Candidemia in children

Theoklis Zaoutis

Review
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Theoklis Zaoutis
The Children's Hospital of Philadelphia, Philadelphia, PA, USA

Address for correspondence:
Theoklis Zaoutis, MD, MSCE, Associate Professor of Pediatrics and Epidemiology, Associate Chief, Division of Infectious Diseases, The Children's Hospital of Philadelphia, 3535 Market Street, Room 1527, Philadelphia, PA 19104, USA.
Tel.: +1 267 426 5570; Fax: +1 215 590 0426;
Zaoutis@email.chop.edu

Abstract

Seriously ill or immunocompromised children are at increased risk of invasive fungal infections, particularly candidemia. *Candida albicans* and *Candida parapsilosis* are the two most frequent causes of candidemia in pediatric patients. Candidemia in children is associated with high morbidity and mortality, increased length of hospital stays, and higher healthcare costs. Early effective antifungal therapy is the key to improved outcomes. Risk factors for candidemia may be used to identify patients suitable for empiric therapy. Such risk factors include prolonged stay in an intensive care unit, immunosuppression, prior bacterial infection, and recent surgery, as well as the use of a central venous catheter, mechanical ventilation, and/or total parenteral nutrition. Recent guidelines from the Infectious Diseases Society of America recommend consideration of fluconazole or an echinocandin for empiric therapy in suitable candidates, with a preference for an echinocandin in patients with moderate-to-severe disease, recent azole exposure, or high risk of *Candida glabrata* or *Candida krusei* infection. Fluconazole or an echinocandin is also preferred initial therapy for non-neutropenic candidemia, depending on disease severity and other characteristics. The guidelines recommend treatment with an echinocandin or lipid formulation of amphotericin B for most patients with neutropenic candidemia, although fluconazole is identified as an alternative for less critically ill patients without recent azole exposure. Risk factors for candidemia – and, hence, criteria for prophylaxis – are less well established in older children than in neonates. Further research is needed to better establish criteria for antifungal prophylaxis in children at high risk for candidemia.

Introduction

Invasive fungal infections are a considerable source of morbidity, mortality, increased length of hospital stays, and high healthcare costs in critically ill or immunocompromised children[1,2]. Most invasive fungal infections in children occur in the hospital setting, and most are caused by *Candida* spp.[1,3]. A recent prospective study of pediatric nosocomial bloodstream infections (BSIs) determined that *Candida* spp. were the third most common microbial cause of BSIs overall (9.4% of isolates), and the most common fungal cause[4]. The most frequent causes of nosocomial BSI were bacteria: coagulase-negative staphylococci (43.3%) and enterococci (9.4%).

Anatomic and physiologic differences between pediatric and adult patients alter susceptibility to infection by different *Candida* spp. and approaches to antifungal treatment, including issues relating to drug toxicity, pharmacokinetics, and dosing. There is also much less data to guide decision making in children with invasive fungal infections than in adults with similar infections. The objective of this paper is to provide a general review of invasive candidiasis, and particularly candidemia, in pediatric patients other than neonates, including risk factors, incidence, species distribution, and antifungal therapy. One of the accompanying pieces in this supplement, by Dr. David Kaufman, focuses on invasive candidiasis in neonates. As in that piece, a case-study-centered approach will be used to advance the discussion of various issues of interest. The material here is based on an expert roundtable presentation, and as such, is not meant to be an exhaustive review of the topic.

Table 1. Risk factors for candidemia in the pediatric ICU.

Risk Factor	Unadjusted Odds Ratio	Adjusted Odds Ratio	95% Confidence Interval
Presence of a central venous catheter (CVC)	33.29	30.30	3.93−233.47
Receipt of total parenteral nutrition through a CVC	79.08	61.61	7.81−486.31
Use of antibiotic with activity against anaerobic bacteria for ≥1 week	5.73	3.93	1.17−13.24
Use of vancomycin for ≥1 week	3.92	2.59	1.14−5.87
Underlying condition of malignancy	3.23	3.55	1.19−10.60

From Zaoutis, 2009[6].

Risk factors for pediatric candidemia and empiric therapy

Case study: pediatric patient presenting with nosocomial bloodstream infection

A 3-year-old boy is treated in the intensive care unit (ICU) for 2 weeks for multiple medical problems, including short gut syndrome, failure to thrive, gastrointestinal surgery, and problems related to prematurity. He is currently receiving total parenteral nutrition and has a central venous catheter (CVC) in place. He recently received a course of broad-spectrum antibiotics for a catheter-associated bacterial BSI. He now presents with new-onset fever and hypotension. Blood cultures are obtained, and a new round of broad-spectrum antibiotic therapy is initiated pending culture results. The patient is not neutropenic.

This case study presents a young pediatric patient with a number of risk factors for invasive infection or BSI, and a recent history of treatment for a bacterial BSI. The patient now presents with signs of new-onset sepsis. Empiric antibacterial therapy is once again initiated. One of the questions posed by this case is whether the patient has risk factors for fungal infection and should also be considered for empiric antifungal therapy.

Risk factors for invasive candidiasis

Risk factors for fungal infection in pediatric patients are generally similar to those in adult patients. Factors present in the case study that have been linked with increased risk of invasive candidiasis/candidemia in pediatric patients include prolonged stay in an ICU, prior bacterial infection, use of a CVC, and total parenteral nutrition (hyperalimentation)[1,3,5]. Immunosuppression (related to malignancy and its treatment, transplantation immunosuppressive therapy, or other factors) has also been linked with increased risk of invasive candidiasis[3]. Additional factors associated with elevated risk of invasive candidiasis include use of mechanical ventilation (endotracheal intubation), dialysis, extended vancomycin use, and recent surgery[1,3,6].

Use of a vascular access device or CVC appears to be a particularly important risk factor. A recent Australian study reported that candidemia was attributed to a vascular access device in 70% of infected children, which was an even higher percentage than in neonates (58%) or adults (44%) with a vascular access device[7]. Another recent study used multivariate regression analysis to identify use of CVCs as an independent risk factor for colonization with *Candida* spp. in children aged 1 month to 14 years in a pediatric ICU for longer than 5 days[8]. Ninety percent of the children in the study who developed candidemia were colonized with *Candida*, 15% with the same species. Table 1 presents the results from a study presented at the 2009 annual Society for Healthcare Epidemiology of America (SHEA) meeting of risk factors for candidemia in the pediatric ICU[6]. Presence of a CVC, total parenteral nutrition, use of antibiotics, and immunosuppression (underlying malignancy) were significant risk factors.

Some risk factors for invasive candidiasis may coexist. For example, increased stay in an ICU often means prolonged use of a CVC, mechanical ventilation, and/or total parenteral nutrition, all well-documented risk factors. In the recent study presented at the annual SHEA meeting, the median length of ICU stay for pediatric patients who developed candidemia was 35 days compared with 2.2 days for the ICU cohort that did not develop candidemia – again illustrating the relationship between prolonged ICU stay and risk of developing candidemia[6].

In addition to being present in blood (candidemia), *Candida* infection can disseminate to end organs, including brain, lungs, liver, heart, kidneys, eyes, and spleen. Disseminated disease is generally considered to be more serious than BSI and to require longer antifungal therapy. A 2004 study by Zaoutis and colleagues reported that persistent candidemia (>3 days) with a CVC in place (odds ratio [OR] = 3.0; 95% confidence interval [CI] = 1.2–7.8; $p = 0.02$) and immunosuppression (OR = 2.9; 95% CI = 1.2–7.0; $p = 0.02$) were independent risk factors for disseminated disease in children with candidemia[9]. Another recent study of pediatric patients in Turkey reported that disseminated candidiasis was an independent risk factor for candidemia-related death (OR = 8.1, $p = 0.01$)[10].

Other variables reported in the Turkish study to be independent risk factors for mortality in pediatric patients with candidemia included stay in the ICU (OR = 8.1, $p = 0.001$), prolonged antibiotic therapy (OR = 5.2, $p = 0.014$), use of total parenteral nutrition

(OR = 4.4, $p = 0.038$), and mechanical ventilation (OR = 4.9, $p = 0.01$)[10]. Similarly, Zaoutis and coworkers identified location in the pediatric ICU at the time of infection (hazard ratio [HR] = 6.3; 95% CI = 1.6–24.3) and presence of an arterial catheter (HR = 2.4; 95% CI = 1.1–5.8) as independent risk factors for mortality in children with candidemia[11]. More recently, Pasqualotto and colleagues used multivariate analysis to identify failure to remove the CVC as an independent risk factor for early mortality among pediatric patients with candidemia[12]. Clearly, many of the risk factors for development of invasive candidiasis/candidemia are also risk factors for mortality in patients with candidemia.

Empiric treatment of suspected invasive candidiasis in non-neutropenic pediatric patients

In the case study, the 3-year-old child has several risk factors for invasive candidiasis/candidemia and infection-related mortality. The question then becomes: should this patient be considered for empiric antifungal therapy? The 2009 guidelines for candidiasis management from the Infectious Diseases Society of America (IDSA) state that "empirical antifungal therapy should be considered for critically ill patients with risk factors for invasive candidiasis and no other known cause of fever, and it should be based on clinical assessment of risk factors, serologic markers for invasive candidiasis, and/or culture data from non-sterile sites..."[13]. The guidelines further advise that the same therapeutic approach should be followed for children as adults, with attention to differences in dosing regimens. While there is no information concerning culture data from nonsterile sites or serologic markers for disease for the case here, the patient has the other characteristics listed and, hence, should be considered for empiric antifungal therapy.

More specifically, the guidelines recommend empiric treatment with fluconazole or an echinocandin for suspected invasive candidiasis in non-neutropenic patients[13]. An echinocandin is preferred in non-neutropenic patients with moderate-to-severe disease, recent exposure to an azole, or who are at high risk of infection due to *Candida glabrata* or *Candida krusei*. Recent azole exposure increases the likelihood of infection with an azole-resistant species, and azoles show less activity against *C. glabrata* or *C. krusei* than against other *Candida* spp. Amphotericin B deoxycholate (AmB-d) or a lipid formulation of AmB (LFAmB) are suitable alternatives for non-neutropenic patients with suspected invasive candidiasis if there is intolerance to or limited availability of other antifungals. Caspofungin is the only echinocandin currently approved by the US Food and Drug Administration (FDA) for use in pediatric patients. However, there is growing evidence supporting the use of micafungin in pediatric patients with non-neutropenic

invasive candidiasis[14–18], some of it coming out while the 2009 IDSA guidelines were being compiled or after its publication. At this time, there is only very limited pharmacokinetic or clinical data concerning anidulafungin therapy in pediatric patients[15].

For suspected invasive candidiasis in neutropenic patients, the 2009 IDSA guidelines recommend LFAmB, an echinocandin, or voriconazole, and cite fluconazole, itraconazole, and AmB-d as alternatives, noting there is a greater risk of toxicity with AmB-d than with LFAmB[13]. The guidelines also state that azoles should not be used for empiric therapy in patients who received an azole for prophylaxis.

Other epidemiologic features of pediatric candidiasis

Case (continued): blood culture results

Empiric antifungal therapy was considered but not initiated while awaiting blood culture results. The patient's blood culture results were subsequently received and were positive for a Candida spp. and, more specifically, Candida parapsilosis.

Incidence of candidemia and fungal sepsis

As suspected based on signs and symptoms and the presence of various risk factors for candidemia, the blood culture results for the case study indicate infection with a *Candida* spp. As discussed earlier, *Candida* is the third most common microorganism causing nosocomial BSI in pediatric patients, accounting for roughly 9% of all causes[4]. Furthermore, *Candida* spp. are the most common cause of invasive fungal infection, followed by *Aspergillus* spp[1]. However, it should be noted that diagnosis of candidemia by blood culture is slow and insensitive, although it is the current gold standard.

Based on a review of 10,319,418 cases of sepsis observed in US acute-care hospitals from 1979 through 2000, the rate of sepsis from any cause increased by 8.7% over this approximate 20-year period, while the incidence of sepsis due to fungal organisms increased by 207%[19]. Presumably a similar increase of fungal sepsis is observed in pediatric and adult patients. A study of adults and children hospitalized in the US in 2000 demonstrated a similar frequency of candidemia in pediatric and adult patients (43 cases vs. 30 cases per 100,000 admissions, respectively), although there were more adult than pediatric admissions (8949 vs. 1118)[2]. Abelson and colleagues reported that the rate of fungemia (85% due to *Candida* spp.) at a tertiary care US hospital increased by 91% from the 1991-through-1996 period to the 1997-through-2001 period (mean of 6.8 vs. 13.0 cases)[20].
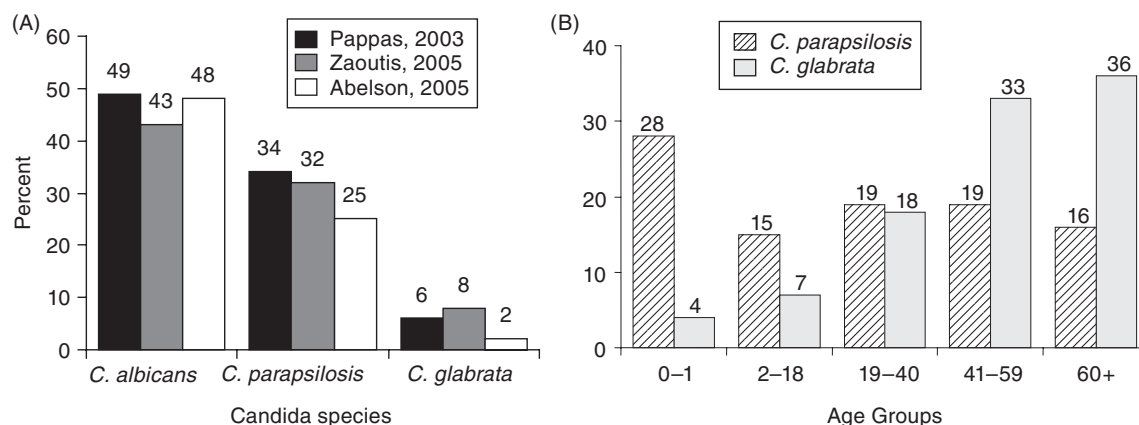
Figure 1. (A) Species distribution for all pediatric patients with invasive candidiasis (Abelson, 2005[20]; Pappas, 2003[22]; Zaoutis, 2005[23]). (B) Species distribution by age group (Malani, 2001[24]).

Mortality and healthcare costs associated with candidemia

The rate of increase in fungal sepsis is particularly noteworthy considering the severe outcomes associated with fungal sepsis or candidemia. Watson and coworkers reported that fungal sepsis was associated with the second highest case fatality (13.0%) in children older than 1 year and up to 19 years old in 1995, just behind pneumococcal sepsis (14.5%)[21]. The rate was higher in children aged 1 to 10 years (16.8%) or 11 to 19 years (11.6%) than in those younger than 1 year (10.8%). Similarly, Zaoutis and colleagues used large databases for adult ($n = 8949$) and pediatric ($n = 1118$) hospitalized patients in the US to demonstrate that pediatric patients (median age 1 year; range 0–7 years) with a diagnosis of candidemia had a 10% higher rate of mortality (95% CI = 6.2–13.8) compared with matched candidemia-unexposed hospitalized patients[2]. Wisplinghoff and colleagues reported that the crude mortality rate with monomicrobial BSI was second highest for those involving *Candida* spp. (19.6%), behind only *Pseudomonas aeruginosa* BSI (28.7%)[4]. The mean age of patients in this study was 2 ± 4 years (range 0–24 years), with half of the patients younger than 1 year.

In addition to mortality, pediatric candidemia has also been linked with longer hospital stays and increased costs, and relatively greater increases than seen in adult patients with candidemia. For example, in the study just mentioned by Zaoutis and coworkers, candidemia in pediatric patients was also associated with a mean 21.1-day increase in length of hospital stay (95% CI = 14.1–27.8) and a mean increase in total per-patient hospital charges of $92,266 (95% CI = $65,058–$119,474). The comparable numbers in adult patients were a mean 10.1-day increase in length of stay (95% CI = 8.9–11.3 days) and mean increase in total per-patient hospital charges of $39,331 (95% CI = $33,604–$45,602)[2]. However, other studies suggest that roughly 30% to 40% of the increases in hospitalization and costs are incurred by very low birth weight neonates[21]. Nonetheless, these findings underscore the importance of finding ways to optimize the prevention or treatment of invasive candidiasis in pediatric patients.

Invasive candidiasis and species distribution

In the case study, the argument was made that an empiric antifungal should be considered. Assuming a decision was made to pursue empiric therapy, the next question is: what species is most likely to be the cause of a fungal infection in a 3-year-old child with the identified risk factors? As illustrated in Figure 1A, *Candida albicans* and *C. parapsilosis* are the first and second most common species causing invasive candidiasis/candidemia in pediatric patients[20,22,23]. As people age and become adults, *C. glabrata* becomes the second most common non-albicans cause of invasive candidiasis or candidemia, replacing *C. parapsilosis* (Figure 1B)[24].

The distribution of *Candida* spp. in candidemia is important, in part, because some species seem to be associated with better outcomes compared with others. For example, in both adult and pediatric patients, candidemia due to *C. parapsilosis* is associated with lower mortality rates than cases involving *C. albicans*. Figure 2 illustrates this finding[22]. In this study, *C. parapsilosis* related candidemia was also associated with lower mortality rates compared with *Candida tropicalis* or *C. glabrata* related candidemia in adults. With respect to younger patients (<13 years old), there probably were not enough patients with *C. glabrata* or *C. tropicalis* candidemia to draw any firm conclusions. The other conclusion that can be drawn from Figure 2 is that crude mortality rates seem to be generally lower in younger (pediatric) than older (adult) patients with candidemia regardless of the *Candida* spp. involved.
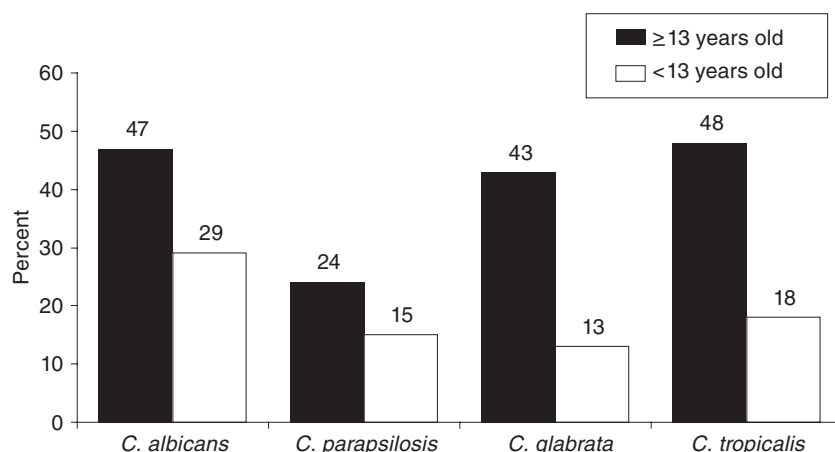
Figure 2. Mortality associated with selected *Candida* spp. among younger (<13 years old; $n = 144$) and older (≥13 years old; $n = 1447$) patients with candidemia[22].

Management of pediatric candidiasis

Case (continued): initiating antifungal therapy

The patient is initiated on caspofungin therapy (a single 70-mg/m² loading dose on day 1, followed by 50 mg/m² daily on subsequent days). Daily blood cultures are planned to document the clearance of candidemia and to monitor the effectiveness of therapy.

Antifungal treatment of candidemia in non-neutropenic patients

The laboratory findings for the case study indicate that the child has candidemia due to *C. parapsilosis* infection. A decision is made to administer caspofungin at the usual pediatric dose: 70 mg/m² on day 1, followed by 50 mg/m² thereafter, 12 mg/kg daily. Caspofungin is chosen, instead of fluconazole, because the symptoms of hypotension and fever are indicative of moderate-to-severe disease. This approach is consistent with recommendations from the 2009 IDSA guidelines for the management of candidiasis[13].

However, it should be noted that pediatric data are much more sparse than for adult patients, for dosing, individual treatment effectiveness, and comparisons between treatments. This is particularly the case for newer agents, including LFAmB and the echinocandins (particularly anidulafungin). Hence, many of the recommendations for management of pediatric candidiasis are based largely on expert opinion and experience in the absence of abundant data from published clinical trials. Also, results from additional pediatric research has become available and published since the publication of the 2009 IDSA guidelines. These potential shortcomings of the 2009 IDSA guidelines should be kept in mind when considering pediatric recommendations from the guidelines.

According to 2009 IDSA guidelines, fluconazole (12 mg/kg daily for pediatric patients) or an echinocandin is recommended as initial treatment for candidemia in non-neutropenic patients[13]. Moreover, the guidelines state that an echinocandin is preferred in patients with moderate-to-severe disease or recent azole exposure, and fluconazole for less critically ill patients with no recent azole exposure[13]. For patients initially started with an echinocandin, the IDSA guidelines recommend transition to fluconazole, if the patient is clinically stable and has isolates likely to be susceptible to fluconazole (and hence no recent azole exposure). Echinocandins are fungicidal against *Candida* spp., whereas fluconazole and other azoles are fungistatic against the most clinically relevant *Candida* spp.[25], which may be part of the reason for preferring an echinocandin in more critically ill patients.

With respect to specific pathogen causes of candidemia, the guidelines recommend treatment with fluconazole for *C. parapsilosis* infection[13]. Echinocandin treatment is de-emphasized because some studies have reported higher echinocandin minimum inhibitory concentrations (MICs) for *C. parapsilosis* than other *Candida* spp., suggesting this pathogen may be somewhat less responsive to echinocandin therapy, although several clinical trials did not show this to be the case[13,26]. For patients initially treated with an echinocandin (e.g., prior to documentation of *C. parapsilosis* infection), echinocandin therapy may continue, provided the patient is clinically improved and follow-up cultures are negative for the pathogen[13].

For patients infected with *C. glabrata*, the 2009 guidelines state a preference for echinocandin treatment, without transition to fluconazole or voriconazole unless there is confirmation of isolate susceptibility[13]. This is because all available azoles (fluconazole, itraconazole, voriconazole,

and posaconazole) exhibit less activity against *C. glabrata* (and *C. krusei*) than other *Candida* spp. In particular, *C. glabrata* is more likely to exhibit dose-dependent susceptibility or resistance to voriconazole than to echinocandins, and while active against *C. krusei*, voriconazole requires more frequent administration and demonstrates less predictable pharmacokinetics than echinocandins. For its part, posaconazole demonstrates in vitro activity against both *C. glabrata* and *C. krusei*, but it is not available as an intravenous formulation and there are relatively few data to support its use among patients with candidemia. However, for patients who initially received fluconazole or voriconazole and are clinically improved with negative follow-up culture results, it is reasonable to continue azole treatment to completion[13].

AmB-d or LFAmB are alternative therapies if there is intolerance or limited availability of other antifungal agents[13]. Transition from initial treatment with AmB-d or LFAmB to fluconazole is recommended for all clinically stable patients with isolates likely to be susceptible to fluconazole.

In terms of duration of antifungal therapy, the IDSA guidelines state that treatment should be continued for 2 weeks after documented clearance of *Candida* from the bloodstream and resolution of candidemia-related symptoms, provided there is no evidence of metastatic complications, that is, disseminated disease[13]. In practice, this typically means about 2 to 3 weeks of treatment: a few days to clear the infection and then for 2 weeks afterwards. Treatment shifts to longer durations for patients with disseminated disease.

Figure 3 illustrates trends in antifungal therapy for pediatric invasive candidiasis/fungal infections, based on a retrospective analysis of data collected in the Pediatric

Health Information System database from 25 US children's hospitals[27]. There has been a general shift away from AmB-d treatment to greater use of LFAmB and echinocandin, and, to a lesser degree, fluconazole and voriconazole. It should be noted that these trends are based on a total of 62,842 pediatric patients who received antifungal therapy for fungal infections, a relatively limited database.

Antifungal treatment of candidemia in neutropenic patients

While the case study reviewed here involves a child with non-neutropenic candidemia, many patients encountered in the pediatric ICU exhibit neutropenic candidemia, including those immunosuppressed due to cancer chemotherapy. What would be the recommended treatment for a young child, similar to the one here, with neutropenic candidemia?

The 2009 IDSA guidelines recommend treatment with an echinocandin or LFAmB for most patients with neutropenic candidemia[13]. As mentioned, at this time caspofungin is the only echinocandin approved by the FDA for the treatment of invasive candidiasis in pediatric patients, specifically those aged 3 months and older. There is growing experience with other echinocandins in children and neonates[28–32]. Anidulafungin has been studied in children 2–17 years of age and should be dosed at 1.5 mg/kg/day[32]. Micafungin has been studied in children and neonates; children should be treated with 2–4 mg/kg daily, but neonates may require as much as 10–12 mg/kg daily to achieve therapeutic concentrations[33]. Data for each of the echinocandins suggest safety and efficacy in the pediatric population. Caspofungin, but not micafungin or anidulafungin, has been evaluated as treatment for pediatric febrile
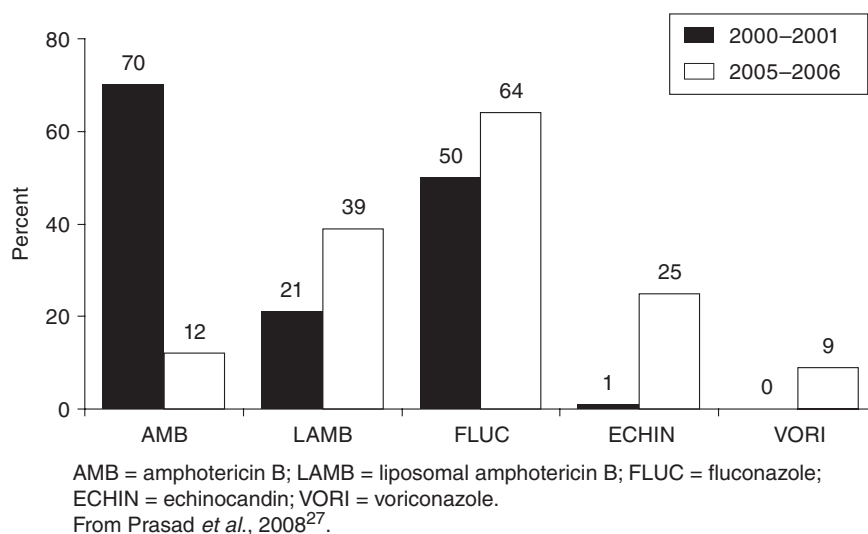

AMB = amphotericin B; LAMB = liposomal amphotericin B; FLUC = fluconazole; ECHIN = echinocandin; VORI = voriconazole.
From Prasad *et al.*, 2008[27].

Figure 3. Trends in antifungal therapy for invasive candidiasis.

neutropenia[15]. Taken together with the fact that caspofungin is the only FDA approved echinocandin for pediatric patients with invasive candidiasis, it remains the treatment of choice among this drug class for pediatric patients with febrile neutropenia due to *Candida* spp. infection. For this patient population, caspofungin should be administered as a single 70-mg/m^2 loading dose on day 1, followed by 50 mg/m^2 daily thereafter. The pharmacokinetics of AmB-d appear to be similar in neonates and adults; few studies have examined the use of LFAmB in neonates or children[13].

For patients who are less critically ill and without recent azole exposure, the guidelines recommend fluconazole (12 mg/kg/d) as an alternative to an echinocandin or LFAmB[13]. The reason an echinocandin or LFAmB is recommended over fluconazole or other azoles in more critically ill patients probably has to do (at least in part) with the fact that echinocandins and LFAmB are fungicidal agents, whereas azoles are usually fungistatic. Voriconazole (7 mg/kg every 12 hours allowed for children up to approximately 12 years of age) is recommended in situations where coverage of molds (e.g., *Aspergillus* spp.) as well as *Candida* spp. is desired[13].

For non-*albicans* spp., an echinocandin is preferred for candidemia due to *C. glabrata*[13]. LFAmB is considered an effective but less attractive alternative, due to higher cost and the potential for toxicity, and fluconazole or voriconazole may be continued in patients already receiving these agents who are clinically improved with negative follow-up culture results. An echinocandin, LFAmB, or voriconazole is recommended for candidemia due to *C. krusei*, and fluconazole or LFAmB is considered preferred initial therapy for infections due to *C. parapsilosis*. For non-neutropenic patients, treatment with an echinocandin may be continued to completion in those already receiving a member of this class for neutropenic candidemia due to *C. parapsilosis* and who are clinically stable and with negative follow-up culture results.

The recommended duration of therapy for neutropenic patients with candidemia is generally similar to that for non-neutropenic patients with candidemia, if there is no evidence of persistent fungemia or metastatic complications: 2 weeks after documented clearance of *Candida* from the bloodstream, resolution of symptoms attributable to candidemia, and resolution of neutropenia[13].

Infectious Diseases Society of America recommendations for intravenous catheter removal

In addition to antifungal therapy, the IDSA guidelines also recommend removal of intravenous catheters from patients with candidemia when feasible, particularly those who are not neutropenic[13]. Studies involving adults or neonates with candidemia have demonstrated that catheter removal is associated with shorter duration of candidemia and reduced mortality (reviewed in Pappas *et al.*, 2009[13]), but there is less evidence involving older children with candidemia. A 2004 study by Zaoutis and coworkers reported that "persistently positive blood cultures for *Candida* with a CVC in place" was a significant independent risk factor for disseminated candidiasis in children with a median age of 3.5 years (range: 0.6–14.3) (OR = 3.0; 95% CI = 1.2–7.8; p = 0.02)[9]. Persistent candidemia (>3 days), regardless of catheter status, was not associated with dissemination.

The IDSA guidelines strongly recommend intravenous catheter removal for non-neutropenic patients with candidemia, and state that intravenous catheter removal should be considered for neutropenic patients with candidemia[13]. The evidence for the benefits of catheter removal (in neonates and adults) is strongest for non-neutropenic patients. The situation in neutropenic patients is less straightforward because disseminated disease is more common, and it is often difficult to distinguish whether the source of candidemia is catheter- or gastrointestinal-related. In addition, catheter removal in neutropenic patients more often creates substantial intravenous access difficulties.

Conclusions

Candidemia is a serious condition associated with high morbidity and mortality and elevated healthcare costs in pediatric patients. Children at highest risk are those with prolonged ICU stay, reduced immune function, prior bacterial infection, and recent surgery, as well as use of a CVC, total parenteral nutrition, mechanical ventilation, and/or dialysis. Similar risk factors are associated with increased risk of death due to candidemia. Treatment recommendations are similar for pediatric and adult patients, taking into consideration the need for dose modifications with certain antifungal agents in pediatric patients. Empiric therapy with fluconazole or an echinocandin should be considered in patients at high-risk for candidemia and signs or symptoms consistent with such a diagnosis. Fluconazole or an echinocandin are also recommended as initial treatment for documented candidemia in non-neutropenic patients. Treatment with an LFAmB or caspofungin is recommended for most patients with neutropenic candidemia. Treatment modifications may be warranted based on disease severity, the *Candida* spp. involved, and prior azole use. Early treatment with optimal antifungal therapy is required to improve outcomes in pediatric patients with candidemia.

Transparency

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