or central venous catheters and at points of contact with adhesive tape or armboards. In some cases *Aspergillus* had contaminated the adhesive tape and armboard covers. In other cases the fungus presumably contaminated breaks in the skin or mucosa from environmental sites including the ambient air. In our hospital *Aspergillus* species were isolated from the environment (on settle plates in patients' rooms and swabs from ceiling tiles) and from one armboard before wrapping but not from any of the armboard components. Based on our investigations it was recommended that armboards be avoided where possible or changed every 24 hours. Subsequently there has been increased emphasis on the use of long term central venous catheters in this population. Although decreasing, cases of primary cutaneous *Aspergillus* still occur at our institute.

The cutaneous presentation of aspergillosis may be more common in pediatric patients. Of the 45 cases reported in the literature in immunocompromised patients, 25 (56%) have occurred in children (Table 2). This increases to 67% when our 15 cases are included. The fact that armboards may be used more commonly to stabilize intravenous lines in children than in adults may explain this observation.

Cutaneous *Aspergillus* lesions in healthy patients either resolve spontaneously or are easily cured with debridement or topical antifungal therapy.[17, 25-27] Management is less successful in the compromised host. Given the propensity for vascular invasion, organisms may enter the blood stream and disseminate to viscera, lung, brain, etc., with a fulminant course and ultimate death.[20, 21, 31] Despite this risk cures have been reported in the compromised host after treatment with systemic amphotericin B with or without local debridement.[20, 21, 24, 30] Success is attributed to early suspicion, aggressive antifungal chemotherapy, wide debridement and recovery from neutropenia.[9]

TABLE 2. Reported cases of primary cutaneous aspergillosis

Reference	No. of Cases	Host	*Aspergillus* species	Treatment	Outcome
8	1 pediatric	Leukemia	*Aspergillus flavus*	Unknown	Disseminated
10	4 pediatric	3, trauma 1, leukemia	Unknown	Ampho B Debridement	4, cure
16	1 adult	Normal	*Aspergillus terreus*	Local $CuSO_4$	Cure
17	1 adult	Normal	*Aspergillus niger*	Griseofulvin Nystatin	Cure
18	1 pediatric	Neonate	*Aspergillus flavus*	Excision	Cure
19	1 pediatric	Leukemia	*Aspergillus flavus* *Aspergillus niger*	Ampho B Excision	Cure
20	9 adult	7, leukemia 1, lymphoma 1, aplastic anemia	*Aspergillus flavus*	Ampho B ± 5-FC ± debridement	6, cure 2, disseminated 1, died (other)
22	1 adult	Normal	*Aspergillus terreus*	Unknown	Unknown
23	4 pediatric	3, leukemia 1, brain tumor	*Aspergillus terreus* *Aspergillus flavus* *Aspergillus niger*	Ampho B (3) ± debridement	3, cure 1, died
24	5 pediatric	4, leukemia 1, aplastic anemia	*Aspergillus flavus* *Aspergillus terreus* *Aspergillus flavipes*	Ampho B (5) Rifampin (2) 5-FC (1)	2, cure 3, died
25	1 adult	Normal	*Aspergillus fumigatus*	Oral nystatin	Cure
26	1 adult	Normal	*Aspergillus niger*	Local iodine	Cure
27	1 adult	Burn wound	*Aspergillus niger*	?	Cure
28	1 adult	Renal transplant	*Aspergillus fumigatus*	Topical ampho B Debridement	Disseminated
29	1 adult	Normal	*Aspergillus terreus*	Incision	Cure
30	1 pediatric	Leukemia	*Aspergillus flavus*	Ampho B Granulocytes	Cure
31	3 pediatric 1 adult	2, leukemia 2, aplastic anemia	*Aspergillus flavus*	Ampho B (4) 5-FC (2) Nystatin (1)	1, cure 3, disseminated
32	1 pediatric	Leukemia	*Aspergillus flavus*	Nystatin	Died
33	4 adult	Burn wounds	Unknown	Debridement (2) Sulfamylon	3, died 1, cure
34	18, ages not reported	Burn wounds	Unknown	Debridement Nystatin (9) Topical Ampho B (10) Ampho B (15)	9, disseminated 5, died (other) 4, cure
35	4 adult	Leukemia	*Aspergillus flavus*	Ampho B Debridement (2) Sulfadiazine	3, cure 1, died
36	1 pediatric	Chronic granulomatous disease	*Aspergillus flavus*	Ampho B	Cure
37	1 adult	Liver transplant	*Aspergillus fumigatus*	Ampho B	Died
38	1 adult	Heart transplant	Unknown	Ampho B Itraconazole	Cured
39	1 pediatric	Leukemia	*Aspergillus flavus*	Unknown	Unknown
40	3 adult	2, leukemia 1, myeloma	Unknown	Ampho B	2, cure 1, died
41	1 pediatric	Chronic hepatitis	Unknown	Ampho B	Died
42	2 adult	AIDS	*Aspergillus fumigatus*	Fluconazole (1) Polymyxin B (1)	1, disseminated 1, died (other)
43	1 pediatric	Leukemia	*Aspergillus flavus*	Ampho B	Cured
This report	16 pediatric	7, leukemia 5, BMT 2, lymphoma 1, sarcoma 1, myocarditis	*Aspergillus flavus* *Aspergillus fumigatus* *Aspergillus niger* *Aspergillus terreus* *Aspergillus nidulans*	Ampho B (16) Debridement (9) Topical Ampho B (5) Rifampin (1) 5-FC (2)	8, cure 5, disseminated 3, died 2, recurred

Ampho B, amphotericin B; 5-FC, 5-flucytosine; BMT, bone marrow transplant; AIDS, acquired immunodeficiency syndrome.

The cure rate for invasive cutaneous aspergillosis appears higher than for invasive infection presenting at other sites. Of the literature cases (Table 2), the overall cure rate in immunocompromised patients is 26 of 44 (59%). In our series 8 of 16 (50%) cases presenting with skin lesions resolved without evidence for dissemination. Cutaneous *Aspergillus* infection recurred in 2 patients during subsequent episodes of neutropenia, likely reflecting incomplete eradication. In the patients in whom the lesions resolved without dissemination, neutropenia recovered within 2 to 3 weeks after initiation of iv amphotericin B. In the patients who died with their infection, either remission of the leukemia was not achieved (3 cases) or their bone marrow transplant failed to engraft (3 cases).

The cure rate in patients with primary cutaneous lesions (50%) was better than that for the group as a whole (26%). This improved outcome may relate to the fact that the skin lesions are easily identifiable allowing for early diagnosis and treatment before significant dissemination occurs. In our series patients with cutaneous lesions were started on amphotericin B after a mean of 15 days of neutropenia and 16 days of broad spectrum antibiotics as compared with 21 and 31 days, respectively, in patients presenting at a

respiratory site. However, the responses of the underlying diseases and recovery from neutropenia also appeared to be important factors in outcome.

Despite reports of cure, there is still a significant morbidity and mortality associated with the cutaneous disease especially when dissemination occurs. Skin lesions may be an early sign of invasive *Aspergillus* infection in neutropenic children. Hosts at risk should be examined daily for such lesions particularly at sites of intravenous line insertions or trauma induced by armboards or tape, and if found they should be biopsied and treated aggressively. Given the relationship to armboards we would recommend that they be avoided if possible in children at risk.

Problems with diagnosis. The patients in our series who presented in a respiratory site fared less well with 15 of 16 patients dying from their infection. This may reflect the increased difficulty in making a premortem diagnosis in a respiratory site, especially in children.[44] The chest x-ray findings are often nonspecific and many of these patients are pancytopenic, are hypoxic or have coagulation abnormalities increasing the risk of complications of invasive procedures such as bronchoscopy necessary for confirmation of the diagnosis. Further the disease can be patchy and despite invasive techniques the tissue obtained may show areas of injury or infarction but may miss the characteristic hyphae needed to confirm a diagnosis. In our series only 5 of 12 patients subsequently found to have disseminated aspergillosis at autopsy had positive results from a biopsy of radiologically involved lung.

In order to initiate antifungal treatment early it is important to keep a high level of suspicion in patients at greatest risk.[45, 46] A number of noninvasive techniques have been studied in attempts to predict the likelihood of pulmonary aspergillosis. Aisner et al.[47] found positive nasal cultures to be predictive of invasive aspergillosis in patients with acute nonlymphocytic leukemia. The usefulness of the isolation from other respiratory sites has been debated with reported sensitivities of sputum isolation ranging from 13 to 67%.[7, 48–50] The sensitivity may be higher in patients with hematologic malignancy.[49] In our institute routine surveillance cultures of nasal swabs or sputum for *Aspergillus* are not performed; however, they may be taken in a suspected case. Noninvasive cultures were positive in 6 of 16 cases (sputum 5 cases, nasal swab 1 case). Sputum cultures and nasal swabs were negative in 9 and 3 cases, respectively.

Because of the difficulties in diagnosis, many cases of invasive aspergillosis continue to be diagnosed at autopsy.[51–53] In early series antemortem diagnosis was rarely made and mortality approached 100%. In later series the importance of early diagnosis was stressed inasmuch as early aggressive therapy with amphotericin B was associated with better outcome. Aisner et al.[54] describe 6 patients who survived their infection. All were diagnosed and treated within 96 hours of the appearance of their pulmonary infiltrates, whereas 11 patients with a delay in treatment died of their infection. The response of the underlying illness also appears to be important to outcome inasmuch as 5 of 6 patients who improved also had hematologic remission, in contrast with 0 of 11 who died. In our series all patients who had improvement of their infection had recovery of their neutropenia. It appears that the role of aggressive antifungal therapy is to achieve fungal stasis until the granulocytes recover. The role of white blood cell transfusions or colony-stimulating factors is unknown.

Because of the difficulties in making a specific mycologic diagnosis and the high mortality despite treatment once disease is well-established, it is recommended that empiric amphotericin B be initiated in high risk patients suspected of having a systemic fungal infection.[55–57] This approach has been effective in decreasing morbidity and mortality in patients with acute leukemia.[57, 58] Despite knowledge of these recommendations, amphotericin B was initiated late in our cases. Without a control group we cannot know whether our patients would have fared better with earlier empiric antifungal treatment. Current guidelines would support amphotericin B use substantially earlier.

Preventative strategies. Given the overall poor outcome in our patients with invasive aspergillosis (mortality, 74%), a more important approach to these high risk patients is in prevention. Prevention of nosocomial aspergillosis requires reduction in the spore content of the ambient air through filtration and increase in air exchange rate.[59, 60] Fungal spores are inhaled into the lung, the main portal of entry for invasive infection. Environmental isolates are also the most likely source for primary cutaneous lesions. Outbreaks of invasive aspergillosis have been described in association with hospital construction or renovation.[61–71] Our first cases of invasive aspergillosis occurred coincidentally with a period of hospital construction. At this time the environment and armboards may have become contaminated with *Aspergillus* spores. Although infection control policies were put into effect, cases continued.

In the published reports of nosocomial aspergillosis, decreases in the incidence of infection have been described after: (1) the use of special filters (high efficiency particulate air) in unrecirculated air; (2) the cleaning and decontamination of ventilating systems; and (3) the minimization of exposure of seriously immunocompromised patients to major construction activity.[60, 62, 64] Although these procedures may be beneficial, they are expensive and can be provided

only for those patients at highest risk, especially for patients with hematologic malignancies and after bone marrow transplantation.

An alternative strategy may be to decrease the colonization of the upper airway with various oral or topical antifungal agents. Most studies investigating the role of ketoconazole,[72] oral amphotericin,[73] amphotericin B spray[74, 75] and fluconazole[76, 77] are aimed at the prevention of disseminated candidiasis. Whether a decrease in *Aspergillus* infections will also be observed is speculative and only large prosective multicenter trials will be able to answer this question. Because many of these compounds have low intrinsic, antifungal activity against *Aspergillus* (nystatin, ketoconazole, fluconazole) it is unlikely that an effect will be observed. Preliminary data suggest that amphotericin B intranasal spray may be efficacious.[75] Newer oral azoles such as itraconazole with increased intrinsic anti-*Aspergillus* activity may prove more effective.[78–80] It is unlikely that any of these agents will prevent the primary cutaneous form of infection.

CONCLUSION

Invasive aspergillosis is an uncommon but serious infection in immunocompromised children, particularly those with hematologic malignancies and those receiving bone marrow transplantation. In children the infection more commonly presents as a primary cutaneous lesion, typically occurring at sites of trauma related to armboards and intravenous insertion sites. Patients at risk should be regularly examined for the presence of these lesions, and if found they should be biopsied and treated aggressively. The early diagnosis of such lesions may allow for earlier intervention with systemic antifungal agents and a better outcome. Armboards should be avoided in high risk children whenever possible. Invasive aspergillosis continues to be associated with a significant mortality despite therapy. New strategies for the prevention of these infections in hosts at risk are required.

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