Candidal Meningitis in Children with Cancer

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Candidal meningitis is a rare disease that is seen most frequently in neonates, neurosurgical patients, and the immunocompromised host. We describe a series of 12 children with cancer (all of whom had leukemia) who had candidal meningitis develop. Univariate analysis revealed that duration of fever, antibiotic therapy, and profound neutropenia and use of total parenteral nutrition were significantly associated ($P < .05$) with candidal meningitis in children with cancer, compared with matched control subjects. Only duration of profound neutropenia ($P = .08$) and use of total parenteral nutrition ($P = .06$) approached significance in the multivariate analysis. One species of *Candida, Candida tropicalis,* was responsible for 11 of the 12 cases, indicating increased pathogenicity of this organism in CNS disease. The cases were invariably fatal, supporting aggressive treatment of candidal meningitis in immunocompromised patients and further study of the prevention, diagnosis, and management of *C. tropicalis* meningitis.

Candidal meningitis is a rare disease that was first reported in 1933 [1]. It is seen most commonly in critically ill neonates [2, 3], neurosurgical patients [4], and patients with risk factors for invasive fungal disease and disseminated candidiasis [5]. Very few cases of candidal meningitis have been described in patients with cancer. There have been rare cases in patients with other immunocompromised states, including myeloperoxidase deficiency [6], severe combined immunodeficiency [7], and AIDS [8, 9]. Twenty-eight cases of candidal involvement of the brain in patients with cancer have been reported in autopsy series [10, 11], and 10 cases of candidal meningitis diagnosed before death (9 in patients with leukemia [12–14] and 1 in a patient with Hodgkin's disease [15]) have been reported.

In previous reports, the species most frequently responsible for candidal meningitis has been *Candida albicans.* However, cases of meningitis caused by *Candida tropicalis* [12, 13, 15–18], *Candida lusitaniae* [19–21], and *Candida parapsilosis* [22] have also been reported. The reported risk factors for candidal meningitis, which are similar to those for invasive fungal infections in general, include use of broad-spectrum antibiotics, immunocompromised status, use of steroids [4, 11, 23], use of total parenteral nutrition (TPN) [3, 12], and injection drug abuse [24]. Candidal endocarditis [11], neurosurgical procedures, and preceding or concomitant bacterial meningitis are also recognized risk factors [11, 23]. However, to our knowledge, no case-control studies have been done to confirm any observed associations. Morbidity and mortality rates associated with candidal meningitis are high, although use of amphotericin B, both alone and in combination with flucytosine (5-fluorocytosine), has increased the cure rate and has reduced the number of deaths caused by this disease [25–28]. Despite advances in treatment, however, survival has been described in only 2 patients (both adults) with cancer and candidal meningitis [13, 14].

In the present study, we describe 12 cases of candidal meningitis that occurred in children with cancer over an 18.5-year period, and we report clinical presentations, treatment, and outcomes. These 12 patients were compared with matched control subjects to determine risk factors for acquisition of disease. This is the first case-control study done on this subject.

Methods

Patients. The subjects of this study were patients at St. Jude Children's Research Hospital (Memphis) who were enrolled in prospective studies designed primarily to evaluate chemotherapy regimens. The medical records of all patients with CSF specimens positive for *Candida* species between January 1980 and August 1998 were reviewed. All patients with a diagnosis of cancer and a clinical illness compatible with meningitis were included in the study. Aspects of several of the cases presented here have been reported elsewhere [12, 18].

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Table 1. Clinical characteristics of 12 pediatric patients with leukemia and candidal meningitis.

Characteristic	No. (%) of cases
Underlying disease	
Diagnosis	
Acute lymphocytic leukemia	8 (75)
Acute myelogenous leukemia	4 (25)
State of disease	
Induction	5 (42)
Reinduction after relapse	5 (42)
Remission	1 (8)
Status post–bone marrow transplantation	1 (8)
Clinical presentation	
Fever	12 (100)
Level of consciousness	
Normal	6 (50)
Lethargic or obtunded	3 (25)
Semicomatose or comatose	3 (25)
Seizures	4 (33)
Headache	3 (25)
Nuchal rigidity	3 (25)
Cranial nerve abnormalities	2 (17)
Skin lesions	4 (33)
Asymptomatic other than fever	5 (42)

Case-control study. To match the type and severity of immune suppression, control subjects were matched 2 to 1 to case patients: the case patients who were selected were enrolled both immediately before and after the case patient who was receiving the same cancer chemotherapy protocol. Selected demographics and potential risk factors obtained from the medical records of the control subjects were then compared with those of the case patients, for a similar period during immunosuppression (i.e., throughout the period of induction or reinduction, or until engraftment after bone marrow transplantation). Risk factors selected for univariate analysis included the following: age; sex; duration of fever, antibiotic use, and steroid use; use of TPN; degree and duration of neutropenia (measured by absolute neutrophil count [ANC]); presence of a central venous catheter or Ommaya reservoir for administration of chemotherapy; hyperglycemia; underlying CNS disease; colonization or infection with *C. tropicalis* or any *Candida* species at another site; and intrathecal chemotherapy. Risk factors with rare occurrence (<5%) among the population were excluded from further analysis. Variables that demonstrated $P \leqslant .05$ in the univariate analysis were then submitted to multivariate analysis. Potential confounding variables were deleted from the multivariate analysis. ORs, which were adjusted for other factors, were calculated from the final model. All statistical analyses were performed by use of SAS software (SAS Institute, Cary, NC).

Results

Twelve cases of candidal meningitis were identified in nonsurgical patients. Characteristics of these patients, including underlying diseases and clinical presentations, are presented in table 1. Ten of the 12 patients were receiving intensive chemotherapy during either induction of their primary disease or reinduction after relapse of their malignancy (all 12 patients had leukemia). The median time from either diagnosis of primary malignancy or relapse of malignancy to identification of meningitis was 24 days (mean, 24 days; range, 7–42 days). One patient had meningitis develop following bone marrow transplantation after a preparatory regimen including intensive chemotherapy and prior to engraftment. Fever was a presenting symptom in all 12 patients, and, although one-half of the patients had a decreased level of consciousness at presentation, fever was the only clinical sign or symptom in 5 patients. Diagnosis of meningitis in these patients either was inadvertent during lumbar puncture for administration of intrathecal chemotherapy or was actively pursued because of clinical suspicion in the presence of disseminated candidiasis.

An Ommaya reservoir was present in only 1 case patient (3% of the study population), and *C. tropicalis* colonization occurred in none of the control subjects; therefore, no further analysis could be performed. Results of univariate analysis for the remaining variables are shown in table 2. For continuous variables, the OR is based on 1 unit of increase (e.g., year for age, and day for duration of fever, antibiotic use, steroid use, and neutropenia). The duration of fever, antibiotic use, and neutropenia (ANC, <100 cells/mL) and use of TPN were significantly different in the univariate analysis and therefore were included in the multivariate model. Duration of an ANC <500 cells/mL was omitted in favor of duration of an ANC <100 cells/mL, and hyperglycemia was deleted in favor of TPN use, because duration of an ANC <100 cells/mL and TPN use were positively correlated. Despite consideration of multiple models, no statistically significant differences between the case patients and control subjects were identified. Inclusion of risk factors such as ANC <100 cells/mL, duration of fever, and duration of antibiotic use may also confound the model because of a significant correlation of the risk factors. Therefore, the model was reduced to include only duration of an ANC <100 cells/

Table 2. Predisposing factors for candidal meningitis in pediatric patients with leukemia.

Factor	Case patients (n = 12)	Control subjects (n = 24)	OR (95% CI)	P
Age, mean y	10	9	1.04 (0.91–1.19)	.53
Sex, females/males	7/5	10/14	2.00 (0.46–8.62)	.35
Fever, mean d	7.8	4.0	1.26 (1.10–1.56)	.03[a]
Antibiotic use, mean d	12	6.5	1.25 (1.03–1.51)	.03[a]
Steroid use, mean d	7.8	12	0.92 (0.82–1.04)	.19
Total parenteral nutrition use	6 (50)	2 (8)	10.5 (1.26–89)	.03[a]
Hyperglycemia	7 (58)	5 (21)	3.79 (0.95–15)	.06
ANC <500/mL, mean d	18.3	11.6	1.10 (0.99–1.23)	.08
ANC <100/mL, mean d	15.1	7.8	1.14 (1.01–1.28)	.03[a]
Central venous catheter	9 (75)	14 (58)	2.89 (0.30–28)	.36
Received intrathecal chemotherapy	8 (67)	15 (63)	0.30 (0.03–3.12)	.31
CNS disease	5 (42)	6 (25)	2.20 (0.57–8.4)	.25
Candida (any species) colonization	11 (92)	12 (50)	7.77 (0.89–67)	.06
Candida tropicalis colonization	8 (67)	0	ND (ND)	ND

NOTE. Data are no. (%) of patients, unless indicated otherwise. ANC, absolute neutrophil count; ND, not determined because OR was not calculable.

[a] Selected for multivariate analysis.

Table 3. Results of selected studies for 12 pediatric patients with leukemia and candidal meningitis.

	Culture result			CSF finding						
Case	Surveillance	Blood	CSF	WBC/mm^3	P/L/M, %	Protein level, mg/dL	Glucose level, mg/dL	Gram staining	CT finding	Brain finding(s) at autopsy
1	*C. trop.*	*C. trop.*	*C. trop.*	0	8/65/27	61	120	NOS	ND	Abscesses in brain parenchyma
2	*C. trop.*	*C. trop.*	*C. trop.*	1	0/100/0	23	60	Yeast	Normal	Normal
3	*C. alb.*	—	*C. trop.*	210	80/14/6	240	100	NOS	Normal	Abscesses in brain parenchyma and spinal cord
4	*C. alb.*	*C. trop.*	*C. trop.*	0	12/86/2	ND	ND	Yeast	ND	Abscesses in brain parenchyma
5	*C. alb.*	—	*C. trop.*	120	0/100/0	30	83	NOS	Normal	Normal
6	*C. trop.*	*C. trop.*	*C. trop.*	0	10/35/55	500	3	Yeast	Normal	Abscesses in spinal cord and meninges only
7	*C. trop.*	—	*C. trop.*	300	0/60/40	166	182	Yeast	Normal	Abscesses in spinal cord only
8	*C. trop.*	*C. trop.*	*C. trop.*	73	0/86/14	63	27	Yeast	Hydrocephalus	ND
9	*C. alb.*	—	*C. alb.*	0	0/100/0	31	66	NOS	Normal	ND
10	*C. trop.*	*C. trop.*	*C. trop.*	6	0/24/76	25	76	Yeast	ND	ND
11	*C. trop.*	*C. trop.*	*C. trop.*	11	0/86/14	73	67	NOS	Normal	Normal
12	*C. trop.*	*C. trop.*	*C. trop.*	2	20/60/20	73	52	Yeast	ND	ND

NOTE. *C. alb., Candida albicans; C. trop., Candida tropicalis;* ND, not done; NOS, no organisms seen; P/L/M, polymorphonuclear cells/lymphocytes/mononuclear cells.

mL and TPN use, and the results of this analysis demonstrated adjusted ORs of 1.15 and 11.7, respectively. Both of these variables approached statistical significance, with *P* values of .08 and .06, respectively.

The results of laboratory studies supporting the diagnoses of candidal meningitis are reported in table 3, along with neuroimaging and autopsy results. All 12 patients were colonized with *Candida* species, although *C. albicans* colonization alone was detected in 3 patients who had meningitis caused by *C. tropicalis* develop. It is noteworthy that all 8 patients who had surveillance cultures that were positive for *C. tropicalis* acquired this organism within 3 weeks of diagnosis of meningitis. Eight of 12 patients had candidemia concurrent with meningitis. Blood cultures were positive between 1 and 13 days (mean, 3 days; median, 1 day) before CSF cultures were positive. Of the 12 patients described here, 11 had *C. tropicalis* meningitis, whereas only 1 had *C. albicans* isolated. In contrast, *C. albicans* was isolated from all 7 excluded patients thought to have contaminated CSF specimens. The most striking finding of the analyses of CSF specimens was the presence of yeast during microscopic examination of specimens from 7 of 12 patients. Neuroimaging of the head was done by CT in 8 of 12 case patients and revealed abnormalities related to meningitis in only 1 case patient (table 3). However, 4 of the 12 patients had clinical evidence of disseminated candidiasis in other organs (the lungs in 2 patients and the abdominal organs [liver, spleen, and kidney] in the other 2 patients).

All 12 patients died of candidal meningitis. The median time from diagnosis to death was 3 days (mean, 11 days; range, 1–67 days). Six of 12 patients received ⩾3 days of amphotericin B therapy before diagnosis of candidal meningitis, and 11 received antifungal therapy in the interval between diagnosis and death. In 1 instance, the patient died without receiving any antifungal therapy. Details of antifungal therapy for the 12 case patients are presented in figure 1. Three patients received amphotericin B through an Ommaya reservoir for 1–9 days, and 3 patients received WBC transfusions for 1–21 days. One patient who received a WBC transfusion had a severe anaphylactic reaction that may have contributed to her rapid death.

Autopsies were requested for all 12 case patients but were

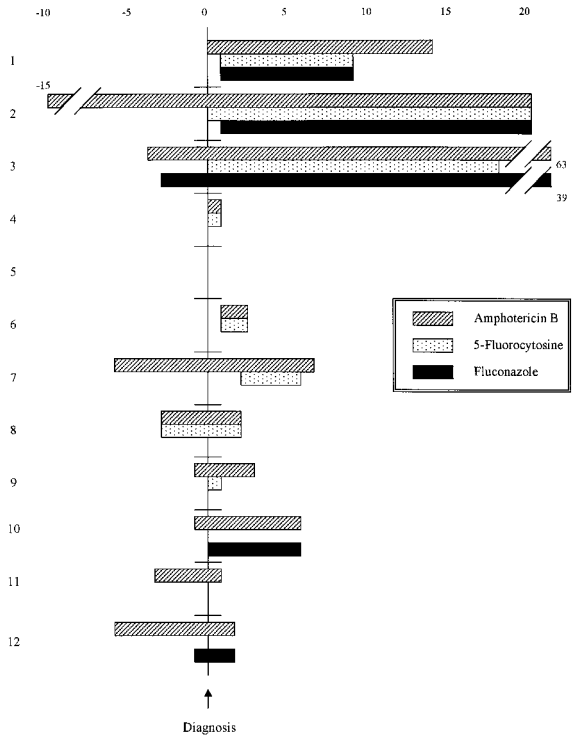

Figure 1. Antifungal use in 12 pediatric patients with leukemia and candidal meningitis. Days of antifungal use (amphotericin B, flucytosine [5-fluorocytosine], and fluconazole) are represented by bars for each patient (case patients 1–12). The numbers across the top of the figure are days before and after diagnosis (day 0).

done for only 8. In 7 of these 8 patients, disseminated multiorgan disease—most often, multiple candidal abscesses throughout the solid organs and brain—was present at autopsy (table 3). At autopsy, *Candida* was present in the CNS of 6 case patients. It generally involved both the brain parenchyma and the meninges, although the spinal cord alone was involved in 1 case patient and the spinal cord and meninges only were involved without the parenchyma in another patient. Autopsy of 1 patient showed only focal pulmonary disease. Three of the 8 patients had involvement of the gut (small intestine, appendix, or stomach and esophagus).

During the 18.5-year study, an additional 7 patients had CSF cultures that were positive for *C. albicans* in a setting in which candidal meningitis was thought to be unlikely. Six of these culture specimens were obtained after deaths unrelated to candidal infection; 3 patients (all of whom had solid tumors [Ewing's sarcoma, fibrosarcoma, and neuroblastoma]) died of respiratory failure related to progressive malignancy, 2 died of overwhelming bacterial sepsis (and had underlying diagnoses of acute lymphocytic leukemia and neuroblastoma), and 1 died of viral pneumonitis (and had underlying diagnosis of acute lymphocytic leukemia). In each of these case patients, *C. albicans* was isolated from CSF at autopsy, without pathological evidence of candidal infection of CNS or disseminated candidiasis, and the organism was believed to be a contaminant. In the seventh case patient, *C. albicans* was isolated from a CSF specimen obtained during routine administration of intrathecal chemotherapy for acute lymphocytic leukemia, although the patients had no signs or symptoms of meningitis. A follow-up culture, obtained without administration of antifungal therapy, proved to be negative. In the course of the study, 1 surgical patient had meningitis with *C. albicans.* This patient was a 2-year-old boy with ependymoma who had infection develop following resection of his tumor and who was treated with amphotericin B and flucytosine. This patient was not neutropenic, had not received chemotherapy or immunosuppressive drugs, and recovered without sequelae. Those patients in whom the organism was considered to be a contaminant were excluded from analysis, as was a neurosurgical patient with postoperative infection.

Discussion

Historically, candidal meningitis has been a disease associated with a high mortality rate. In studies done before amphotericin B was first used for treatment of this disease in 1958, the mortality rates were 32%–56% [14, 25]. Since the advent of amphotericin B, the mortality rate associated with this disease has dropped to between 7% and 17% [14, 25]. Much of this improved survival is attributed to treatment with a combination of amphotericin B and flucytosine [4, 7, 25–27]. Other than the cases described in this report, only 3 cases of candidal meningitis have been described in patients with cancer. All 3 patients were adults, and only 1 of the 3 died of meningitis. The first case occurred in a patient who was receiving steroid therapy during remission of Hodgkin's disease, who was not neutropenic, and who had a fatal meningitis develop [15]. The second case occurred during remission of chronic myelogenous leukemia in a patient who was receiving steroid treatment, who was not neutropenic, and who survived [14]. The third case occurred in a patient who was in remission from acute myelogenous leukemia and who survived meningitis, although details of the case were not sufficient to determine the state of the patient's underlying disease or neutrophil function [13]. In contrast to these 3 cases and the mortality rate among neonates and neurosurgical patients, all 12 of our patients died shortly after diagnosis.

Factors predisposing to disease in our case patients, compared with our control subjects, were similar to those reported for immunocompromised patients with fungemia [12, 29–32]; they include fever, use of broad-spectrum antibiotics, profound neutropenia, and TPN use. Degree and duration of neutropenia likely constitute the strongest risk for disease. Although a small sample size may have biased the risk assessment, this is the largest series of candidal meningitis in patients with cancer that has been reported to date, and it is the first case-control study analyzing risk factors for such disease. Assessment of risk is made more difficult by confounding risk factors and by current guidelines for management of patients with neutropenia and fever, which lead to use of broad-spectrum antibiotics and which necessitate long-term central venous access. In many of the case patients reported here, meningitis was only 1 component of disseminated candidal infection, and the risk factors therefore may reflect risk factors for candidiasis in general. In autopsy series, involvement of brain parenchyma is frequently found as a component of fatal disseminated candidiasis [10, 33], and premortem differentiation of primary CNS involvement versus secondary CNS involvement may be difficult.

Animal models have demonstrated that granulocytes are important in resolution of systemic fungal infections [34–37] and experimental candidal meningitis [38]. The increased mortality rate in this series is likely due, in part, to the lack of neutrophils available to combat progression of the disease. Although only 35% of children with cancer who are treated at St. Jude Children's Research Hospital have leukemia, all 12 nonsurgical patients in this series had leukemia as their primary diagnosis. The reasons for this strong association with leukemia are not clear but are likely related to the prolonged neutropenia frequently seen with intensive chemotherapy for leukemia. A second reason for the association might be the increased propensity for *Candida* species, particularly *C. tropicalis,* to cause fungemia in children with leukemia [18], although these factors may be interrelated.

Another factor that may have contributed to the 100% mortality rate in this series was the high percentage of patients infected with *C. tropicalis.* Previous studies of immunocom-

promised hosts suggest that *C. tropicalis* may be more invasive or pathogenic than *C. albicans* [12, 30, 39, 40]. Studies of immunocompromised mice demonstrated that *C. tropicalis* is more capable of invading through damaged gastrointestinal mucosa than is *C. albicans* and that it is more virulent in this model [41, 42], and an autopsy study of patients who died of disseminated candidiasis indicated that *C. tropicalis* may have an increased propensity to invade through the gastrointestinal tract in humans [43]. Three of 8 patients autopsied in this series had involvement of the gut that was consistent with invasion by this route. Studies at our institution indicate an 11.2% risk of invasive disease among immunocompromised patients colonized with *C. tropicalis,* compared with a 2% risk of invasive disease among those colonized with *C. albicans* [18]. However, because *C. tropicalis* still accounted for less than one-half of all cases of fungemia in that series, it is not just the increased propensity to cause bloodstream infection that leads to the increased frequency of *C. tropicalis* meningitis in our series; other factors must be involved. It may be that *C. tropicalis* circulates in the bloodstream for longer periods or in higher numbers, or it may be that this species is able to cross the blood-brain barrier more easily than is *C. albicans.* Studies in a neutropenic rabbit model demonstrated that *C. tropicalis* fungemia is more lethal and more difficult to treat than is *C. albicans* infection, but *C. tropicalis* meningitis has not yet been studied in this model (T. W. Walsh, personal communication, 1998). Further studies of the pathogenicity of this organism are warranted.

The clinical features of 5 of the 12 case patients reported here offer little to set them apart from routine patients with neutropenia and fever for whom no diagnosis is made. For the symptomatic patients, the most common finding was a decreased level of consciousness, a clinical sign that could be attributed to a variety of causes in the setting of intensive chemotherapy and, often, concomitant cranial radiation therapy. Findings of CSF examinations were equally unremarkable, with mild pleocytosis and/or mildly elevated protein levels seen in a few cases. Significant hypoglycorrhachia was seen in only 2 of 12 patients. The most reliable early indicator of infection was Gram staining; CSF specimens obtained from 7 patients during the first lumbar puncture were positive. In 2 of the 12 case patients, no abnormalities were noted by Gram staining or CSF indices. The dearth of focal signs of meningitis and the few mild abnormalities revealed by CSF indices are similar to findings of other series of candidal infections of the CNS [11, 23] and are likely to be related to a lack of neutrophils, resulting in a reduced or absent inflammatory response.

The need for a high index of suspicion for meningitis in the setting of neutropenia and fever, especially if candidemia or any other deep fungal infection is present, would appear to be crucial if an early diagnosis is to be made. Although lumbar puncture is not routine for patients with fungemia, it should be done early in any case where there are signs or symptoms of CNS involvement. Because many of our patients had no symptoms (with the exception of fever) at diagnosis and were discovered to have candidal meningitis during routine lumbar punctures for intrathecal chemotherapy, consideration should be given to performing bacterial and fungal cultures and Gram staining of all CSF specimens from neutropenic patients, regardless of the reason for obtaining the specimen.

Previous reviews have recommended use of amphotericin B and flucytosine in combination as the most effective therapeutic regimen for candidal meningitis [4, 25–28]. This recommendation has mostly been based on cases in neonates and neurosurgical patients. The patient with leukemia who has meningitis may be different with regard to both a propensity for *C. tropicalis* as the infecting agent and a lack of granulocytes available to aid in controlling the infection after intensive chemotherapy. In this series of children with leukemia, all 12 patients died, despite the use of antifungal therapy for 11 of them (figure 1). All 11 of these patients received amphotericin B treatment, and 6 had been receiving it empirically for fever in the setting of neutropenia or for fungemia for $\geqslant$3 days at the time of diagnosis of meningitis. In all cases, the addition of antifungal agents was for treatment of suspected or proven fungal disease; antifungal prophylaxis was not used for any patients. The development of meningitis during amphotericin B treatment may be a reflection of the increased pathogenicity and virulence of *C. tropicalis* infections, or it may be related to the profound and prolonged neutropenia noted in these patients. Additional antifungal agents, most often flucytosine, were added to the therapeutic regimens in most cases, without success. WBC transfusions were administered in 3 patients, without an apparent impact on the fatal outcome of this disease.

It is evident from previous reports and from the cases reported here that early diagnosis and aggressive therapy are warranted for patients with leukemia. It may be that recovery of granulocytes is necessary for survival, and experimental evidence from studies of meningitis in neutropenic animals [38] and patients [36] indicates that granulocyte transfusions may be helpful. A recent study of a novel antifungal agent of the echinocandin class in a neutropenic rabbit model suggests that these agents may be as efficacious as either amphotericin B or fluconazole in the treatment of *C. albicans* meningitis [44], and in vitro studies of terbinafine indicated that it may have some efficacy against *Candida* when used in combination with other agents [45]. Because of the uniformly poor response to treatment in this series, it is difficult to recommend any definitive therapies for patients with leukemia. On the basis of experience with the drug and animal models, amphotericin B should remain the mainstay of therapy for candidal meningitis. Fluconazole clears *Candida* from the CNS in animal models, but it does so more slowly than amphotericin B (T. W. Walsh, personal communication, 1998) [46], and failures of fluconazole treatment have been reported [47, 48]. Failure to respond and acquisition of infection during therapy with standard doses of

amphotericin B in our patients indicate that higher doses of amphotericin B should be attempted (1.0–1.5 mg/kg/d).

In the case of renal insufficiency, liposomal preparations of amphotericin B may be substituted, beginning at 5 mg/kg/d and increasing to 7.5 or 10 mg/kg/d if no initial response or progression of disease is observed. AmBisome (Vestar, San Dimas, CA) has been studied in the setting of AIDS and cryptococcal meningitis, and treatment with this agent results in significantly earlier CSF clearance than does treatment with amphotericin B, with equal clinical efficacy and less nephrotoxicity [49]; however, its efficacy against candidal meningitis is unproven. Flucytosine should be added as a second agent when feasible. Fluconazole is an alternative second agent should flucytosine be poorly tolerated or contraindicated. Failure to respond or progression during therapy should be an indication to attempt more-aggressive or experimental therapies, such as granulocyte transfusions, or novel antifungal agents, such as the pneumocandins and echinocandins. There currently is no role for intrathecal administration of amphotericin B, because it does not result in appreciably higher drug levels in brain parenchyma and because it can cause chemical ventriculitis or arachnoiditis [50]. Although there is morbidity associated with intravenous administration of amphotericin B, the outcomes illustrated in this series of patients clearly indicate that early and aggressive therapy with this and additional antifungal agents regardless of potential toxicity is warranted.

In conclusion, in the present study, we describe 12 cases of candidal meningitis in children with leukemia who were treated at our institution over an 18.5-year period. Univariate analysis revealed that duration of fever, broad-spectrum antibiotic therapy, and neutropenia (ANC, <100/mL) and use of TPN were significantly greater in case patients than in control subjects, although no factors were significant in the multivariate analysis. The mortality rate in this series was 100%, which was possibly the result of the profound and prolonged neutropenia in these children after intensive chemotherapy and the pathogenicity and virulence of *C. tropicalis* (the infecting agent in 11 of the 12 case patients). The severe disease and high mortality rate reported here support the need for early diagnosis by lumbar puncture and aggressive therapy for all cases of candidal meningitis in immunocompromised patients. Further study of candidal meningitis is needed, particularly with regard to the pathogenesis and treatment of *C. tropicalis* infections.

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