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REVIEW

Invasive fungal infections in critically ill children: epidemiology, risk factors and antifungal drugs

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Abstract

Background: Invasive fungal infections (IFIs) are important infectious complications amongst critically ill children. The most common fungal infections are due to *Candida* species. *Aspergillus*, *Zygomycetes* and *Fusarium* are also emerging because of the empirical use of antifungal drugs. This updated review discusses the epidemiology of IFIs as well as antifungal drugs, dosing and potential adverse effects in critically ill children.

Methods: A PubMed search was conducted with Clinical Queries using the key terms "antifungal", "children", "critical care" AND "paediatric intensive care unit" OR "PICU". The search strategy included clinical trials, randomized controlled trials, meta-analyses, observational studies and reviews and was limited to the English literature in paediatrics.

Results: *Candida* and *Aspergillus* spp. are the most prevalent fungi in paediatric IFIs, causing invasive candidiasis infections (ICIs) and invasive aspergillosis infections (IAIs), respectively. These IFIs are associated with high morbidity, mortality and healthcare costs. *Candida albicans* is the principal *Candida* spp. associated with paediatric ICIs. The risks and epidemiology for IFIs vary if considering previously healthy children treated in the paediatric intensive care unit or children with leukaemia, malignancy or a severe haematological disease. The mortality rate for IAIs in children is 2.5–3.5-fold higher than for ICIs. Four major classes of antifungals for critically ill children are azoles, polyenes, antifungal antimetabolites and echinocandins.

Conclusions: Antifungal agents are highly efficacious. For successful treatment outcomes, it is crucial to determine the optimal dosage, monitor pharmacokinetics parameters and adverse effects, and individualized therapeutic monitoring. Despite potent antifungal medications, ICIs and IAIs continue to be serious infections with high mortality rates. Pre-emptive therapy has been used for IAIs. Most guidelines recommend voriconazole as initial therapy of invasive aspergillosis in most patients, with consideration of combination therapy with voriconazole plus an echinocandin in selected patients with severe disease. The challenge is to identify critically ill patients at high risks of ICIs for targeted prophylaxis. Intravenous/per os fluconazole is first-line pre-emptive treatment for *Candida* spp. whereas intravenous micafungin or intravenous liposomal amphotericin B is alternative pre-emptive treatment.

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Introduction

Invasive fungal infections (IFIs) are important causes of morbidity and mortality amongst immunocompromised and critically ill paediatric patients.[1–5] Paediatric patients are different than adults (especially those who are critically ill), and information is not as readily available in this population. *Candida* and *Aspergillus* spp. are the most prevalent fungi leading to IFIs in paediatric patients.[1–6] In the paediatric intensive care unit (PICU), invasive candidiasis infections (ICIs) are more frequently observed than invasive aspergillosis infections (IAIs), which are observed mainly in children with an underlying haematological malignancy and solid tumours.[6]

ICIs and IAIs are associated with high rates of morbidity, mortality and healthcare expenses. The incidence of IFIs has increased in the past two decades.[7–9] ICIs are five times more frequent than IAIs.[6,10–14] Strong recommendations for prophylaxis of IAIs have been established.[15] *Candida albicans* is the principal *Candida* spp. in ICIs but a trend towards the emergence of non-*albicans Candida* has also been observed, possibly due to the use of fluconazole prophylaxis in some of these paediatric patients with ICIs.[8,11]

This narrative review discusses the epidemiology, mortality and risk factors for ICIs and IAIs as well as the current literature on antifungal drugs, dosing and adverse effects of these medications amongst critically ill children.

Methods

A PubMed search was performed using Clinical Queries and the key terms "antifungal", "children", "critical care" AND "paediatric intensive care". The search strategy included meta-analyses, clinical trials and observational studies, randomized controlled trials, and reviews and was restricted to the English language and paediatric population.

Review

In patients in the PICU with severe disease (haematological disorder or malignancy), the reported incidence of IFIs is approximately 5% with a high mortality rate of approximately 60%.[16–18] In the past 20 years, the frequency of paediatric IFIs has increased steadily due to the higher prevalence of susceptible children surviving following aggressive immunosuppressive and cytotoxic therapy, broad-spectrum antibiotics and haematopoietic stem cell transplantation. *Candida* spp. and *Aspergillus* spp. are the most common fungal pathogens in PICU patients.

Patients at risk of IFIs include children on chemotherapy, children who have undergone haematopoietic stem cell or solid organ transplantation, children with neutropenia, immunosuppressed children due to treatment for an auto-immune condition, and children with primary or acquired immunodeficiency.[3,4,6] Extremely premature infants and children with a long stay in a PICU are also at increased risk of IFIs but this is out of the scope of this review.[3,4,6] PICU-confined patients are at a high risk of developing IFIs as result of various risk factors, including central venous line (CVL), intercurrent bacterial infection, parenteral nutrition, immunocompromised condition, recent surgery, mechanical ventilation, prolonged use of vancomycin and prolonged hospitalization.[3,4]

ICIs in critically ill children

Distribution of ICIs and *Candida* species and outcomes vary amongst PICUs mainly due to differences in practices amongst institutions, differences in geographical niches of *Candida* spp., and differences in antifungal prophylaxis and treatment protocols.[6] In a 2001, national French survey of infections that included over 21,000 hospitalized children aged under 18 years, 1.2% of newborns and 3.3% of children presented with a nosocomial infection, whereas the rate in PICU patients was approximately 15%; ICIs accounted for 4.4% of all infections amongst hospitalized children.[19] A Greek PICU survey reported a median incidence of 6.4 cases per 1000 PICU admissions over a 5-year period.[20] A Spanish study demonstrated a median incidence of 6.9 cases per 1000 PICU admissions over a 2-year period.[21] Lower incidences of ICIs were reported in the USA (3.5 cases/1000 PICU admissions) and Egypt (3 cases/1000 inpatient days).[9,22] *C. albicans* is the leading cause of ICIs in the PICU.[6] The study from the USA reported that 46% of the isolates were *C. albicans*, which is similar to the Egypt study (40%) and those from Europe (37.6%).[9,22] There is also an increasing prevalence on species other than *C. albicans* accounting for 10–15% of isolates.[6] Candidaemia is also associated with a prolonged PICU stay (median 35 days), hospital stay (4 days) and an increase in hospital charges.[9]

In the PICU, ICIs present as disseminated candidiasis or candidaemia. A large study conducted in the USA in 2000, showed a higher rate of candidaemia amongst children than amongst adult patients.[13] Dutta and Palazzi reported an increase in candidaemia amongst children from 0.06 to 0.3 per 1000 hospitalizations from the years 2000 to 2009.[23]

C. albicans is the most common fungal pathogen in ICIs amongst paediatric patients (55%).[11] *Candida tropicalis* is found amongst children with malignancy or neutropenia; *Candida glabrata* amongst surgical patients with a CVL and *Candida parapsilosis* amongst young patients

receiving parenteral nutrition.[11] Pfaller et al. reported data from 79 global paediatric medical centres and found that 50% of patients with IFIs experienced fungaemia with *C. albicans* (28.5%) and other *Candida* spp.[24]

Candida spp. colonization was found in 70% of PICU patients, and the risk of colonization is particularly important in young children.[25,26] Zaoutis et al. reported an incidence of candidaemia in the PICU of 3.5/1000 admissions.[9] Hence, *Candida* spp. is an important agent causing sepsis in critically ill children.[6,10–12,14] Posfay-Barbe et al. reported an infection rate of 10% by *Candida* spp. in patients <18 years of age in hospitals in the USA.[18] Richards et al. showed that *Candida* spp. was found in 9.4% of bloodstream infections in PICUs in the USA.[14] An Israeli investigation reported *Candida* spp. in 14.4% of fungaemia in PICUs.[27] Hence, the incidence of ICIs is generally higher in Europe and lower in the USA and Egypt.

Apart from PICU hospitalization, other risk factors for ICIs include parenteral nutrition, a CVL *in situ*, immunocompromised status, dialysis, recent surgery, intercurrent bacterial infection, prolonged vancomycin use and mechanical ventilation.[12] The risk for developing disseminated candidiasis in PICU patients with a CVL increases three-fold if the catheter has been in place for more than 3 days.[28] The Infectious Diseases Society of America recommends that CLVs should be promptly removed when candidaemia is documented.[9] Some authors have suggested the use of prophylactic antifungal treatment if the risk of candidaemia is higher than 10%.[29,30]

Amongst PICU patients, *Candida* spp. colonization was four-fold higher in patients if a CVL is present.[9,25] Scores or indexes based on localization of *Candida* spp. colonization have been developed in adults to identify people at risk of developing ICIs.[31–33] Such studies in paediatric patients are currently not available. Lortholary et al. reported a higher risk of infection with a resistant fungal strain if fluconazole or caspofungin had been recently used.[34]

Sung reported that 10% and 6% of paediatric patients with leukaemia developed *Candida* spp. infection during the induction and consolidation treatment phases, respectively, with *Candida* spp. accounting for 25.9% of infection-related mortality.[35] The authors observed that the rate of *Candida* spp. infections can increase 2.5-fold during an intensive induction phase. Hence, the timing of chemotherapy bears important implications on the risk for ICIs in these patients. An underlying malignancy increases the predicted probability of ICIs from 17.5% to 46% in PICU patients.[9]

IAIs in critically ill children

There is little specific data regarding children with IAIs.[6,7,10] The available data are non-homogeneous and make analysis difficult. Over the past decade, there has been a three-fold to four-fold increase in the incidence of IAIs due to the improvement of management and survival of patients with immunocompromised conditions.[10,36] In the USA, the annual incidence of IAIs in hospitalized immunocompromised patients was 0.4% in 2006, with three-quarters of these children being immunosuppressed or having malignancies.[6,10] In 2008, Crassard et al. reviewed probable or proven IAIs in a paediatric haematological department and found the median interval between malignancy onset and IAI diagnosis to be 8.5 months; 15% of patients with an IAI had acute myeloid leukaemia (AML) or acute lymphocytic leukaemia (ALL).[37] The incidence of IAIs was 5.35% in AML and 1.5% in ALL and the mortality attributable to IAIs was 37.5%. Other studies reported similar variations in incidence of IAIs in accordance with the underlying disease.[38,39] The most common fungal strains in patients were *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus nidulans*, *Aspergillus terreus* and *Aspergillus niger*.[7] The first causative organism was *A. flavus* according to two previous studies.[40,41] The most common species encountered in pulmonary disease in children is *A. fumigatus*, whereas *A. flavus* is predominantly found in dermatological infections.[7] The incidence of *A. niger* can be up to 6.5% in septic granulomatous disease.[39]

The most frequent location of *Aspergillus* spp. infection is the lung, and is found in 59–91.6% of infections.[7,38,41,42] Walmsley et al. reported that IAIs were present in up to 41% of skin lesions.[41] Other investigators reported 10–20% of cutaneous aspergillosis in haematology–oncology centres.[7,38]

Dotis et al. identified 90 cases of aspergillosis since 1950 in a systematic literature review for paediatric central nervous system IAIs.[43] Predominant underlying disease includes leukaemia, followed by solid tumours and various other conditions in children aged older than 1 year.

Community-acquired or hospital-acquired infections can be contracted in immunocompromised children. Risks factors of IAIs include haematological malignancies, allogeneic bone marrow transplantation, granulocytopenia, use of corticosteroids, immunosuppressive therapies, immunodeficiencies and organ transplantation.[42,44] The risk of IAIs increases with higher steroid dosages (notably of prednisone above 2 mg/kg/day), as often used in the management of bone marrow transplantation.[42] Cushing syndrome can favour IAIs due to its high endogenous secretion of cortisol.[44]

Prolonged antibiotic administration, persistent neutropenia, viral respiratory infection, cytomegalovirus infection and HIV infection, especially in individuals with *Aspergillus* infection, are confounding risk factors for

IAIs.[36] Patients with relapsed lymphocytic leukaemia and AML are at higher risks for IAIs.[39]

Mortality of ICIs and IAIs

The attributable mortality of the two IFIs is different because patients with IAIs often have underlying haematological malignancies. Candidaemia was associated with a 21-day increase in the average hospital stay and an increase in total hospital costs of over $US90,000 per patient.[13] Candidaemia was associated with a mortality rate of 30% for children and 43–54% in infants.[13] Some authors reported that *C. parapsilosis* ICI is less aggressive than *C. albicans* ICI (27% *versus* 47%).[12] The presence of a CVL and ICI diagnosis in PICU patients were independent risks for higher mortality.[45]

Despite appropriate treatment, the mortality rate of paediatric IAIs and ICIs is ~70% and 20–30%, respectively.[6,10,42,46] Regardless of patient age, a 357% increase in deaths related to IAIs has been reported within the past decade in the USA.[42] Paediatric patients with IAIs have a 20% increase in mortality rate and over 13-fold increase in relative risk for death compared with children without IAIs. Paediatric patients with IAIs had a longer hospital stay than immunocompromised patients without IAIs.[39] The therapeutic response of IAIs usually does not exceed 50% even with appropriate treatment. The mortality rate for treated patients with IAIs has been reported to be as high as 52.5%.[7] Likewise, an overall IAI mortality rate of 58% was reported.[47] In cases of disseminated IAI or with central nervous system involvement, a mortality rate of 88.1% was reported, followed by 86.7% in cases of bone marrow transplantation and 85.7% in those with AIDS. Highly active antiretroviral therapy has reduced the incidence and improved the prognosis of IAIs in patients with AIDS and HIV.

The overall mortality rate for paediatric patients with ALL and AML is low (1% and 3%, respectively). However, if patients with ALL or AML develop an IAI, the mortality rate increases 14-fold for ALL and 5-fold for AML (to 21% and 20%, respectively).[6,10,39] Central nervous system aspergillosis-related mortality exceeds 80%.[47] The overall mortality of central nervous system aspergillosis since the 1950s was 65.4%, with a distinct reduction after 1990 possibly due to improved patient care.[43]

Antifungal medications

The optimal antifungal regimen and dosing is dependent on risk stratification, spectrum of activity, mechanism of action, pharmacokinetic and pharmacodynamic properties, and adverse event profile of the antifungal medications.[1,2,5] Globally, the evolution of drug resistance amongst these antifungals is an emerging threat to health.[48]

Four classes of antifungal agents are available.[49] Selected major antifungal drugs are summarized herein. Table 1 shows major antifungal drugs and their spectrum of antifungal activities; Table 2 shows the available formulations of these drugs and Table 3 summarizes the major monitoring parameters of these antifungal drugs.

Azoles

Azoles are a broad class of antifungal drugs that inhibit the enzyme lanosterol 14-α-demethylase, which converts lanosterol to ergosterol, an important component of the fungal cellular membrane.[1,2,5,50,51] Disruptions of ergosterol biosynthesis damage the cell membrane and result in cell lysis and death. Drug interactions are a significant problem with azole drugs because these agents are metabolized by the cytochrome P450 (CYP450 system).[1,2,5,50,51] Azoles have a ring structure that contains two or three nitrogen atoms.[52] The imidazoles have an imidazole ring with two nitrogen atoms, whereas the triazoles have a ring with three nitrogen atoms.[52] Examples of imidazoles include clotrimazole, econazole, isoconazole, ketoconazole, miconazole and tioconazole. Examples of triazoles include fluconazole, isavuconazole, itraconazole, posaconazole and voriconazole.

Azole agents vary with regards to pharmacokinetic profiles, spectrum of activity and toxicities.[53] Fluconazole, for instance, has an excellent activity against yeasts but not against moulds. Itraconazole provides an extended antifungal spectrum but its use in critically ill patients is limited due to inconsistent bioavailability. Voriconazole is a first-line antifungal drug for IAIs but with unpredictable bioavailability and unique side-effects.[54–57] Isavuconazole and posaconazole have the broadest spectrum of activity. Triazoles have largely replaced the systemic use of ketoconazole and older azoles because of their improved safety profiles, superior pharmacokinetics and higher efficacy for systemic mycoses. Itraconazole represents another important drug for IFIs. In a PICU report, all the patients with nosocomial disseminated candidiasis recovered within 6–14 days after itraconazole (10 mg/kg/day in two divided oral doses for up to 14 days). Early oral itraconazole is well tolerated by children and effective in disseminated candidiasis.[58] Voriconazole is recommended for paediatric IAIs (7 mg/kg intravenously, every 12 hours).[42] Approved alternative therapies include liposomal amphotericin B, caspofungin and amphotericin B lipid complex. Posaconazole and itraconazole are alternatives but a paediatric dose for posaconazole is not established, and itraconazole dosing is difficult in paediatric patients. Switching to another drug with a different mechanism of action or combination therapy are options in patients who do not benefit from initial treatment.[42] The azoles are efficacious against many fungi without any serious nephrotoxic effects.

Table 1. Summary of antifungal activity spectra.[50]

	Antifungal drugs									
	Fluconazole	**Posaconazole**	**Voriconazole**	**Itraconazole**	**Isavuconazole**	**Amphotericin B**	**Liposomal amphotericin B**	**Flucytosine**	**Caspofungin**	**Micafungin**
Fungi										
Aspergillus fumigatus										
Aspergillus terreus										
Candida albicans										
Candida glabrata										
Candida guilliermondii										
Candida krusei										
Candida lusitaniae										
Candida parapsilosis										
Candida tropicalis										
Cryptococcus spp.										
Dematiaceous moulds										
Fusarium spp.										
Mucormycosis										
Dimorphic										
Blastomyces										
Coccidioides										
Histoplasma										
Sporothrix										

Key

	Good
	Moderate
	Poor
	Not available

Table 2. Summary of the formulations available.

	Oral	Intravenous
Azoles antifungals		
Fluconazole	✓	✓
Posaconazole	✓	–
Voriconazole	✓	✓
Itraconazole	✓	–
Isavuconazole	✓	✓
Polyenes		
Amphotericin B	–	✓
Liposomal amphotericin B	–	✓
Antimetabolites		
Flucytosine	✓	–
Echinocandins		
Caspofungin	–	✓
Micafungin	–	✓

Polyenes

Polyenes are the oldest fungicide of the soil actinomycete *Streptomyces nodosus*.[5] They act by binding to ergosterol in the fungal cell membrane and cause leakage of cell contents and eventually cell death.[5,50] The only systemic agent in the polyene class of antifungals is amphotericin B (Tables 1–3).[59–62] The mode of action of amphotericin B and its new derivatives involves cholesterol metabolism.[59] Amphotericin B is used for serious systemic fungal infections, including aspergillosis, mucormycosis, blastomycosis, coccidioidomycosis, candidiasis and cryptococcosis.[59,60] It is typically given intravenously.[59,60] The drug is reserved for critically ill or immunocompromised patients with severe IFI due to its extensive side-effects, including nephrotoxicity. It is a first-line medication for invasive cryptococcal meningitis, mucormycosis, certain IAIs and ICIs.[63] Amphotericin B is a highly effective drug with low incidence of drug resistance in many IFIs. Intravenous amphotericin B administration in therapeutic doses has led to multiple organ injuries. Nephrotoxicity is a frequently reported adverse drug effect that can be irreversible. Amphotericin B deoxycholate is well known for its severe and potentially lethal nephrotoxicity and infusion-related reactions.[1,2,5,50,59] It can often cause a serious reaction within 3 hours after infusion, consisting of chills, high fever, nausea, vomiting, anorexia, headache, tachypnoea, dyspnoea, hypotension, generalized weakness and drowsiness.[59,60] The violent reaction of chills and fevers has been called 'shake and bake'. The reaction may involve prostaglandin synthesis and cytokine release from macrophages.[66,67] The deoxycholate formulations may stimulate histamine release from basophils and mast cells.[68] This nearly universal febrile reaction necessitates a critical professional determination as to whether the onset of high fever is a drug effect or a novel symptom of a fast-progressing disease. Anaphylactic reaction may also occur.[59,60]

Three lipid preparations have been developed, namely amphotericin B colloidal dispersion (Amphotec, no longer routinely used), amphotericin B lipid complex (Abelcet) and liposomal amphotericin B (Ambisome), to attenuate these side-effects. Higher concentrations in the reticuloendothelial organs (lung, spleen and liver) can be achieved with the lipid preparations, thus producing fewer infusion-related reactions and less nephrotoxicity than the conventional amphotericin B.[1,2,5,50]

Liposomal amphotericin B is indicated in patients with pre-existing kidney injury.[64,65] Electrolyte imbalances, such as hypomagnesaemia and hypokalaemia, are also common.[69] Other serious side-effects include hepatotoxicity and myocarditis.[59,60] Severe anaemia, blood dyscrasias (thrombopenia and leukopenia), life-threatening arrhythmias (e.g. ventricular fibrillation) and cardiac failure have been reported.[56] To decrease the likelihood and severity of symptoms, initial doses should be low and slowly increased. Paracetamol, diphenhydramine, hydrocortisone and pethidine can be used to treat or prevent the symptoms.[70] Amphotericin B is relatively safe in pregnancy.[59,60]

Antifungal antimetabolites

Flucytosine or 5-fluorocytosine (5-FC) is an antifungal medication that was originally investigated as an oncology drug but found to have antifungal properties (Table 3).[50,71] It is converted into 5-fluoruracil inside fungal cells and is further converted into metabolites that interfere with DNA and protein synthesis.[5,50,71] 5-FC has limited use in paediatric critical care and is only used in combination with other antifungal agents such as amphotericin B for cryptococcal disease. Resistance to the antifungal develops rapidly when 5-FC is used as monotherapy.[5,50] 5-FC is specifically used with amphotericin B for serious *Candida* infections and cryptococcosis.[71] 5-FC can be given by mouth and intravenously.[71] Common side-effects of 5-FC include loss of appetite, vomiting, diarrhoea, psychosis and bone marrow suppression.[71] Anaphylaxis can occasionally occur.[71] It is not clear if use of 5-FC in pregnancy is safe for the fetus.[71]

Echinocandins

With a mechanism of action distinct from other antifungals, echinocandins are the latest class of antifungal drugs to be introduced in clinical practice.[1,2,5,50,72,73] This class of antifungals is generally very safe. Echinocandins

Table 3. Summary of the important monitoring parameters.

	Trough level	When to measure? (after starting drug or changing dose or formulation)	Pharmacokinetics	Others
Azoles				
Fluconazole[1,2,5,50,72,73]	Not required		• Distributes well into cerebrospinal fluid • Long half-life allows once-daily dosing • High bioavailability makes it excellent for patients who tolerate oral medications • Dose adjustment required in patients with renal dysfunction • Substrate and inhibitor of CYP3A4; thus, has many significant drug interactions	• Administer with or without food • Monitor for rash, hepatotoxicity and QT prolongation
Posaconazole[1,2,5,50,72,73,88]	Prophylaxis: >0.7 μg/mL Treatment: >0.7–1 μg/mL	5–7 days	• Substrate and inhibitor of CYP3A4; thus, has many significant drug interactions	• Effective absorption with high-fat meal and may be impaired in gastrointestinal disruption • Monitor for rash, hepatotoxicity, neurotoxicity, gastrointestinal upset and QT prolongation **IV preparation** Contains cyclodextrin, which can accumulate in renal dysfunction[12]
Voriconazole[1,2,5,50,72,73,89,90]	1–6 μg/mL	2–5 days	• Exhibit non-linear pharmacokinetics • 50% reduction is recommended for patients with mild-to-moderate chronic hepatic insufficiency (Child–Pugh Classes A and B) • Dose adjustments not necessary for patients with renal dysfunction • Not recommended for patients with urinary candidiasis as active form is minimally excreted in urine • Substrate and inhibitor of CYP3A4; thus, has many significant drug interactions	• Administer preferably on an empty stomach, 1–2 h before or after a meal (oral bioavailability is reduced by 30% when taken with a high-fat meal) • Monitor for rash, hepatotoxicity, neurotoxicity, QT prolongation and visual disturbances • Visual effects are reversible upon discontinuation • Avoid sun exposure as reports of skin cancer with prolonged use (>1 year) use **IV preparation** Contains cyclodextrin, which can accumulate in renal dysfunction

(Continued)

Table 3. (Continued)

	Trough level	When to measure? (after starting drug or changing dose or formulation)	Pharmacokinetics	Others
Itraconazole[1,2,5,50,72,73,89,90]	>0.5 μg/mL	10–15 days	• Bioavailability is highly variable; therefore, itraconazole should not be used interchangeably • Has long half-life of 25–50 h, allowing for once-daily dosing • Active drug does not appear in urine; thus, itraconazole cannot be relied on to treat urinary tract infection • Substrate and inhibitor of CYP3A4; thus, has many significant drug interactions	• Liquid solution should be taken on an empty stomach and capsules should always be taken with a full meal • Absorption can be lowered by agents that decrease gastric acidity such as proton pump inhibitors; try having patient take itraconazole with a soda • Monitor for rash, hepatotoxicity, neurotoxicity, gastrointestinal upset and QT prolongation • Negative inotrope thus contraindicated in patients with heart failure
Isavuconazole[1,2,5,50,72,91,92]	2–4 μg/mL	3 weeks	• Excellent bioavailability and not affected by food or gastric acidity • Very long half-life so to attain therapeutic levels more rapidly	• Monitor for rash, hepatotoxicity, neurotoxicity, gastrointestinal upset and QT prolongation • May shorten QT interval
Polyenes				
Amphotericin B (fungizone)[1,2,5,50,72–74]	Not required		• Monitor for renal toxicity, electrolyte disturbances (esp. hypokalaemia and hypomagnesaemia) and hepatotoxicity • Dosage adjustment for renal and hepatic dysfunction are unnecessary	• Amphotericin B nephrotoxicity can be attenuated by the process of sodium loading; consider pre/concurrent hydration with 10 mL/kg normal saline • Consider premedication with antipyretics, antihistamines and corticosteroids to reduce the incidence of infusion-related adverse effects (include fever, chills, rigors) • Test dose of 1 mg for hypersensitivity reaction can be administered
Liposomal amphotericin B (ambisome)[1,2,5,50,72–74]	Not required			

(Continued)

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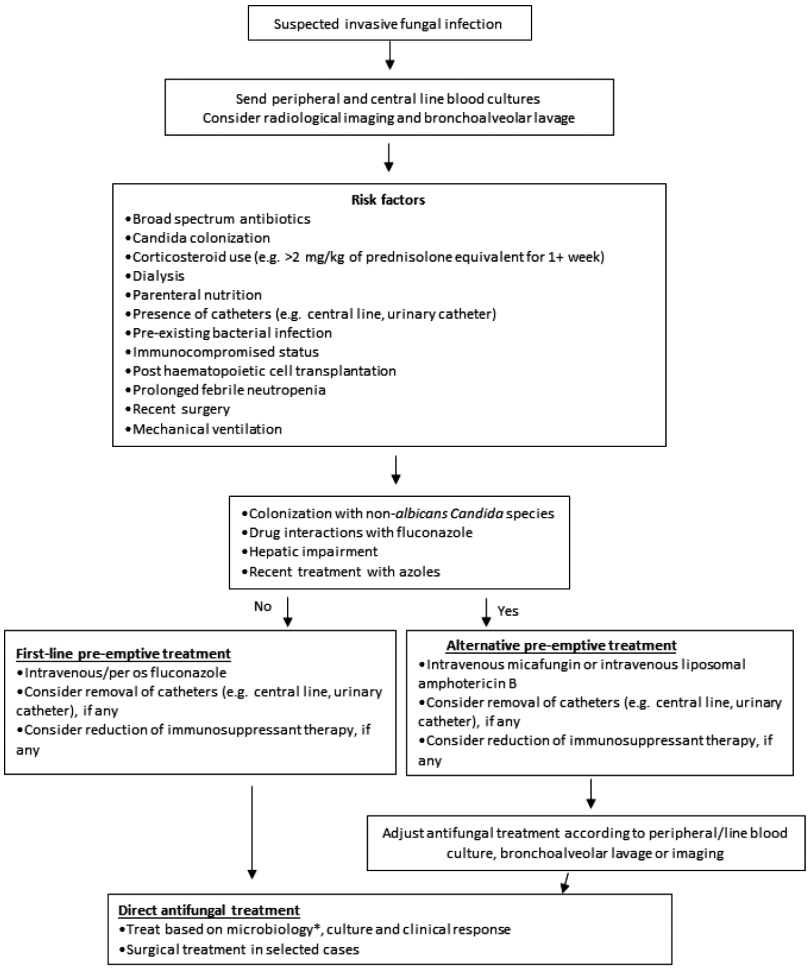
Table 3. (Continued)

	Trough level	When to measure? (after starting drug or changing dose or formulation)	Pharmacokinetics	Others
Antimetabolites				
Flucytosine (5-FC)[5,50]	Trough: 25–50 μg/mL Peak: 50–100 μg/mL	Peak should not exceed 100 μg/mL to avoid bone marrow toxicity and hepatotoxicity	• Distributes widely in tissues and facilitates antifungal activity of amphotericin B in sites with poor penetration such as cerebrospinal fluid, cardiac valves and vitreous humor	• Can cause bone marrow suppression • Gastrointestinal complaints are common but less severe
Echoinocandins				
Caspofungin[1,2,5,50,78,93]	Not required		• Not metabolized through CYP system; thus, less interactions and side-effects than azoles • Do not accumulate in urine; thus, not effective for urinary tract infection • Dose adjustment is not needed in patients with renal insufficiency, including patients receiving haemodialysis or continuous renal replacement therapy	• Mild histamine-mediated infusion-related reactions (rash, facial swelling, pruritus and/or bronchospasm), which can be ameliorated by slowing the infusion rate • Hepatotoxicity is also possible but uncommon
Micafungin[1,2,5,50,94]	Not required			

Figure 1. Flowchart for the management of invasive fungal infections.



inhibit the synthesis of (1,3)-β-D-glucan (a component of the fungal cell wall), which results in reduced cell wall integrity and subsequent cell death.[1,2,5,50,72–74] Micafungin, caspofungin, anidulafungin and rezafungin are cyclic lipopeptide echinocandins that are semi-synthetic.[75–77] Their specific chemical structure offers potential to obtain novel derivatives with better pharmacological properties resulting in more effective treatment, especially for infections caused by *Candida* and *Aspergillus* species. Echinocandins are used intravenously particularly to treat resistant *Candida* spp. infections.[76–78] Echinocandins have excellent activity against most *Candida* species as well as the growing and dividing forms of *Aspergillus*. However, one of the setbacks is the lack of available oral formulations.[1,2,5,50,72,73] Side-effects and troublesome adverse reactions associated with echinocandins are generally much milder than other antifungal agents.[77,78] Intravenous infusion of echinocandins may cause facial flushing, oedema, pruritus, rash, thrombophlebitis, dyspnoea, bronchospasm, hypotension and fever.[79] The incidence of these symptoms varies depending on the echinocandin administered. Fever is reported in approximately 35% of patients, whereas it is only reported in 1% of patients treated with micafungin. The rate of antibiotic infusion may be reduced to lower the likelihood of side-effects.[76,80,81] It has been reported that nausea, vomiting and diarrhoea occur in 7% of patients, and 3–25% of patients treated with caspofungin develop phlebitis. In comparison, less than 2% of patients experience these symptoms after treatment with micafungin and anidulafungin.[76] Caspofungin is associated with a higher frequency of hepatic dysfunction (i.e. 1–15%) compared with other echinocandins. Micafungin may increase risk of hepatic malignancy.[82] Anaemia, leukopenia, neutropenia and thrombocytopenia comprise less than 10% of all adverse effects due to echinocandins.[79] Echinocandins should be avoided in pregnancy due to teratogenic and embryotoxic effects.[83]

Drug interactions

Apart from the side-effects already mentioned, physicians should be aware of the drug interactions of many antifungal medicines.[54,84–86] The azoles exhibit significant drug–drug interactions. The magnitude of each interaction varies with the individual azole. Azole antifungals, such as itraconazole and ketoconazole, are both substrates and inhibitors of the cytochrome P450 family 3A4 (CYP3A4) leading to an increased concentration when administered with other medications such as immunosuppressants, chemotherapeutic drugs, calcium channel blockers, tricyclic antidepressants, benzodiazepines, macrolides and selective serotonin reuptake inhibitors.[54,86] Generally, echinocandins are very well tolerated and do not exhibit relevant drug–drug interactions.

Antifungal prophylaxis in the PICU setting should be tailored to the needs of each patient guided by the individual's risk factors and local epidemiology.[87] Hand hygiene is the most critical element in controlling the spread of infection. It is important that appropriately designed sinks and alcohol gel dispensers are readily available at the point of use and that an appropriate handwashing technique is used. The PICU infection control policy can be implemented in a structured and systematic care bundle approach. Care bundles use checklists and audit to regulate compliance. Use of prophylactic antifungal drugs is not recommended except for critically ill oncology and immunocompromised patients admitted to the PICU. Intravenous or per os fluconazole is the first-line pre-emptive treatment for *Candida* spp. whereas intravenous micafungin or intravenous liposomal amphotericin B are alternative pre-emptive treatments.

We propose a flowchart for the management of IFIs (Figure 1). Pre-emptive therapy and recommendations have been well defined in IAIs.[9] The real challenge is the identification of critically ill patients with a high risk of ICIs in the PICU so that targeted antifungal prophylaxis can be started pre-emptively to reduce IFI-associated comorbidities and mortality.

Conclusions

This article reviews the important therapeutic agents used for antifungal prophylaxis and treatment in critically ill children. These antifungal agents are highly efficacious. Optimal dosing, monitoring of pharmacokinetics parameters, potential adverse effects and individualized therapeutic monitoring are important for successful treatment outcomes.

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