

ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: prevention and management of invasive infections in neonates and children caused by *Candida* spp.

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Abstract

Invasive candidiasis (IC) is a relatively common syndrome in neonates and children and is associated with significant morbidity and mortality. These guidelines provide recommendations for the prevention and treatment of IC in neonates and children. Appropriate agents for the prevention of IC in neonates at high risk include fluconazole (A-I), nystatin (B-II) or lactoferrin ± *Lactobacillus* (B-II). The treatment of IC in neonates is complicated by the high likelihood of disseminated disease, including the possibility of infection within the central nervous system. Amphotericin B deoxycholate (B-II), liposomal amphotericin B (B-II), amphotericin B lipid complex (ABLC) (C-II), fluconazole (B-II), micafungin (B-II) and caspofungin (C-II) can all be potentially used. Recommendations for the prevention of IC in children are largely extrapolated from studies performed in adults with concomitant pharmacokinetic data and models in children. For allogeneic HSCT recipients, fluconazole (A-I), voriconazole (A-I), micafungin (A-I), itraconazole (B-II) and posaconazole (B-II) can all be used. Similar recommendations are made for the prevention of IC in children in other risk groups. With several exceptions, recommendations for the treatment of IC in children are extrapolated from adult studies, with concomitant pharmacokinetic studies. Amphotericin B deoxycholate (C-I), liposomal amphotericin B (A-I), ABLC (B-II), micafungin (A-I), caspofungin (A-I), anidulafungin (B-II), fluconazole (B-I) and voriconazole (B-I) can all be used.

Keywords: Antifungal agents, candida disease, children, Europe, neonates

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Introduction

The process of defining therapeutic recommendations in this document is consistent with paediatric development regulations and guidelines from the European Medicines Agency (EMA) [1,2]. The EMA has a relatively pragmatic approach to the licensure of pharmaceutical agents for neonates and children. The EMA accepts the requirement for extrapolation of evidence for efficacy from studies in adults to paediatric patients, or from older to younger paediatric patients when the following criteria are met: (i) a medicinal product is to be used for the same indication(s); (ii) the disease process or target sensitivity is similar; and (iii) the outcome of therapy is likely to be comparable [1,2].

Pharmacokinetic studies performed in all the age ranges of paediatric patients likely to receive a compound, together with safety studies, may provide adequate information for use by allowing selection of paediatric doses that will produce drug exposure similar to those observed in adults. In situations where the comparability of the disease course or outcome of therapy is expected to be similar, but the relevant drug exposure in adults is not known, a pharmacokinetics/pharmacodynamics approach combined with safety and other relevant studies may avoid the need for clinical efficacy studies [1]. More complex disease–drug combinations may require specific studies.

The grading scheme used in this manuscript is consistent with guidelines developed for adults [141]. However, there are some subtle differences for paediatric patients. The Expert Group considered three components for grading of each drug–syndrome combination: (i) evidence for efficacy, which was frequently, but not invariably, obtained from studies in adults; (ii) the quality of the pharmacokinetic data and models performed in either neonates or children that enable an informed decision about an appropriate regimen for the specific population; and (iii) specific safety data obtained in neonates or children that support the use of a given compound in that specific population. These guidelines are intended to facilitate optimal antifungal therapy for neonates and children with invasive candidiasis. They are not necessarily exhaustive. Contraindications, drug–drug interactions and specific warnings for each compound should be considered by treating physicians. Furthermore, these guidelines should be coupled with diagnostic and therapeutic algorithms tailored to the specific case mix and local fungal epidemiology of each institution. The incorporation of these therapeutic guidelines with a risk stratification strategy is also recommended, especially for prophylaxis and empirical antifungal therapy.

Overview of syndromes and pathogenesis of invasive candidiasis in paediatrics

Neonates

Invasive candidiasis (IC) is a common and serious infection in premature neonates [3]. Invasive candidiasis may present as candidaemia, urinary tract infection and involvement of essentially any other tissue or structure. A syndrome that is particularly unique to premature infants is haematogenous *Candida* meningoencephalitis (HCME), where there is invasion of the central nervous system (CNS) by *Candida*. This syndrome occurs in 15–20% of cases of IC and may contribute to the increased mortality and long-term neurodevelopmental abnormalities [3,4].

The risk factors for development of IC in the neonatal intensive care unit (NICU) include prematurity, central vascular catheterization, abdominal surgery, necrotising enterocolitis (NEC), exposure to broad-spectrum antibacterial agents (e.g. third-generation cephalosporins and carbapenems), parenteral nutrition, antacids and endotracheal intubation. Infants with a smaller gestational age have a higher incidence of IC (e.g. neonates with gestational age of 23–24, 25–27 and ≥ 28 weeks have an incidence of 10–20%, 5–10% and <5%, respectively [5]). Similarly, smaller infants have a higher incidence of IC (e.g. neonates with birth weight <750 g, 750–1000 g and >1000 g have an incidence of IC of >10%, 5–10% and <5%, respectively).

Candida albicans is the most frequent *Candida* species causing IC in neonates [6,7]. *Candida parapsilosis*, *Candida tropicalis* and other *Candida* species are seen less commonly. Unlike adults, *Candida glabrata* and *Candida krusei* are infrequent causes of IC in the NICU.

Older children

The invasive *Candida* syndromes in older children closely resemble those seen in adults. *Candida* spp. are important causes of healthcare-associated infections in children and adolescents with indwelling central venous catheters, in paediatric cancer patients receiving treatment for haematological malignancies and in paediatric haematopoietic stem cell transplant (HSCT) recipients. Severe sepsis and/or septic shock occurs in approximately 30% [8,9]; mortality rates range between 10 and 25% in most series [9] and are close to 50% in patients admitted to the ICU [8,10,11]. IC is also an important syndrome in solid organ transplant recipients. The incidence in this setting remains relatively poorly defined, but is c. 5–10% in liver, small bowel and pancreas transplantation [12]. In the individual reports that are available, the incidence of IC for paediatric heart, lung and liver transplant recipients is 3.9%, 5% and 19%, respectively [10,13,14].

Prevention of IC in neonates (see Table 1)

General principles

Antifungal prophylaxis may be an appropriate strategy, especially for the most vulnerable patients (e.g. extremely low-birth-weight [ELBW] neonates [i.e. <1000 g]). Avoidance of horizontal transmission in the NICU is paramount and requires rigorous infection control measures [15]. Treatment of maternal vaginal candidiasis prior to delivery may prevent subsequent neonatal colonization [15]. Rational use of broad-spectrum antibacterial agents (especially third-generation cephalosporins and carbapenems) and central venous catheters is probably important, although there is no specific evidence to support these interventions. The Expert Group has evaluated three prophylactic strategies for IC in premature neonates: (i) oral nonabsorbable antifungal agents; (ii) oral administration of *Lactobacillus* and lactoferrin; and (iii) i.v. and oral administration of fluconazole.

Nonabsorbable antifungal agents

Nonabsorbable antifungal agents are used to decrease the burden of *Candida* in the gut and therefore the probability of translocation into the bloodstream. Currently available agents include nystatin (1 mL suspension, 100 000 U/mL, every 8 h, during high-risk period) and miconazole oral gel 15 mg Q8 h.

There is a reasonable amount of data that support the use of nystatin for neonates <1500 g (B-II). This recommendation is based on randomized controlled trials that have compared the utility of oral nystatin versus no medication for the prevention of IC [16,17]. A subsequent Cochrane review and meta-analysis suggest that oral nystatin results in a significant reduction in IC, but has no impact on mortality [18]. Two further studies have compared nystatin with fluconazole [19,20]. While the impact of nystatin on IC is variable (some studies [16,17,19] suggest that the use of nonabsorbable agents results in a reduction in colonization and IC [e.g. from c. 44 to 12% and c. 4–32 to 1.8–6%, respectively, while others do not [20]], there is no impact on mortality, and longer-term outcomes have not been assessed. A potential problem with the use of nonabsorbable agents is inadvertent damage of the very fragile gut epithelium of premature infants and the subsequent development of necrotizing enterocolitis (NEC). A grading of B-II reflects the potential concern for the development of NEC, the absence of an overall effect on mortality and methodological weaknesses in these studies.

Miconazole is an alternative nonabsorbable agent for the prevention of IC in neonates. The only trial that has

examined the utility of miconazole for this indication in neonates suggests that there is a reduction in rectal colonization by *Candida*, but no impact upon IC [21]. Given the potential for the development of triazole resistance that may preclude the subsequent use of fluconazole, the Expert Group suggests a grading of D-II.

Administration of *Lactobacillus* and lactoferrin

The administration of *Lactobacillus casei* subsp. *rhamnosus* is intended to prevent the establishment of a microbiological niche for *Candida* spp. in the gut. Studies of oral probiotic administered (10^6 colony-forming units per day) from the third day of life until either the end of the sixth week of life or until discharge from the NICU suggest that this approach prevents enteric colonization by *Candida* species, but has no impact on the overall incidence of IC [22]. Lactoferrin is an alternative agent that may be effective via the abrogation of the invasive potential of *Candida* spp. The administration of bovine lactoferrin (100 mg/day), alone or in combination with *Lactobacillus rhamnosus* GG, significantly reduces the incidence of late-onset sepsis in very low-birth-weight (VLBW, <1500 g) neonates, including those episodes attributable to *Candida* [23]. Bovine lactoferrin does not affect the incidence of *Candida* colonization but reduces the incidence of IC in VLBW neonates [24]. The Expert Group considers that lactoferrin alone or in combination with *Lactobacillus* is equally reasonable (B-II).

Fluconazole prophylaxis

The use of fluconazole (i.v. or oral) is supported by robust data that attest to both the efficacy and safety of this agent. Five RCTs [19,25–28], eight historical control studies [29–36] and one meta-analysis [37] have examined the utility of fluconazole for the prevention of IC in neonates. Collectively, all these studies suggest that prophylactic administration of fluconazole 3–6 mg/kg/dose (i.v. or oral) twice weekly results in a reduction in *Candida* colonization and a 91% decrease of IC in neonates <1000 g. While there is a reduction in mortality, this is not statistically significant (RR 0.74 [CI 0.51–1.09]) [37,38]. Potential theoretical concerns with the routine use of fluconazole include neurodevelopmental toxicity and emergence of drug resistance. Reassuringly, a recent study suggests no toxicity after 8–10 years, nor the emergence of less susceptible or inherently resistant *Candida* species in the NICU [39]. Of note, studies examining fluconazole prophylaxis were conducted in NICUs with relatively high incidence of IC (e.g. >12%). Most NICUs have an incidence of IC of <5% for neonates <1000 g, and some <2% [40]. The potential benefits of fluconazole prophylaxis may be less with a low incidence of IC.

The Expert Group recommends that the use of fluconazole is combined with a risk stratification strategy. Thus, fluconazole 3–6 mg/kg/dose twice weekly i.v. or orally is appropriate for all neonates <1000 g in NICUs with relatively high frequency of IC (A-I). For NICUs with a lower incidence of IC (i.e. <2%), the decision to use the same fluconazole prophylaxis regimen should be made on a case-by-case basis and embedded in a risk stratification strategy (e.g. <1000 g, additional risk factors for IC such as central venous catheterization, receipt of third-generation cephalosporins or carbapenems) (B-II).

Treatment of IC in neonates (See Table 2)

General principles

Because cultures from deep sites are frequently negative, a definitive diagnosis of IC in neonates may be problematic [3]. Information on local epidemiology may help guide initial therapy [6]. Any premature infant with microbiological or clinical evidence of invasive candidiasis should be assumed to have disseminated disease, and this should prompt a thorough clinical examination and relevant investigations. In particular, the possibility of HCME should be considered, and if deemed probable, antifungal therapy should be designed to treat the CNS [41]. This important pharmacodynamic difference between neonates and adults means that the strategy of combining efficacy data from adults with well-designed PK studies in neonates may not be appropriate. In this regard, the Expert Group notes that evidence to support various compounds in neonatal settings is accrued either from: (i) case series describing the outcome of drug therapy in neonates or (ii) *in vivo* to clinical bridging studies. The latter has been recently applied to the echinocandins.

Amphotericin B formulations

Amphotericin B deoxycholate 1 mg/kg/day can be used for the treatment of IC in neonates (B-II). This recommendation is supported by relatively limited clinical data for IC [42] and HCME [43]. The recommendation is also supported by limited pharmacokinetic data [44]. There is no specific clinical information for optimal regimen for the treatment of HCME, although amphotericin B deoxycholate is effective in a pre-clinical model of HCME [45]. Liposomal amphotericin B 2.5–7 mg/kg/day can be used for IC in neonates [46–48] (B-II) and is safe [49]. While there is no specific clinical information for the optimal regimen for HCME, liposomal amphotericin B penetrates the CNS in a preclinical model of HCME and has antifungal activity in the brain [45]. ABLC 2.5–5 mg/kg/day i.v. is an alternative agent to both LAmB and DAMB

(C-II). Evidence for efficacy and the population pharmacokinetics of ABLC have been described in neonates [50]. Furthermore, preclinical data suggest ABLC is effective for HCME [45]. The lower grading compared with other amphotericin B formulations reflects continuing uncertainty regarding the use of this agent for IC in general (for both children and adults) and the relative paucity of clinical data compared with other formulations.

Triazoles

There are relatively few studies that have specifically examined the efficacy of fluconazole for neonates. Fluconazole (12 mg/kg with consideration given to a loading dose of 25 mg/kg although further safety studies are required) can be used to treat IC in neonates who have not previously received this agent (B-II). This recommendation is based on data for efficacy and safety in neonates [51–53]. Recent population pharmacokinetic studies have been used to define an appropriate regimen [54,55]. There are no preclinical or clinical data that are available to guide definitive regimens for HCME. Potential limitations of fluconazole include a relatively narrow spectrum of antifungal activity compared with other antifungal agents, and a fungistatic (as opposed to fungicidal) antifungal effect.

Echinocandins

The echinocandins are increasingly used for treatment of IC in the NICU. The recommendation for micafungin 4–10 mg/kg/day (B-II) is based on a PK–PD bridging study and detailed PK studies [56–58]. Micafungin 4 mg/kg approximates drug exposures achieved in adults. If HCME is thought to be likely, a higher dosage (e.g. 10 mg/kg) should be used because of the dose-dependent penetration of micafungin into the CNS [57]. The Expert Group notes the ‘black box’ warning for micafungin issued by the EMA indicating micafungin should only be used if other agents are not appropriate. This warning is based upon an increased incidence of hepatic tumours in rats receiving prolonged dosing of micafungin. To date, there is no corresponding clinical signal, despite extensive clinical use of micafungin throughout the world. Furthermore, similar studies have not been performed for the other echinocandins, raising uncertainty as to whether this preclinical finding is a class effect. Preclinical data and PK–PD bridging studies suggest that an elevated dosage of anidulafungin may be required to treat HCME [59]. While limited PK is available [60], further clinical PK studies are required, and until results from these studies are available, the Expert Group has not graded anidulafungin for use in this setting. The currently recommended infant dosage of caspofungin (25 mg/m²/day) is based on achieving comparable AUCs to those seen in adults [61]. While clinical efficacy has been

demonstrated in a small number of case reports and case series [62–64], there is no evidence that this dosage is necessarily adequate to treat infants with HCME. Moreover, the use of body surface area as a metric of size may be inaccurate in neonates. For these reasons, and until further data are available, the Expert Group suggests a grading of C-II is appropriate.

Prevention and treatment of invasive candidiasis in children (See Table 3 and 4)

General principles

Primary prophylaxis is a widely accepted strategy for patients at high risk of developing IC. The underlying incidence of IC is the most important factor for determining whether prophylaxis is a reasonable strategy, with 10% frequently being used as a value where the risk–benefit analysis is favourable. The incidence for patients with acute myeloid leukaemia, recurrent leukaemia and following allogeneic HSCT is 5–15% [65–68]. For patients with acute lymphoblastic leukaemia and solid tumours who are receiving dose-intense chemotherapy with or without autologous stem cell rescue, the reported incidence rates are <5% [68,69]. Apart from these general considerations, the institutional epidemiology is the most important consideration for designing an appropriate prophylactic regimen.

Prevention of invasive candidiasis in allogeneic HSCT recipients

Fluconazole (8–12 mg/kg QD i.v. or orally; studied from day 0 to day +75) may be used in allogeneic HSCT recipients (A-I). This recommendation is based on randomized clinical trials performed in adults who have demonstrated a reduction in invasive *Candida* infections [70,71], a persistent survival benefit in one study [71,72], the existence of paediatric PK and safety data [73–75], and a paediatric label from the EMA. Fluconazole should only be used when the risk of invasive mould infections is suitably low or in combination with a screening programme for these pathogens.

Itraconazole suspension (2.5 mg/kg Q12h; started after completion of the conditioning regimen; not approved by the EMA in patients <18 years of age), which has additional activity against *Aspergillus* spp., may also be used for children ≥2 years of age (B-II). The evidence for the use of this agent for HSCT recipients is derived from randomized clinical trials in adults [76,77] and relatively small paediatric pharmacokinetic studies [78–80]; the latter is the reason for the designation of level II evidence. TDM should be performed to verify absorption, compliance and the attainment

of effective and nontoxic concentrations. A trough concentration target of 0.5 mg/L when estimated using HPLC is reasonable [81,82]. A further option for children aged ≥2 years is voriconazole (day 1: 9mg/kg Q12 h, then 8 mg/kg Q12h i.v): 9 mg/kg Q12 h PO (max. 350 mg Q12 h) for 2–12 years and 12–14 years with <50 kg; adult dose for patients 12–14 years >50 kg and for patients >14 years; studied from day 0 until at least day +100) (A-I). The basis for this recommendation includes a randomized clinical trial performed in adults that demonstrates comparable prophylactic efficacy to fluconazole [83] and adequate PK and safety data [84–89]. An additional consideration is activity against *Aspergillus* spp. Prophylactic use of voriconazole should be coupled with therapeutic drug monitoring; a trough concentration of ≥1 mg/L is probably a reasonable target [89–91]. For adults with GVHD and augmented immunosuppression, posaconazole (200 mg Q8 h) has been shown to prevent invasive fungal infections, although there was no effect on overall mortality [92]. Limited data in children 13–17 years of age suggest minimal differences in pharmacokinetics compared with adults [93]. Therefore, posaconazole may be appropriate for children who are receiving immunosuppression for GVHD (B-II). The Expert Group suggests a lower recommendation than adults because of relatively rudimentary pharmacokinetic studies in paediatric patients. If posaconazole is used, therapeutic drug monitoring should be considered, and a trough concentration of 0.7 mg/L after 1-week therapy is a reasonable therapeutic target [94,95].

Micafungin (1 mg/kg/day i.v. administered from the beginning of the preparative regimen to day +30) may be used (A-I). This recommendation is based upon robust paediatric PK [96,97], safety [98], regulatory approval for this indication and a large randomized clinical trial with inclusion of paediatric patients [99].

Prevention of invasive candidiasis in children with AML and recurrent leukaemia

The recommendations for patients with AML and/or recurrent leukaemia are similar to the allogeneic HSCT setting; the risk of developing invasive mould disease may be significant and should be considered [69]. Fluconazole (8–12 mg/kg/day i.v./orally (max. 400 mg) after the last dose of chemotherapy and until neutrophil recovery) [100] (A-I) should only be used when the risk of invasive mould infections is suitably low or in combination with a screening programme for these pathogens. Micafungin (1 mg/kg/day i.v.) is approved for prophylaxis of invasive *Candida* infections in patients with profound and prolonged neutropaenia [ANC <500 for ≥10 days] [99](A-II). The Expert Group

TABLE 1. Prevention of invasive candidiasis in neonates

Recommendation and grading	Comments	References
Oral nystatin, 1 mL 100 000 IU Q8 h (B-II)	Reduction in fungal infection, but no change in mortality, potential gut damage & NEC	[18–20]
Miconazole oral gel 15 mg Q8 h (D-II)	Concerns regarding generation of triazole resistance	[21]
Lactoferrin 100 mg/day alone or in combination with <i>Lactobacillus</i> 10 ⁶ colony-forming units per day from the third day of life until either the end of the sixth week of life or until discharge from the NICU (B-II)	Reduction in fungal infection by <i>Lactobacillus</i> and lactoferrin	[22–24]
Fluconazole 3 or 6 mg/kg 2 times per week iv or orally in ALL neonates <1000 g in NICUs with high frequency of IC (A-I)	Reduction in <i>Candida</i> colonization, fungal infection, but no change in overall mortality. Concerns for neurodevelopmental toxicity, emergence of resistant species	[19,25–37,39]
Fluconazole 3 or 6 mg/kg 2 times per week iv or orally in NICUs with a lower incidence of IC (i.e. <2%) for neonates: (a) with birth weight <1000 g, (b) who have risk factors (i.e. central venous catheters, third-generation cephalosporins and carbapenems) for the development of IC (B-II)	Decision for prophylaxis is on an individual basis	References as immediately above

TABLE 2. Therapeutic options for infants with invasive candidiasis and/or HCME

Recommendation and Grading	Comments	References
Amphotericin B deoxycholate 1 mg/kg/day (B-II)	PK in neonates relatively poorly defined, leading to some uncertainty regarding optimal dosage for HCME	Clinical trials in adults [123,124] Pharmacokinetics in neonates [44] Evidence for efficacy and toxicity [43,135]
Liposomal amphotericin B 2.5–7 mg/kg/day (B-II)	PK in neonates remains undefined, leading to some uncertainty regarding optimal dosage for neonates The optimal dosage for HCME is not known Relatively limited data for the treatment of IC	Pharmacokinetics in neonates: nil Evidence for efficacy in neonates [46–48]
Fluconazole 12 mg/kg/day, with consideration given to a loading dose of 25 mg/kg (B-II)		Evidence for efficacy [51–53] Pharmacokinetics in neonates: [54,55]
Micafungin 4–10 mg/kg/day i.v. (B-II)	The EMA has issued a 'black box' warning on the basis of an elevated incidence of hepatic tumours in rats receiving prolonged dosing and drug exposures higher than typically seen in clinical contexts. These studies have not been performed for other echinocandins The currently licensed dosage is 2–4 mg/kg/day. If HCME is present, preclinical models and PK-PD bridging studies suggest a higher dosage is required for effective therapy	Evidence for efficacy derived from preclinical models [57] Pharmacokinetics in neonates: [56,58]
Caspofungin 25 mg/m ² /day (C-II)	Relatively limited PK and dosing designed to approximate drug exposure in adults, rather than HCME	Evidence for efficacy [62–64] Pharmacokinetics in neonates: [61]
ABLC 2.5–5 mg/kg/day (C-II)	The Expert Group rated ABLC 'C' because of the relative paucity of clinical data The optimal regimen for the treatment of HCME is not known	Pharmacokinetics in neonates [50] Preclinical data suggests that ABLC is an effective agent for the treatment of HCME [45]

suggests level II evidence is appropriate because of the absence of specific studies in this patient population. Posaconazole prevents invasive fungal infections and provides a survival advantage for patients with AML/MDS compared with patients receiving fluconazole or itraconazole [101]. Based on limited PK and safety data [93,102], posaconazole (200 mg Q8 h following completion of chemotherapy until neutrophil recovery; plus TDM) (B-II) is an option for adolescents >12 years of age.

Further alternatives include the following: (i) itraconazole (2.5 mg/kg Q12h following chemotherapy with concomitant TDM; not approved by the EMA for patients <18 years of age) [103] (B-II); (ii) liposomal amphotericin B (1 mg/kg/every other day) (B-I) based on studies in adult patients with leukaemia [104] and concomitant paediatric pharmacokinetic and safety data [105,106]; and (iii) voriconazole (day 1: 9 mg/

kg Q12 h, then 8 mg/kg BID i.v.); 9 mg/kg Q12 h PO (max.: 350 mg Q12 h) for 2–14 years; adult dose for patients >14 years; plus TDM) [83,107] (A-II). Of note, both micafungin and liposomal amphotericin B may be useful for patients with acute lymphoblastic leukaemia (ALL) who are receiving repeat treatments with vincristine and in whom antifungal triazoles are contraindicated [108].

Prevention of invasive candidiasis in autologous HSCT recipients and in children with ALL

Patients who have received high-dose chemotherapy with autologous stem cell rescue (autologous HSCT), who also have profound and prolonged neutropaenia (ANC <500 for ≥10 days) despite hematopoietic growth factors and/or severe mucositis, may benefit from primary antifungal prophylaxis [100]. Because the risk of developing invasive mould

TABLE 3. Primary prophylaxis of invasive candidiasis in children

Clinical Context	Recommendation and Grading	Comments	References
Allogeneic HSCT	Fluconazole 8–12 mg/kg QD i.v. or orally; studied from day 0 until day +75 post transplant (A-I)	Fluconazole should only be used if the institutional incidence of invasive mould infections is low, or if there are active diagnostic and therapeutic algorithms for mould infections	Clinical trials in adults [70–72] PK studies in children [73] Safety and efficacy in children [74,75]
Allogeneic HSCT	Micafungin 1 mg/kg QD i.v.; studied from the start of the preparative regimen until day +30 (A-I)	Spectrum of antifungal activity also extends to <i>Aspergillus</i> spp.	Clinical trials in adults with inclusion of paediatric patients [99] PK studies in children: [96,97] Safety and efficacy in children [98]
Allogeneic HSCT	Voriconazole 8 mg/kg BID (day 1: 9 mg/kg BID) for i.v., and 9 mg/kg BID for oral administration (max.: 350 mg BID) for the ages of 2–14 years and the approved adult dose for patients 15 years and older and 12–14 year olds weighing >50 kg; studied from day 0 until at least day +100 (A-I)	Spectrum extends to <i>Aspergillus</i> spp. and other medically important opportunistic moulds TDM should be performed; dosing target/ trough concentration of ≥ 1 mg/L	Clinical trials in adults [83] PK studies in children: [84–88] TDM dosing target: [89–91] Safety/efficacy in children: [84–89,136–138]
Allogeneic HSCT	Itraconazole suspension 2.5 mg/kg Q12 h for patients ≥ 2 years of age; to be started after completion of the conditioning regimen; studied until at least day +100 (B-II)	Spectrum extends to <i>Aspergillus</i> spp. and other medically important opportunistic moulds Not approved in patients <18 years TDM is suggested; dosing target: trough concentration of ≥ 0.5 mg/L	Clinical trials in adults: [76,77] PK studies in children [78–80] TDM dosing target [81,82] Safety/efficacy in children [79]
Allogeneic HSCT	Posaconazole suspension 200 mg Q8 h orally for patients with \geq grade II GVHD and ≥ 13 years of age (B-II)	Spectrum extends to <i>Aspergillus</i> spp. and other medically important opportunistic moulds Not approved in patients <18 years TDM is suggested; dosing target: trough concentration of ≥ 0.7 mg/L	Clinical trials in adults: [92] PK studies in children: [93] TDM dosing target [94] Safety/efficacy in children: nil
AML and recurrent leukaemia	Fluconazole 8–12 mg/kg i.v. or orally after last dose of chemotherapy until neutrophil recovery (A-I)	Fluconazole should only be used if the institutional incidence of invasive mould infections is low, or with an active diagnostic and therapeutic algorithms for clinical signs and symptoms suggestive of these infections	Clinical trials in adults [100] PK studies in children [73] Safety/efficacy in children: [74,75]
AML and recurrent leukaemia	Micafungin 1 mg/kg QD i.v.; after last dose of chemotherapy until neutrophil recovery (A-II)	Prophylactic efficacy inferred from study in HSCT patients Alternative for patients with leukaemia receiving vincristine	As above
AML and recurrent leukaemia	Itraconazole suspension 2.5 mg/kg Q12 h for patients ≥ 2 years of age; after last dose of chemotherapy until neutrophil recovery (B-II)	Spectrum extends to <i>Aspergillus</i> spp. and other medically important opportunistic moulds Not approved in patients <18 years TDM is suggested; dosing target: trough concentration of ≥ 0.5 mg/L	Clinical trials in adults [103] PK studies in children: [78–80] TDM dosing target: [81,82] Safety/efficacy in children [79]
AML and recurrent leukaemia	Liposomal amphotericin B 1 mg/kg QOD i.v. (B-I)	Spectrum extends to <i>Aspergillus</i> spp. and other medically important opportunistic moulds Alternative antifungal agent for patients with leukaemia receiving vincristine	Clinical trials in adults [104] PK studies in children [105] Safety/efficacy in children [106]
AML and recurrent leukaemia	Voriconazole 8 mg/kg BID (day 1: 9 mg/kg BID) for i.v., and 9 mg/kg BID for oral administration (max.: 350 mg BID) for the ages of 2–14 years and the approved adult dose for patients 15 years and older and 12–14 year olds weighing >50 kg; after last dose of chemotherapy until neutrophil recovery (B-I)	As above	As above
AML and recurrent leukaemia	Posaconazole 200 mg TID orally for patients ≥ 13 years of age; after last dose of chemotherapy until neutrophil recovery (B-II)	As above	As above
Autologous HSCT	Fluconazole 8–12 mg/kg i.v. or orally after last dose of chemotherapy until neutrophil recovery (A-I)	Patients with expected profound and prolonged neutropaenia (ANC <500 ≥ 10 days) despite use of growth factors and/or severe mucositis may benefit from antifungal prophylaxis	References as above
Autologous HSCT	Micafungin 1 mg/kg QD i.v.; after last dose of chemotherapy until neutrophil recovery (A-I)	As above	References as above
Autologous HSCT	Itraconazole suspension 2.5 mg/kg Q12 h for patients ≥ 2 years of age; after last dose of chemotherapy until neutrophil recovery (B-II)	As above	References as above
Autologous HSCT	Liposomal amphotericin B 1 mg/kg QOD i.v. (B-I)	As above	References as above

HSCT, haematopoietic stem cell transplantation; PK, pharmacokinetics; TDM, therapeutic drug monitoring.
Note that individual ALL patients exhibiting prolonged and profound neutropaenia (ANC <500 for ≥ 10 days) and receiving high doses of glucocorticosteroids may benefit from antifungal prophylaxis [68]. As these risk factors are shared by opportunistic moulds, a mould active agent is preferred (CIII).

infections is <5% [108], primary options include micafungin (1 mg/kg QD; studied from the start of high-dose chemotherapy until engraftment) [99] (A-I) and fluconazole (8–12 mg/kg/day i.v./orally (max. 400 mg) (A-I) [100]. Alternative

options include itraconazole (2.5 mg/kg Q12h with TDM; not approved in subjects <18 years of age) [103] (B-II) and liposomal amphotericin B 1 mg/kg/every other day i.v. (B-I) based on data derived from adult patients leukaemia [104].

TABLE 4. Treatment of invasive candidiasis in children

Recommendation and Grading	Comments	References
Amphotericin B deoxycholate 0.6–1 mg/kg/day (C-I)	Lipid preparations of amphotericin B have a more favourable toxicity profile Issues related to supply in some European countries	Clinical trials in adults [123,124] PK studies in children [132] Evidence for safety and efficacy in children with invasive candidiasis: Nil
Liposomal amphotericin B 3 mg/kg/day (A-I)		Clinical trials in adults and children [48,127] PK studies in children [105] Safety in children [48]
Fluconazole 8–12 mg/kg/day (B-I)	Fungistatic antifungal activity	Evidence for efficacy in adults [123,139] PK studies in children [73] Evidence for safety and efficacy in children [75]
Voriconazole (day 1: 9 mg/kg Q12h, then 8 mg/kg BID i.v.); and 9 mg/kg BID for oral administration (max.: 350 mg BID) for the ages of 2–14 years and the approved adult dose for patients 15 years and older and 12–14 year olds weighing >50 kg; after last dose of chemotherapy until neutrophil recovery (B-I)	Fungistatic antifungal activity Spectrum extends to <i>Candida glabrata</i> and <i>Candida krusei</i> TDM should be considered	Evidence for efficacy in adults [134] PK studies in children: [84–88] TDM dosing target: [89–91]
Micafungin <40 kg 2–4 mg/kg (A-I)	Well conducted PK trials to define dosages that lead to comparable drug exposures in children The EMA has issued a 'black box' warning on the basis of an elevated incidence of hepatic tumours in rats receiving prolonged dosing and drug exposures higher than typically seen in clinical contexts.	Efficacy established in clinical trials in children and adults [48,127] PK studies in children: [96,97] Safety/efficacy in children [98]
Anidulafungin 3 mg/kg as a single loading dose followed by 1.5 mg/kg/day (B-II)	Some uncertainty about optimal paediatric regimen because of relatively limited PK data No data for efficacy and safety in children	Evidence for efficacy in adults [128] PK studies in children [129]
Caspofungin Loading dose 70 mg/m ² /day, followed by 50 mg/m ² /day. Option to increase to 70 mg/m ² /day if clinically indicated, maximum absolute dose of 70 mg/day (A-I)		Evidence for efficacy in adults [124] PK studies in children [125] Evidence for safety in children [126]
Amphotericin B Lipid Complex (B-II)	Relatively limited clinical data for efficacy and safety No PK data for children	Evidence for efficacy and safety [131,140] PK in children: nil

While no general recommendation can be made for de novo acute lymphoblastic leukaemia, individual patients exhibiting prolonged and profound neutropaenia (ANC <500 for ≥10 days) and receiving high doses of corticosteroids may benefit from antifungal prophylaxis [68]; because these risk factors are shared by opportunistic moulds, a mould active agent is preferred (CIII).

Prevention of invasive candidiasis in solid organ transplant recipients and critically ill nonneutropaenic children

Because robust data on epidemiology and risk factors are absent, firm recommendations for the prevention of IC are somewhat difficult. The most appropriate agent depends on the underlying incidence of invasive aspergillosis, which in turn is a function of the transplant type and institutional incidence of mould infections. If the incidence of invasive aspergillosis is suitably low, then fluconazole 8–12 mg/kg/day i.v. or orally is reasonable in the majority of cases (recommendation not rated).

Similar uncertainties exist for critically ill nonneutropaenic children in the paediatric intensive care unit (PICU). While no evidence-based recommendations can be made, fluconazole 8–12 mg/kg/day i.v. or orally is a reasonable option for the prevention of invasive candidiasis in critically ill nonneutropaenic children in the intensive care unit, especially in cases of extensive abdominal surgery (recommendation not rated).

Secondary Prophylaxis

Secondary chemoprophylaxis, as a term, is ill-defined for invasive candidiasis and may overlap with continued treatment or maintenance treatment in chronic disseminated candidiasis with an agent that has proven efficacy against *Candida* spp. [109]. Similar to adults, secondary chemoprophylaxis is not indicated in case of prior uncomplicated candidaemia without any sign of deep seated infection – including situations in which the patient is exposed to a new immunosuppressive condition such as prolonged neutropaenia induced by chemotherapy, autologous or allogeneic HSCT (CIII).

Empirical and pre-emptive antifungal therapy

Empirical antifungal therapy is considered by many experts a standard of care in haemato-oncological patients with prolonged neutropaenia (ANC <500 for ≥10 days) and refractory or new fever, despite broad-spectrum empirical antibacterial therapy. It may provide targeted prevention in a high-risk situation and early treatment of yet occult infections. Based on large randomized clinical trials with inclusion and separate analysis of paediatric patients [110–113], adequate paediatric PK and safety data, recommended options in paediatric patients of all age groups include liposomal amphotericin B (1–3 mg/kg QD) (A-I) and caspofungin (loading dose 70 mg/m²/day, followed by 50 mg/m²/day. Option

to increase to 70 mg/m²/day if clinically indicated with a maximum dose of 70 mg/day) (A-I). Of note, incidence and extent of nephrotoxicity of liposomal amphotericin B in children appears to be lower than in adults, hence the higher rating compared with adults. Fluconazole may be used if the incidence of invasive aspergillosis is low or if a mould-specific diagnostic algorithm is being used (B-II) [114]. Amphotericin B deoxycholate 0.7–0.8 mg/kg/day may be reasonable if this compound is available, and the higher toxicity is tolerable from a clinical perspective (B-II).

Empirical therapy in adult ICU patients has been shown to be of no benefit when using a fever criterion [115], but no data exist for nonneonatal paediatric patients. While several studies in adult ICU patients show potential utility of scoring systems as the basis for pre-emptive treatment of invasive candidiasis (see for example [116–120]), no data exist in other populations and in paediatric patients, and therefore, no recommendations are made.

Treatment of invasive candidiasis and candidaemia in children

General principles

Many of the general principles pertinent to the management of invasive candidiasis in children are derived from adults, and these are as follows: (i) antifungal therapy should be administered as quickly as possible (extrapolated from [121,122]); (ii) the optimal duration of therapy is 14 days after blood cultures are sterile, provided there is no unresolved deep infection or a severe persistent underlying immunological deficit (extrapolated from [123]); (iii) the appropriate choice of an anti-*Candida* agent may be influenced by local epidemiology because of the reduced susceptibility or resistance of some species to certain antifungal classes/agents; (iv) clinical evaluation for deep sites of infection, including an ophthalmological examination is required in all cases of candidaemia; (v) consideration should be given to removing or at least replacing intravenous catheters and/or other implanted prosthetic devices in a timely manner; and (vi) there is no firm recommendation regarding combination antifungal chemotherapy, but this may be considered in some situations (e.g. severe life-threatening infection, compromised drug penetration (e.g. cases of CNS infection, osteomyelitis, complicated urinary tract infections and complicated intra-abdominal infections).

Echinocandins

The echinocandins are first-line agents for the treatment of IC in children. The Expert Group does not consider that there are significant microbiological nor pharmacological differences

between caspofungin, micafungin and anidulafungin. Differences in recommendations reflect the different stages in the development of these compounds for paediatric patients. Caspofungin (70 mg/m² loading dose followed by 50 mg/m²/day i.v.) can be used for the treatment of IC (A-I). This recommendation is based on established efficacy in adults, a well-designed PK study [124,125], documented safety [126] and the existence of a paediatric label from the EMA. Similarly, micafungin (2–4 mg/kg/day i.v.) can also be used (A-I); this recommendation is based on a randomized control trial in adults and children [48,127], extensive pharmacokinetics [96,97], safety data [98] and the existence of a paediatric label. Anidulafungin (3 mg/kg loading dose, followed by 1.5 mg/day) is an alternative agent (B-II). While there is a RCT in adults [128] and some paediatric PK data [129], the Expert Group suggests a lower level recommendation for children because of uncertainty regarding the optimal paediatric dosage and relatively limited paediatric safety data. The Expert Group anticipates an 'upgrading' of anidulafungin with further clinical and PK studies and future regulatory approval for use in paediatric patients.

Amphotericin B formulations

Liposomal amphotericin B 3 mg/kg/day is an alternative first-line agent (A-I). This is based on a RCT in adults and children, concomitant pharmacokinetic studies [48,105,106,127] and safety data in children [48]. A higher rating compared with adults (i.e. B-I) is based on the lower incidence of toxicity in children [48,106]. ABLC is an alternative agent for IC, and there is some clinical experience in children [130,131]. Because of an absence of pharmacokinetic studies, and some uncertainty regarding the optimal regimen for invasive candidiasis, the Expert Group rated this agent B-II. Amphotericin B deoxycholate 0.6–1 mg/kg can be used for IC (C-I). This recommendation is supported by clinical data from adults [123,124] and concomitant PK data for children [132,133]. Amphotericin B deoxycholate is graded lower than lipid preparations principally because of a less favourable toxicity profile. Nevertheless, the Expert Group recognizes the use of amphotericin B deoxycholate for treatment of IC may be appropriate if other amphotericin B formulations are not available and also recognize a different grading compared with adults.

Triazoles

The triazoles have been widely used for treatment of invasive candidiasis in children. The use of fluconazole 8–12 mg/kg/day i.v. [B-I] is based on extensive RCT data in adults and paediatric PK studies [73,123,124,128] and extensive safety data [75]. The lower rating than suggested for prophylaxis reflects a fungistatic mode of activity. Nevertheless, fluconazole

ole may be a reasonable initial choice for children with IC who are haemodynamically stable and if there is a low institutional incidence of less susceptible or frankly resistant *Candida* species. There is some uncertainty regarding the use of fluconazole for *Candida glabrata* infections because this organism tends to exhibit higher MICs. *Candida krusei* is intrinsically resistant to fluconazole, and this agent should not be used in this context. Voriconazole (day 1: 9 mg/kg Q12 h, then 8 mg/kg BID i.v.); 9 mg/kg Q12 h PO (max. 350 mg Q12 h) for 2–12 years and 12–14 years with <50 kg; adult dose for patients 12–14 years >50 kg and patients >14 years) can be used for IC. A recommendation of B-I is based on a RCT in adults coupled with several well-designed PK studies in children [84–89,134]. Therapeutic drug monitoring should be performed. The 'B' rating reflects the fungistatic pattern of killing that appears common to the triazoles. Voriconazole is more potent *in vitro* against *Candida glabrata* than fluconazole and has activity against *Candida krusei* and may be a reasonable choice for these infections.

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W.W.H. has received grant support from National Institute of Health Research (NIHR), Medical Research Council, National Institute for the Replacement, Refinement and Reduction, of Animals in Research, Pfizer, Gilead, Schering-Plough, Merck and Astellas, and has served as a consultant for Pfizer, Astellas, Gilead, F2G, Vectura and Schering-Plough. He receives travel support from ESCMID.

E.C. has participated as invited speaker to symposia organized by Gilead, Pfizer, Astellas, Merck, Novartis and he has been member of advisory boards for Astellas and Pfizer.

A.H.G. has received research support from Enzon, Schering, Gilead, Merck and Schering. He has acted as speaker and/or consultant for Astellas, Cephalon, Gilead, Merck, Pfizer, Schering and Vicuron.

E.R. has received research support from Pfizer, Enzon, Schering, Gilead and Merck and he has made contributions in advisory boards of Gilead, Astellas and Pfizer. He has also received payment for talks on behalf of Gilead, Cephalon, Pfizer, Wyeth, Schering, Merck, Aventis and Astellas.

M.A. received, during the past 5 years, research grants and honoraria for talks and consultancy from Merck, Pfizer and Gilead.

M.C.A. has received grant support from Astellas Pharma, Gilead Sciences, Merck Sharp and Dohme, Pfizer and Schering-Plough. She has been a consultant or at the advisory board for Gilead Sciences, Merck Sharp and Dohme, Pfizer, Pcovery and Schering-Plough. She has been paid for talks on behalf of Gilead Sciences, Merck Sharp and Dohme, Pfizer, Astellas Pharma and Schering-Plough.

S.A.A. has received investigator initiated research grant support from Pfizer and speaker honoraria from Merck and Pfizer. She has been at the Advisory Board for Pfizer-Turkey.

M.B. has received research grants from Pfizer, MSD and Astellas and is/was an advisor or received lecture honorarium from Astellas, Angelini Farmaceutici, Astra Zeneca, Aventis, Bayer, Cephalon, Cubist, Gilead, MSD, Novartis, Shionogi, Pfizer, Teva and Vifor. He is also a board member of Pfizer, Angelini Farmaceutici, Cubist, MSD, Astellas, Novartis and Astra Zeneca.

J.B. has nothing to declare.

T.C. is member of the Speaker bureau and is advisor or consultant for Astellas, Baxter; bioMérieux, EISAI, Evolva, Immunexpress, Eli Lilly Suisse, Novartis, Merck Sharp & Dohme-Chibret AG and Pfizer. Grant support from Baxter, bioMérieux, Merck Sharp & Dohme-Chibret AG and Roche Diagnostic. He also received Royalties from Elsevier, payment for educational presentations from MSD, Institut Pasteur and Gilead Sciences, and travel support from Astellas, Pfizer and MSD.

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J.G. has nothing to declare.

R.H. has been a consultant or at the advisory board for Astellas pharma, Basilea, Gilead Sciences, Merck Sharp and Dohme, Novartis, Pfizer and Schering-Plough. He has been paid for talks on behalf of Astellas, Gilead Sciences, Merck Sharp and Dohme, Pfizer and Schering-Plough. He has also received travel support from Pfizer and Gilead, research grants and investigator fees from Pfizer.

H.E.J. has nothing to declare.

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C.L.-F. has received grant support in the past 5 years from Astellas Pharma, Gilead Sciences, Pfizer, Schering-Plough, and Merck Sharp and Dohme. She has been an advisor/consultant to Gilead Sciences, Merck Sharp and Dohme, Pfizer, Astellas Pharma and Schering-Plough. She has been paid for talks on behalf of Gilead Sciences, Merck Sharp and Dohme, Pfizer, Astellas Pharma and Schering-Plough. She has had travel support from Astellas Pharma, Pfizer, Gilead Sciences and Schering Plough.

O.L. is a member of the MSD board, is a consultant for Astellas and Gilead Sciences and received grants or speaker's fees from MSD, Astellas, Gilead Sciences and Pfizer.

W.M. has received grant support from MSD and Pfizer. He had been an advisor to MSD and Pfizer. He has received honoraria for presentations on behalf of MSD/Schering-Plough and Pfizer.

G.P. has received research grants from Gilead, Pfizer, Astra Zeneca, Novartis, Astellas, GSK and MSD, has acted as paid consultant to Janssen Cilag, Gilead, Astellas and MSD, has received travel support from ESCMID, and is a member of the Gilead, Astellas and MSD speaker's bureaus.

M.D.R. has received grants, speaker's honoraria and travel support from ESCMID, Pfizer, Astellas, MSD and Gilead Sciences. He has also received royalties from Blackwell Publishing, conference support from Astellas Pharma.

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C.V. received grants as speaker/moderator in meetings sponsored by Pfizer, Gilead, MSD, Astellas, Abbott and BMS and received grants for participation in advisory boards by Gilead, Astellas, MSD, Nadirex Internation (Pavia, Italy) and Pfizer. Further, he obtained research grants for his institution from Pfizer, MSD, Gilead, Abbott, Jansen, BMS and Novartis. He is member of the SAG (Scientific Advisory Group) for antibacterials and antifungals of CHMP-EMA and consultant for Italian Medical Drug Agency Member of various levels of local Infection Control, Antibiotic Stewardship, Vaccine and HIV Committees (Genoa, Liguria, Italy).

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