

Australasian guidelines for antifungal therapy in neonates and children with proven, probable and suspected invasive fungal infections

CC Blyth, TA O'Brien and P Palasanthiran on behalf of the Australasian Society of Infectious Diseases (Paediatric Infectious Diseases and Mycoses Interest Groups) and Bone Marrow Transplantation Committee (Australian and New Zealand Children's Haematology/Oncology Group)

Dr Christopher C Blyth

MBBS

Department of Immunology and Infectious Diseases, Sydney Children's Hospital, High Street, Randwick. NSW, Australia
School of Women's and Children's Health, University of New South Wales, High Street, Randwick, NSW. Australia

Dr Tracey A O'Brien

FRACP, MBChB, MHL, BSc

Centre for Children's Cancer and Blood Disorders, Sydney Children's Hospital, High Street, Randwick. NSW. Australia
School of Women's and Children's Health, University of New South Wales, High Street, Randwick, NSW. Australia

Dr Pamela Palasanthiran

MBBS FRACP MD

Department of Immunology and Infectious Diseases, Sydney Children's Hospital, High Street, Randwick. NSW. Australia
School of Women's and Children's Health, University of New South Wales, High Street, Randwick, NSW. Australia

Corresponding Author:

Dr Pamela Palasanthiran

Email: Pamela.Palasanthiran@sesiahs.health.nsw.gov.au

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Abstract

The management of children with invasive fungal infection is becoming more complex with an increasing number of antifungal agents available. Insufficient paediatric studies have been performed with newer agents leaving paediatricians reliant on adult patient data to guide clinical decisions. There are numerous differences between children and adults with invasive fungal infection. Following a systematic review, consensus guidelines have been developed to assist doctors managing children with invasive fungal infection. The efficacy, toxicity and cost of newer antifungal agents have been compared with existing therapies and key recommendations made.

Introduction

The incidence of invasive fungal infection is increasing, especially in at risk populations.^{1;2} Risk factors for invasive fungal infection in children include malignancy, haematopoietic stem cell or solid organ transplantation, neutropenia, chemotherapy, corticosteroid use, congenital and acquired immunodeficiency, prematurity, broad spectrum antimicrobial use and dependence on parenteral nutrition.³⁻⁵ Invasive fungal infections are responsible for significant morbidity and mortality. In studies published since 1996, mortality in children with candidaemia ranged from 19 to 32%.⁶⁻¹⁰ Invasive aspergillosis in children is associated with even greater mortality: 68 to 77%.^{3;5;11;12} Mortality is highest in those with greater degrees of immunosuppression, particularly following haematopoietic stem cell transplantation.¹²

Australasian treatment guidelines for adults with invasive fungal infection have been formulated with updated guidelines currently being developed.¹³ Significant differences between children and adults with invasive fungal infection are reported including predisposing factors, infecting organism and site of infection.^{3;5;14} There are also significant differences between paediatric and adult antifungal pharmacokinetics and toxicity.¹⁵⁻¹⁸

The number of drugs available to treat fungal infections has greatly increased in the last decade. Four classes of drugs for the treatment of invasive fungal infections exist: polyenes, triazoles, echinocandins and nucleoside analogues. In Australia and New Zealand, conventional amphotericin B (CAB), liposomal amphotericin B, amphotericin B lipid complex (ABLC), amphotericin B colloidal dispersion (ABCD), fluconazole, itraconazole, voriconazole, posaconazole, caspofungin and flucytosine are available for use in invasive fungal infection. New azoles and echinocandins are expected to be available in the near future.

This set of paediatric guidelines is based on the best available current evidence (Box 1). Standard definitions were used (Box 2). The guidelines aim to promote rational prescribing of antifungal agents for Australian and New Zealand children with proven, probable and suspected invasive fungal infections. When paediatric studies were judged by the authors to be inadequate, adult studies have been used to supplement data. Antifungal susceptibility profiles (Box 3), paediatric antifungal dose guidelines (Box 4) and key recommendations (Box 5) are given.

Spectrum of antifungal activity

Antifungal susceptibility patterns of the organism confirmed or suspected should be used to guide antifungal therapy. Antifungal susceptibilities of common fungal pathogens are summarized in Box 3.¹⁹ Amphotericin B preparations are active against most fungal species. *C. lusitaniae* is reported to have variable susceptibility to amphotericin B, however this has not been found in Australia. *Scedosporium* and *Fusarium* species have reduced susceptibility to amphotericin B and it is common practice to use high doses of amphotericin B (ie $\geq 5\text{mg/kg}$ of a lipid preparation) for infections due to zygomycetes.¹⁹

Fluconazole has activity against many yeasts but limited activity against moulds.¹⁹ Reduced susceptibility to fluconazole is also seen with *C. krusei* and *C. glabrata*. *C. tropicalis* has been reported to have reduced susceptibility to fluconazole in international studies but this is rarely seen in Australia. Itraconazole has anti-*Aspergillus* activity and variable activity against other moulds. Voriconazole has activity against most yeasts and moulds; zygomycetes and *Scedosporium prolificans* are important exceptions. Zygomycetes are susceptible to posaconazole. *S. prolificans* is resistant in vitro to all available antifungal drugs.

Candida and *Aspergillus* species are susceptible to caspofungin.¹⁹ Caspofungin has poor activity against *Cryptococcus neoformans*, *Scedosporium* species, *Fusarium* species and zygomycetes.

Empiric antifungal therapy in prolonged fever and neutropenia

Summary

- No differences in treatment success and mortality have been demonstrated in paediatric and adult trials comparing empiric conventional amphotericin B and lipid preparations in subjects with prolonged fever and neutropenia [I].
- Fewer breakthrough infections may occur in subjects treated with liposomal amphotericin B [I].
- Conventional amphotericin B and fluconazole appear equally effective in febrile neutropenic subjects not previously administered fluconazole [II].
- Voriconazole is not inferior to liposomal amphotericin in the management of adults and adolescents with fever and neutropenia although equivalence has not been demonstrated [II].

- Caspofungin appears as effective as liposomal amphotericin B in the treatment of febrile neutropenic adults [II].

Despite the limitations of the original studies,^{20;21} it is the accepted standard of care to use antifungal agents in neutropenic subjects who remain febrile despite broad spectrum antibacterial agents.²²

Paediatric trials comparing antifungal agents in prolonged fever and neutropenia are limited. Prentice *et al* compared liposomal amphotericin B (1 or 3 mg/kg/day) with CAB (1 mg/kg/day) in 202 neutropenic children with 96 hours of fever despite appropriate therapy.²³ Safety was the primary endpoint. Treatment success was not significantly different between groups: 51% in children receiving CAB, 64% in those receiving 1mg/kg/day liposomal amphotericin B and 63% in those receiving 3mg/kg/day liposomal amphotericin B ($p = 0.22$) [II].

Therapeutic trials in adults also report no difference in treatment success when CAB (0.6 - 1 mg/kg/day) is compared with liposomal amphotericin B (3 mg/kg/day) or ABCD (4mg/kg/day)[II].²³⁻²⁵ Two meta-analyses failed to demonstrate any difference in mortality between CAB and lipid preparations of amphotericin B in patients with fever and neutropenia (Johansen *et al*. OR: 0.83, 95%CI: 0.62 – 1.12; Barrett *et al*. OR: 0.78, 95%CI: 0.54 – 1.13) [I].^{26;27} Johansen *et al* demonstrated fewer breakthrough fungal infections in those receiving liposomal amphotericin B compared with CAB [I].²⁶ Barrett *et al* also included antifungal therapy in neutropenic and non-neutropenic populations with confirmed candidiasis, aspergillosis and cryptococcosis. In the combined analysis, all cause mortality was reduced in those receiving a lipid preparation (OR: 0.72, 95%CI: 0.54 - 0.97) but no difference in efficacy was demonstrated (OR: 1.21, 95%CI: 0.98 – 1.49).

Of the trials comparing fluconazole and itraconazole with CAB in neutropenic patients, only one was appropriately powered and only two studies included children.²⁸⁻³² All subjects were azole naïve. Azoles were as effective as CAB [II]. Voriconazole was compared with liposomal amphotericin B in paediatric and adult subjects. The overall success rates were 26.0% with voriconazole and 30.6% with liposomal amphotericin B (95% confidence interval for the difference, -10.6 to 1.6%) [II].³³ There were fewer documented breakthrough fungal infections in patients treated with voriconazole than in those treated with liposomal amphotericin B. Walsh *et al* compared liposomal amphotericin B with caspofungin in febrile neutropenic adults. Despite a greater number of caspofungin-treated patients surviving for ≥ 7 days after study completion, no overall difference in treatment success was observed [II].³⁴

Antifungal therapy in candidaemia or invasive candidiasis

Summary

- No difference in treatment success is seen when conventional amphotericin B is compared with fluconazole and voriconazole in non-neutropenic adolescents and adults [II].
- Echinocandins are as effective as conventional amphotericin B and fluconazole in non-neutropenic adults [II].
- Prior antifungal therapy influences the infecting *Candida* species and should guide empiric therapy [III-2].
- Therapy in candidaemia should be continued for at least 14 days following the last positive culture [expert opinion].
- If feasible, initial management should include removal of all existing vascular catheters [III-2].

Candida albicans and *C. parapsilosis* are the most frequent yeasts isolated in children with invasive candidiasis. Species with reduced susceptibility to fluconazole are infrequent pathogens in children.^{1;19;35-37} Prior fluconazole therapy is a risk factor for infection with a fluconazole resistant yeast [III-2].^{37;38} A strong association between *C. parapsilosis* and central venous catheter infection has been documented [III-2].^{35;39}

Randomised controlled trials comparing fluconazole with CAB or itraconazole in paediatric candidaemia are insufficiently powered to assess treatment efficacy.^{40;41} The therapeutic equivalence of fluconazole and CAB has been demonstrated in predominantly non-neutropaenic adolescents and adults with candidaemia [II].⁴²⁻⁴⁴ No significant differences in efficacy between fluconazole and voriconazole are seen in adolescents and adults with candidaemia and oesophageal candidiasis [II].^{45,46} Caspofungin and CAB appear equally effective in adult patients with candidaemia and oropharyngeal/oesophageal candidiasis [II].⁴⁷⁻⁴⁹ Therapeutic equivalence is also seen when fluconazole is compared with caspofungin in adults with oesophageal candidiasis [II].⁵⁰ Little data comparing antifungal therapy in deeper candidal infection exists. An amphotericin preparation (with flucytosine where possible) is favoured as initial therapy in candidal endocarditis and meningitis [IV].⁵¹

Therapy for 14 to 21 days after the last positive blood culture is recommended in children and neonates with candidaemia in the absence of disseminated disease [expert opinion].⁵¹ Some authors suggest that 7 to 14 days of therapy following blood stream sterilisation can be used in children. This recommendation is supported by data from a single case series [IV].⁵²

Intravascular devices are a frequent source of candidaemia. In patients with severe neutropenia and/or receiving chemotherapy, candidaemia is frequently of gastrointestinal origin.⁵³ Studies in non-neutropenic adults, children and neonates demonstrate that early catheter removal is associated with a shorter duration of candidaemia and reduced mortality [III-2].⁵⁴⁻⁵⁶ Early removal is often not possible in unstable patients or in the presence of implantable vascular access devices. If feasible, initial non-medical management should include removal of all existing vascular catheters [expert opinion].⁵¹

Antifungal therapy in invasive aspergillosis

Summary

- There are no adequately powered randomised controlled trials comparing conventional amphotericin B with lipid preparations in probable or proven invasive aspergillosis.
- In pulmonary aspergillosis, 3mg/kg/day of liposomal amphotericin B is as effective as 10mg/kg/day [II].
- Initial therapy with intravenous then oral voriconazole is superior to conventional amphotericin B in invasive aspergillosis and is associated with a survival advantage [II].
- Caspofungin is an alternative in subjects intolerant of, or refractory to, other therapies [IV].
- The duration of therapy should be guided by the clinical and mycological response and immunological recovery [expert opinion].

No randomised controlled trials have been performed in children with invasive aspergillosis. Using comparative data from adults, a number of conclusions can be drawn regarding the relative efficacy of different antifungal agents. CAB was compared with liposomal amphotericin B and ABCD in two small randomised controlled trials. No significant difference in treatment outcome was observed [II].^{57,58} High dose liposomal amphotericin B (10mg/kg/day) was compared with standard dose (3mg/kg/day) in 339 adults with filamentous fungal infections (predominantly pulmonary aspergillosis). No differences in treatment success at 12 weeks (50% vs. 48%) or survival (72% vs. 58%) were observed [II].⁵⁹

Herbrecht *et al* compared CAB (1 - 1.5mg/kg/day) with voriconazole (6mg/kg bd for 24 hours then 4mg/kg bd) in 277 adolescents and adults with proven or probable aspergillosis.⁶⁰ Therapy was initiated with intravenous voriconazole for at least 7 days. Treatment success (53% vs 32%) and survival (71% vs 58%) was greater with voriconazole. The mean duration of study drug was longer in those administered voriconazole (77 days vs. 10 days). Alternative licensed antifungal agents were allowed and were more frequently prescribed in those receiving CAB (80% vs. 36%). The impact of this on treatment success and survival is unknown.

Echinocandins were effective in adults with aspergillosis who were intolerant of or refractory to other antifungals [IV].^{61;62} No comparative trials have been performed.

The duration of antifungal therapy for invasive aspergillosis in children and adults has not been determined. Herbrecht *et al* evaluated subjects clinically and radiologically following 12 weeks of antifungal therapy.⁶⁰ In an open label study of voriconazole use in children with invasive fungal infection (predominately aspergillosis), the median duration of therapy was 93 days (range 1 – 880).⁶³ The length of therapy should be influenced by response to therapy and immunological recovery.

Combination antifungal therapy in children with candidaemia, invasive candidiasis or aspergillosis

Summary

- Insufficient evidence is available to support routine use of combination therapy in candidaemia, invasive candidiasis or aspergillosis.
- Two antifungals from different classes are recommended if combination therapy is used.

Given the high mortality of IFI, the role of combination therapy has been considered. To date, no paediatric combination trials have been published although research is underway. In 219 non-neutropenic adults, persistent candidaemia after 5 days of therapy was more frequently seen with fluconazole alone compared with fluconazole and CAB combination therapy.⁶⁴ No statistically significant difference between the groups was seen in treatment success at 30 days and 90 day mortality. Interpretation is further confounded by differences in severity of illness between study groups. The combination of voriconazole and caspofungin were retrospectively compared with voriconazole alone as salvage therapy in a unmatched population with proven or probable aspergillosis.⁶⁵ Three month survival was superior in subjects receiving combination therapy.

Other fungal pathogens

There are insufficient data on children to assist paediatricians managing infections caused by fungi other than *Candida* and *Aspergillus spp*. Therapy should be guided by known antifungal susceptibility patterns (Box 3), underlying disease, site and extent of infection.

The following antifungal agents are recommended for treatment of cryptococcosis, scedosporiosis, fusariosis and zygomycosis:

- *Cryptococcus neoformans complex*: An amphotericin B formulation is recommended in the induction phase of therapy for cryptococcal infection. The addition of flucytosine is recommended in those with central nervous system infection, HIV infection and children receiving immunosuppressive therapies [II].⁶⁶⁻⁶⁹ Induction therapy should be followed by maintenance therapy, usually with fluconazole. Fluconazole is an alternative agent in patients with localised disease due to *C. neoformans* var. *neoformans* (eg pulmonary and skin disease). Fluconazole is also the agent of choice for long term suppression in the setting of continual immunosuppression [II].
- *Pseudallescheria boydii* (*Scedosporium apiospermum*) and *Scedosporium prolificans*: Voriconazole is the preferred agent for *P. boydii* and *S. prolificans* infection [IV].^{13;63;69;70} The addition of terbinafine for synergy is recommended in subjects with *S. prolificans* infection [IV].^{13;69;71}
- *Fusarium species*: An amphotericin B preparation⁷² or voriconazole⁷³ is the treatment of choice for fusariosis [IV].^{13;69;74}
- Zygomycete *species*: High dose lipid preparation of amphotericin B⁷⁵ in conjunction with surgical debridement is currently recommended for zygomycetes [IV].^{13;69;74} The role of posaconazole is still to be determined.⁷⁶

Salvage fungal therapy

There is no consensus on the definition of refractory fungal infection. In candidemia, treatment failure is defined by Rex *et al* as persistent fungemia or unimproved / progressive signs of sepsis despite ≥ 5 days antifungal treatment.^{43;64} Almyroudis *et al* propose that a composite outcome be used to define refractory invasive mould infections. Refractory infection is defined as worsening of at least 2 of 3 criteria: clinical, radiologic and mycologic, with assessment after a minimum of 7 days of therapy.⁷⁷ It should be noted that the radiological appearance of pulmonary aspergillosis often worsens despite adequate antifungal therapy and that immune reconstitution may be associated with worsening of radiological signs.⁷⁸

Alternative antifungal therapies for candidaemia, invasive candidiasis and aspergillosis are included in the key recommendations (Box 5). If invasive mould infection is suspected, and the infecting species is unknown, voriconazole would be the preferred choice of antifungal given its broader spectrum of activity. The role of combination therapy is yet to be established.

Toxicity of antifungals

Summary

- Lipid preparations are less nephrotoxic than conventional amphotericin B when administered as a standard infusion in studies comprising predominantly adults [I].

- Conventional amphotericin B administered by continuous infusion results in less nephrotoxicity and infusion-related toxicity compared with a standard infusion [II]. Other agents have not been compared with continuous infusion.
- Increasing cumulative doses [III-2], preexisting renal impairment [III-2], hypovolaemia [II], hyponatraemia [II] and the number of concurrent nephrotoxins [II] are associated with an increased risk of amphotericin B induced nephrotoxicity. Concomitant use of cyclosporine or diuretics with amphotericin B increases the risk of nephrotoxicity [III-2].
- Haematopoietic stem cell transplant recipients are the highest risk group for nephrotoxicity and dialysis following amphotericin B administration [III-3].
- Azoles and echinocandins are less nephrotoxic than conventional and liposomal amphotericin B [II].
- Liposomal amphotericin B causes less infusion-related toxicity when compared with conventional amphotericin B and ABLC [II].
- Both azoles and echinocandins cause less infusional toxicity than conventional and lipid preparations of amphotericin B [II].
- The incidence of hepatotoxicity is similar across all antifungal classes [II].
- Significant drug interactions can occur with azoles requiring dose modification or avoidance [IV].

The development of new antifungals has been driven by the toxicities associated with CAB. Amphotericin B preparations can cause renal insufficiency by a number of mechanisms. This is usually reversible, although renal dysfunction may remain for weeks upon cessation.^{45;79} Permanent damage has been reported.^{80;81} In adults, renal toxicity is associated with increased mortality, increased length of stay and total costs.⁸² These outcomes have not been demonstrated in children.

Published rates of CAB induced nephrotoxicity in children vary widely; 1.2 - 52%.^{23;25;83-85} The different definitions of nephrotoxicity make comparison difficult. Nephrotoxicity has been examined in three randomised controlled trials comparing CAB with lipid preparations in children. Comparing CAB (0.8mg/kg/day) with ABCD (4mg/kg/day), Sandler *et al* and White *et al* defined nephrotoxicity as a doubling of baseline creatinine, an increase in serum creatinine of 88umol/L or a 50% decrease in creatinine clearance. Both trials demonstrated reduced nephrotoxicity with ABCD: 52% vs. 12%, $p < 0.01$ [II].^{25;84} Comparing CAB (1mg/kg/day) to liposomal amphotericin B (1-3mg/kg/day), Prentice *et al* defined nephrotoxicity as a doubling of baseline creatinine. The rate of nephrotoxicity was 21% vs 8-11% but failed to achieve statistical significance with $p = 0.10$.²³ None of the trials identified the proportion of children in whom serum creatinine exceeded the upper limit of normal or another predefined measure of renal impairment.

Two meta-analyses of trials including mostly adult patients demonstrated a 49-75% reduction in nephrotoxicity in subjects administered lipid preparations compared with CAB [I].^{26;27} If nephrotoxicity secondary to a lipid preparation did occur, it followed a longer course of therapy [II].^{23;25} As rates of drug-induced nephrotoxicity often vary between children and adults, studies comprising predominantly adults need to be interpreted with caution. Adult and neonatal case series have demonstrated that lipid preparations are safe in subjects with pre-existing nephrotoxicity.⁸⁶⁻⁸⁸ In contrast to the findings of Wingard *et al*,⁸⁹ a recent meta-analysis demonstrated no significant difference in rates of nephrotoxicity seen with different lipid preparations of amphotericin B [I].⁹⁰ Both azoles and echinocandins cause less nephrotoxicity than CAB and liposomal amphotericin B in adults and adolescents [II].^{28;31;33;43;45;60}

Risk factors for amphotericin B induced-nephrotoxicity include amphotericin B dose [III-2], pre-existing renal impairment [III-2], hypovolaemia [II], hyponatraemia [II] and concurrent use of nephrotoxic medications [II, III-2]. Increasing age [II, III-2] and underlying disease [III-2] are not associated with an increased risk.^{23-25;91-97} When independently assessed, cyclosporine and diuretics increase the rate of nephrotoxicity whereas aminoglycosides and vancomycin in isolation appear not to increase the risk [III-2].⁹²⁻⁹⁴ In predominantly adult subjects with fever and neutropenia, the risk of nephrotoxicity more than doubled when two or more concurrent nephrotoxins (cyclosporine, aminoglycosides or foscarnet) were used.²⁴ Avoidance of nephrotoxins and hypovolemia as well as sodium loading prior to amphotericin use may decrease the risk of nephrotoxicity. Adult haematopoietic stem cell recipients with aspergillosis are 5 times more likely to require haemodialysis when administered CAB than solid organ and non-transplant related chemotherapy recipients.⁹¹

A rise in creatinine is frequently seen after starting an amphotericin B preparation.⁷⁹ Renal function and electrolytes should be monitored closely in all children administered an amphotericin B preparation. Mild to moderate nephrotoxicity can be tolerated in many children with serum creatinine returning to normal upon cessation. The tolerance of amphotericin B-induced nephrotoxicity is influenced by concurrent co-morbidities and nephrotoxins, the length of therapy required, degree of nephrotoxicity, rate of deterioration in renal function and the alternative agents available. These decisions should be made on a case by case basis. (See Box 5, recommendation 4)

Infusional toxicities are frequently seen with CAB use. This can occur despite premedication and the development of tolerance.^{98;99} Severe infusional reactions occur rarely in children [IV].²³ Infusional toxicities are rarely reported in neonates [IV].^{86;100} Liposomal amphotericin B causes fewer reactions than CAB and ABLC [II].^{23;24;89;101} CAB and ABLC causes similar rates of infusional reactions [II].¹⁰² Both azoles and echinocandins are responsible for fewer reactions in adolescents and adults than conventional and liposomal amphotericin B [II].^{28;31;33;34;47;60}

Conventional amphotericin B toxicity when administered via a continuous or prolonged infusion has been compared in adults with standard infusion (4 hours).^{103;104} Less nephrotoxicity and infusion-related toxicity occurred [II]. In vitro and in vivo studies demonstrating concentration-dependant killing with a prolonged-post antibiotic effect suggest that achieving optimal peak concentrations may be of importance.¹⁰⁵ The two trials performed were not adequately powered to assess relative efficacy of continuous CAB compared with standard infusion however both demonstrated increased survival with continuous infusion.^{103;104} No adult or paediatric trials have compared continuous CAB infusions with other antifungal agents. The limitations of vascular access in some children may pose problems with continuous infusions.

Despite initial concerns, no randomised controlled trial has demonstrated a significant increase in hepatotoxicity attributable to azoles compared with other agents [II].^{23;28;30;33;40;41;43;47;49;50;60;84;102} In adult trials, rash is seen more frequently with both fluconazole and voriconazole compared with amphotericin B [II].^{28;60} Visual disturbance or eye symptoms are reported frequently in both adults and children taking voriconazole [II].^{17;33;60;63}

Antifungal cost

Newer antifungals are significantly more expensive than CAB and fluconazole. In children, cost is influenced by dose administered (Box 4) and the amount supplied per vial. Given the pharmacokinetic differences, the proportion of an adult dose is also markedly different for example the dose of CAB administered to a 20kg child is 29% of an adult dose compared with 80% of an adult dose for caspofungin. No paediatric antifungal pharmacoeconomic studies have been performed. In an adult pharmacoeconomic study, the cost saving of reduced CAB toxicity was not offset by the increased costs of lipid preparations in a febrile neutropenic population.¹⁰⁶ When voriconazole was compared with conventional amphotericin in adolescent and adult subjects with aspergillosis, a significant cost saving was demonstrated with voriconazole.¹⁰⁷ Interpretation of these adult studies in the paediatric context is difficult given the differences highlighted above.

Conclusions

Invasive fungal infections continue to cause significant mortality and morbidity. There are few adequately powered paediatric trials comparing antifungal agents. In the trials performed, the differences between antifungal agents were not significantly different to those seen in adult trials. Nevertheless, there are significant pharmacokinetic differences between adults and children requiring dose modification (see Box 4). From the best available evidence, we recommend the preferred antifungal agents and alternatives for children with prolonged fever and neutropenia, candidaemia / invasive candidiasis and aspergillosis (see Box 5). Alternative agents are usually only required in the context of resistant organisms, significant adverse reactions or disease progression despite therapy. Given the many other fungal pathogens responsible for disease, these recommendations need to be guided by the clinical course, microbiological confirmation, local epidemiology and fungal resistance testing. There is a need for further research in children to help determine the pharmacokinetics and toxicity of newer antifungal agents, their relative efficacy and cost-effectiveness.

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Conflicts of interest

Nil

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Box 1 - Objectives, methodology, consensus process and evidence of recommendations.

The objective of this guideline is to provide a rational approach to antifungal prescribing by paediatricians. In doing so, we hope to decrease fungal morbidity and mortality, minimise drug toxicity and encourage prescribing in the most cost effective fashion. The target readers are clinicians who treat children of all ages with invasive fungal infections.

Medline, Embase and Cochrane databases were searched from January 1966 to November 2006 for relevant studies. Review of references and conference proceedings led to identification of additional relevant articles including unpublished data. All studies identified by this search were reviewed and have been previously presented.¹⁰⁸ The AGREE instrument was used as a guide to formulate this document.¹⁰⁹

The guideline was reviewed and endorsed by members of the Paediatric Infectious Diseases Group (Australasian Society of Infectious Diseases) and Mycoses Interest Group (Australasian Society of Infectious Diseases) and the Paediatric Bone Marrow Transplant Committee (Australia and New Zealand Children's Haematology/Oncology Group).

All relevant evidence is annotated to reflect the level of evidence used.¹¹⁰

- I Evidence obtained from a systematic review of all relevant randomised controlled trials.
- II Evidence obtained from at least one properly-designed randomised controlled trial.
- III-1 Evidence obtained from well-designed pseudo randomised controlled trials (alternate allocation or some other method).
- III-2 Evidence obtained from comparative studies with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group.
- III-3 Evidence obtained from comparative studies with historical control, two or more single arm studies or interrupted time series without a parallel control group.
- IV Evidence obtained from case series, either post-test or pretest/post-test.

The guideline is current for 3 years unless superseded.

Box 2 - Definitions

For the purpose of these guidelines, the following definitions are used.

- Child: any subject 17 years and younger.
- Prolonged fever and neutropenia: the persistence of fever (a single oral temperature of $\geq 38.3^{\circ}\text{C}$ or a temperature of $\geq 38.0^{\circ}\text{C}$ for ≥ 1 hour) for at least 3-5 days, unresponsive to broad spectrum antibiotics in the absence of an identified pathogen and neutropenia (a neutrophil count of $\leq 0.5 \times 10^9/\text{L}$ or a count of $< 1.0 \times 10^9/\text{L}$ with a predicted decrease to $< 0.5 \times 10^9/\text{L}$ in 24 - 48 hours).^{22,111,112}
- Candidaemia: The identification of a blood culture that yields a *Candida* species in patients with temporally related clinical signs and symptoms compatible with infection.¹¹²
- Invasive candidiasis: Proven or probable invasive infection as defined by Ascoglu *et al.*¹¹²
- Invasive mould infection: Proven or probable invasive infection as defined by Ascoglu *et al.*¹¹²

Box 3 - Antifungal susceptibility for *Candida*, *Aspergillus* and other clinically important fungal pathogens.¹⁹

Yeasts	AmB	Flu	Itra	Vori	Posa	‡5FC	Caspo
<i>Candida albicans</i>	S	S	S	S	S	S	S
<i>Candida parapsilosis</i>	S	S	S	S	S	S	S
<i>Candida glabrata</i>	§S	SDD	SDD	S	S	S	S
<i>Candida krusei</i>	§S	R	SDD	S	S	I or V	S
<i>Candida tropicalis</i>	S	S	S	S	S	S	S
<i>Candida lusitanae</i>	S	S	S	S	S	S	S
<i>Cryptococcus neoformans</i>	S	S	SDD	S	S	S	R

Moulds	AmB	Flu	Itra	Vori	Posa	5FC	Caspo
<i>Aspergillus fumigatus</i>	S	R	SDD	S	S	R	S
<i>Aspergillus flavus</i>	S	R	SDD	S	S	R	S
<i>Pseudallescheria boydii</i> (<i>Scedosporium apiospermum</i>)	I or V	R	I or V	S	S	R	R
<i>Scedosporium prolificans</i>	R	R	R	R	R	R	R
<i>Fusarium</i> spp.	I or V	R	R	I or V	I or V	R	R
<i>Zygomycetes</i> spp (eg: <i>Mucor</i> , <i>Rhizomucor</i> , <i>Rhizopus</i>)	**S	R	R	R	††S	R	R

*S	Sensitive	I or V	Intermediate / Variable resistance
†SDD	Sensitive but dose dependant	R	Resistant

* Susceptibility is based on at least 75% of clinical isolates being susceptible.

† Susceptibility is dependent on achieving the maximal possible blood level of the antifungal agent.

‡ 5-Flucytosine should not be used in isolation without the additional of other antifungals due to the rapid emergence of resistance.

§ A proportion of *Candida glabrata* and *C. krusei* have reduced susceptibility to amphotericin B. When conventional amphotericin B is used to treat infections due to *C. glabrata* and *C. krusei*, doses of 1mg/kg/day may be required.⁵¹

|| *Scedosporium prolificans* displays in vitro resistant to all antifungals. Synergy against *S. prolificans* is often demonstrated in vitro with voriconazole and terbinafine.⁷¹ Clinical evidence of synergy with voriconazole and terbinafine is, however, restricted to case reports only.

**High doses of a lipid preparation are required for infection with zygomycete species (ie. ≥ 5mg/kg/day).

†† Posaconazole has potent in vitro activity against most zygomycetes. However, clinical data is mostly limited to step-down oral therapy after successful induction therapy (high dose IV lipid preparation amphotericin B) or for salvage therapy of invasive mucormycosis.

Box 4 – Recommended paediatric antifungal doses

Drug	Formulation	Clinical setting	Recommended dose
Conventional Amphotericin B*	Intravenous preparation	Fever & neutropenia Yeast infection Mould infection	0.6 – 1 mg/kg/day †0.6 – 1 mg/kg/day 1 - 1.5 mg/kg/day
Liposomal Amphotericin B	Intravenous preparation	Fever & neutropenia Yeast infection Mould infection	1 - 3 mg/kg/day 1 - 3 mg/kg/day ‡3 - 5 mg/kg/day
ABLC	Intravenous preparation	All settings	5 mg/kg/day
ABCD	Intravenous preparation	All settings	‡3 - 5mg/kg/day
Fluconazole	Capsule, suspension and intravenous preparation	All settings	6 – 12 mg/kg/day ¹⁶
Itraconazole [§]	Capsule and suspension. (IV preparation not registered in Australia)	All settings	§2.5 mg/kg 12 hourly ^{113,114}
Voriconazole [§]	Tablet, suspension and intravenous preparation	All settings	**6 - 8 mg/kg 12 hourly. ^{17,115}
Posaconazole ^{††}	Suspension	All settings	400 - 800 mg/day in 2 - 4 divided doses ¹¹⁶
Caspofungin	Intravenous preparation	All settings	**50 mg/m ² daily for children and adolescents. ¹⁸ **2 mg/kg or 25 mg/m ² daily for premature neonates ¹¹⁷

* The risk of infusion reactions and nephrotoxicity is reduced when CAB is given as a continuous infusion.

Although outcome data is encouraging, trials have been insufficiently powered to assess efficacy.

† When conventional amphotericin B is used to treat infections due to *C. glabrata* and *C. krusei*, doses of 1mg/kg/day are recommended.⁵¹

‡ For *Fusarium* and *Zygomycetes species*, 5 mg/kg of a lipid preparation should be used. Higher doses may be required for Zygomycete infections.

§ Therapeutic drug monitoring is recommended in children with invasive fungal disease given the variable metabolism and limited pharmacokinetic data in children. Target trough itraconazole level: > 0.5µg/ml.¹¹⁸
Target trough voriconazole level: 1- 6 µg/ml.^{119,120}

|| Cyclodextrins are present in the intravenous preparations of itraconazole and voriconazole. Caution should be taken when using these in children with creatinine clearance of < 50ml/min.^{121,122}

** Dose modification recommended in adults with cirrhosis (voriconazole) and moderate to severe hepatic insufficiency (caspofungin).^{122,123} No pharmacokinetic data exists in children with liver disease.

†† Posaconazole has been studied in children 8 to 17 years. No data is available for younger child. Posaconazole is only licensed for children 13 years and older

Box 5 – Key recommendations

Recommendation 1 – Prolonged fever and neutropenia

Recommended Agents

***Amphotericin B**

or

†Fluconazole

Alternative Agents[§]

Caspofungin

or

Voriconazole

* For the choice of amphotericin B preparation – see recommendation 4

† Fluconazole is only recommended in fluconazole naïve, low risk patients.

Patients at increased risk of mould infection should receive amphotericin B. This includes:

- haematopoietic stem cell recipients
- children with congenital immunodeficiency
- children with high risk malignancies on aggressive chemotherapy protocols (eg relapsed and high risk leukaemias, high risk solid tumours)
- children expected to have prolonged neutropenia (eg bone marrow failure syndromes, aplastic anaemia.)

Recommendation 2 – Candidaemia or invasive candidiasis

Recommended Agents

†Fluconazole

or

***Amphotericin B**

Alternative Agents[§]

Caspofungin

or

Voriconazole

† Fluconazole is recommended as first line therapy in fluconazole sensitive candidal infections.

In children pretreated with antifungals, fluconazole should not be used until the species has been identified or fluconazole sensitivity is confirmed.

* Amphotericin B (± flucytosine) is recommended as initial therapy for candidal meningitis and endocarditis. For more information, see Pappas *et al.*⁵¹

For the choice amphotericin B preparation – see recommendation 4

Recommendation 3 – Invasive aspergillosis

Recommended Agent

‡Voriconazole

Alternative Agents[§]

***Amphotericin B**

or

Caspofungin

‡ Therapeutic drug monitoring is recommended when using voriconazole in children with invasive fungal infections.

* For choice of amphotericin B preparation – see recommendation 4

[§] Alternative agents are usually only required in the context of resistant organisms, significant adverse reactions or disease progression despite therapy.

Box 5 – Key recommendations, continued

Recommendation 4 – Amphotericin therapy

- All children receiving an amphotericin B preparation should have conditions optimised including reducing the number of potentially nephrotoxic medications where possible, ensuring adequate hydration prior to commencing therapy, close monitoring of renal function and appropriate electrolyte supplementation where indicated. The choice of amphotericin preparation and method of administration should be guided by nephrotoxicity risk and local guidelines.
- Patients at greatest risk of amphotericin B induced nephrotoxicity include:
 - haematopoietic stem cell recipients
 - children with significant renal insufficiency (creatinine \geq 2x upper limit of normal [ULN])Many experts would recommend a lipid preparation when amphotericin B is required in these populations but because definitive paediatric data is lacking, there is not universal consensus on this.
- Other patients at increased risk of amphotericin B nephrotoxicity include:
 - children with renal insufficiency not meeting the above definition (creatinine $<$ 2x ULN).
 - children receiving 2 or more concurrent nephrotoxins.
 - children with a proven / probable mould infection that will require prolonged therapy.The choice between conventional amphotericin B and a lipid preparation in these children should be considered on an individualised case by case basis.
- Patients without risk factors for amphotericin B induced nephrotoxicity can be safely treated with conventional amphotericin B.