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Echinocandins vs. amphotericin B against invasive candidiasis in children and neonates: A meta-analysis of randomized controlled trials

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ABSTRACT

Objective: The aim of this meta-analysis was to assess the efficacy and safety of treatment with echinocandins compared with amphotericin B in paediatric patients with invasive candidiasis.
Methods: PubMed, Embase and Cochrane databases were searched up to August 2018. Only randomized controlled trials (RCTs) evaluating echinocandins and amphotericin B in the treatment of paediatric patients with invasive candidiasis were included. The outcomes were clinical responses and adverse effects.
Results: Five RCTs of 354 patients (191 patients in the echinocandins group and 163 patients in the amphotericin B group) were included in this study. Overall, no significant differences in clinical response were found between echinocandins and amphotericin B (odds ratio [OR], 1.38; 95% confidence interval [CI], 0.68-2.80; $I^2 = 39\%$). Similar results were also observed in the high-risk group (OR, 3.10; 95% CI, 0.10-97.23; $I^2 = 76\%$), the low-risk group (OR, 1.29; 95% CI, 0.36-4.62; $I^2 = 21\%$) and the neutropenia group (OR, 1.56; 95% CI, 0.75-3.26; $I^2 = 0\%$). The risk of discontinuing treatment because of adverse effects was significantly lower in the echinocandins group than in the amphotericin B group (OR, 0.30, 95% CI, 0.12-0.76; $I^2 = 0\%$).
Conclusions: There were no differences in efficacy between the echinocandins group and the amphotericin B group in the treatment of invasive candidiasis in paediatric patients. However, the echinocandins group had a significantly lower risk of discontinuing treatment than the amphotericin B group.

1. Introduction

Invasive candidiasis has become one of the most common types of sepsis in the paediatric population and is associated with high morbidity and mortality in vulnerable children and neonates [1-3]. All-cause mortality for paediatric candidiasis is greater than 15%, and its attributable mortality is 10% [4]. In addition, invasive candidiasis in children can prolong the length of hospital stays to 21 days and cause an extra $92 000 in hospital costs in the US health care system [5]. Two important measures to address this critical problem are: prophylactic usage of antifungal agents to prevent development of invasive candidiasis for patients at risk, and effective antifungal agents to treat this life-threatening disease in critically ill children.

Echinocandins, including caspofungin, micafungin and anidulafungin, are the most recently developed antifungal agents and have been approved by the United States' Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for use in the clinical setting for invasive candidiasis in adult patients. Several guidelines recommend echinocandins as the first-line antifungal agent for treatment of invasive candidiasis in adult patients [6-10]. In contrast, the knowledge of echinocandin usage in paediatric patients is limited, and only caspofungin and micafungin are currently approved by the FDA and EMA for paediatric patients. Several studies have shown that micafungin and caspofungin are well-tolerated and have a favourable response for invasive candidiasis in children [11-14]. However, we wondered whether the efficacy and safety of echinocandins were comparable with that of another commonly used antifungal agent, amphotericin B, in the clinical setting of invasive candidiasis in children and neonates. Therefore, we performed a comprehensive and updated meta-analysis of randomized control trials (RCTs) to provide better evidence of the efficacy and safety of echinocandins compared with

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amphotericin B in treatment of invasive candidiasis in paediatric patients.

2. Methods

2.1. Study search and selection

All clinical studies were identified by a systematic review of the literature in the PubMed, Embase, and Cochrane databases until July 2018 using the following search terms: echinocandins, micafungin, caspofungin, amphotericin B, neonates, newborn, infant, children, adolescent, and randomized (appendix 1). Only RCTs were considered eligible for inclusion if they directly compared the clinical effectiveness of echinocandins with amphotericin B in the treatment of documented paediatric patients with invasive candidiasis. Studies using combination therapy were not included. Studies were also excluded if they focused on in vitro activity or were only a pharmacokinetic or a pharmacodynamic assessment. Articles of all languages of publication were included. Two reviewers (Cheng and Chen) searched and examined publications independently to avoid bias. When these reviewers had a disagreement, a third author (Lai) resolved the issue. The following data were extracted from every included study: year of publication, study design and duration, patient demographic characteristics, dosage of echinocandins and amphotericin B, and adverse effects.

2.2. Definitions and outcomes

The primary outcome was overall clinical response with the resolution of clinical signs and symptoms of invasive candidiasis at the end of therapy. Secondary outcomes included mortality, mycological response rate, and adverse effects. Mycological response was defined as the eradication of candida infections. All adverse events were recorded irrespective of causality. Treatment-related adverse events were those ascribed by the investigator as having a relationship to the study drug as well as those deemed not assessable.

2.3. Data analysis

The Cochrane risk for bias assessment tool was used in this study to assess the quality of enrolled RCTs and the risk of bias for seven domains as follows: sequence generation of random numbers, allocation concealment, blinding of participants, study personnel and outcome assessors, avoidance of incomplete outcome data or selective outcome reporting and discussion of other potential sources of bias [15]. The Review Manager software, version 5.2 was used to conduct the statistical analyses. The degree of heterogeneity was evaluated with the Q statistic generated from the χ^2 test. The proportion of statistical heterogeneity was assessed by I^2 measure. Heterogeneity was considered significant when the P-value was less than 0.10 or I^2 was more than 50%. The fixed effect model was applied when the data were homogenous ($P > 0.10$ and $I^2 < 50\%$), and the random effects model was applied when the data were heterogeneous ($P > 0.10$ or $I^2 < 50\%$). The pooled odds ratio (OR) and 95% confidence interval (CI) were calculated for outcome analyses.

3. Results

3.1. Study selection and characteristics

The search yielded 1631 studies, including 365 articles from PubMed, 1234 articles from Embase, and 32 articles from the Cochrane database. A total of 308 duplicate articles were excluded

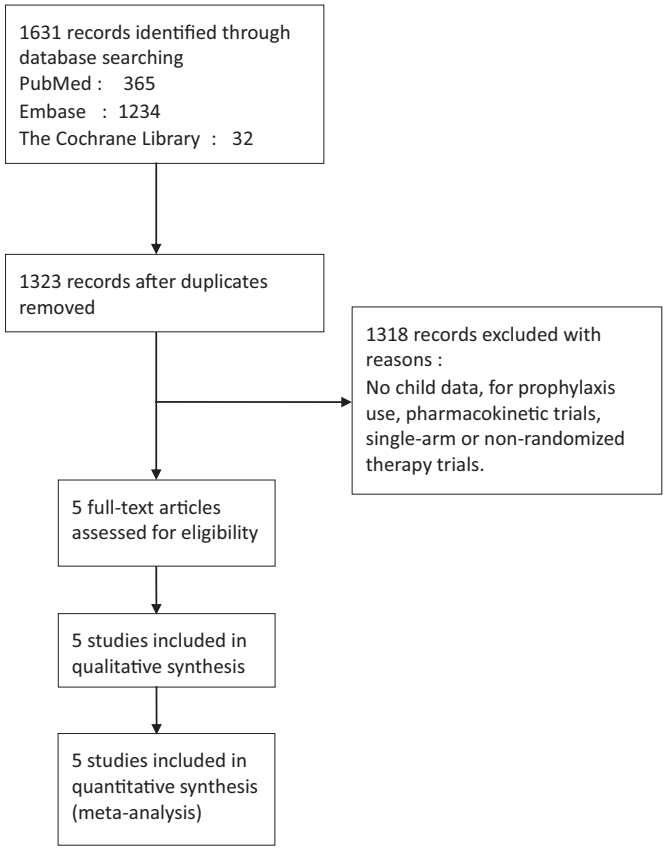

Fig. 1. Flow diagram of the study selection process.

to leave 1323 articles. These articles were screened and a total of five RCTs [16-20] that fulfilled the inclusion criteria were included in the meta-analysis (Fig. 1). All five studies were designed to investigate the outcomes of suspected or confirmed invasive candidiasis in paediatric patients receiving antifungal therapy with echinocandins or amphotericin B (Table 1) [16-20]. Only one study [20] was a single-centre study; the other four studies [16-19] were multicentre or multinational studies. Three studies [18-20] assessed the effects of antifungal agents for cases of proven invasive candidiasis, and two studies [16,17] assessed cases for the empirical use of antifungal agents for febrile neutropenia in children with suspected invasive candidiasis. Three studies [16,17,20] compared the efficacy of caspofungin and amphotericin B, and two studies [18,19] compared micafungin and amphotericin B. Liposomal amphotericin B was used in three studies [16,17,19] and deoxycholate amphotericin B was used in two studies [18,20]. The total number of patients in the RCTs in the meta-analysis was 354 (191 patients in the echinocandins group and 163 patients in the amphotericin B group). One study [20] included neonates, one [18] included infants (2-120 days), and other studies included children (0-16 [16], 2-17, [16] and 0-18 [17] years). Table 2 shows the major candida species of proven invasive candida cases in three studies [18-20]. Overall, *Candida albicans* was the most common pathogen (n = 68, 42.5%), followed by *C. parapsilosis* (n = 34, 21.3%), *C. tropicalis* (n = 30, 18.8%) and *C. glabrata* (n = 4, 2.5%). All the studies were open-label studies, and most of the domains were classified as having a low risk of bias (Figs. 2 and 3).

3.2. Clinical outcomes and microbiological response

Overall, there were no significant differences in clinical response between the echinocandins and amphotericin B groups

Table 1
Characteristics of the included studies.

Study, published year	RCT study design	Study duration	Study population	No. of patients		Dose regimen	
				Echinocandins	Amphotericin B	Echinocandins	Amphotericin B
Mohamed et al, 2012 [20]	Prospective, double blind	2008-2010	Neonate with proven IC	15	17	Caspofungin, 2 mg/kg/day	D-AmB, 1 mg/kg/day
Queiroz-Telles et al, 2008 [19]	Multinational, double blind	2003-2005	Children less than 16 years old with proven IC	52	54	Micafungin, 2 mg/kg/day for ≤ 40 kg and 100 mg for > 40 kg	L-AmB 3 mg/kg/day Max: 5 mg/kg/day
Maertens et al, 2010 [16]	Multicentre, prospective, double bind	2004-2006	Children between 2 and 17 years with suspected IC	56	26	Caspofungin, Loading with 70 mg/m^2 and then 50 mg/m^2	L-AmB, 3 mg/kg/day
Casselli et al, 2012 [17]	Multicentre, prospective	2006-2010	Children less than 18 years old with suspected IC	48	56	Caspofungin, Loading with 70 mg/m^2 and then 50 mg/m^2	L-AmB, 3 mg/kg/day, or no treatment
Benjamin et al, 2018 [18]	Multicentre, double blind	2013-2015	Infant > 2-120 days with proven IC	20	10	Micafungin, 10 mg/kg/day	D-AmB, 1 mg/kg/day

IC, invasive candidiasis; AmB, amphotericin B; RCT, randomized controlled trial

Table 2
Common candida species in three studies including proven invasive candidiasis.

Study	No. (%) of candida species							
	Mohamed et al, 2012		Queiroz-Telles et al, 2008		Benjamin et al, 2018		All	
Candida species	Echinocandins group (n = 15)	Amphotericin B group (n = 17)	Echinocandins group (n = 48)	Amphotericin B group (n = 50)	Echinocandins group (n = 20)	Amphotericin B group (n = 10)	Echinocandins group (n = 83)	Amphotericin B group (n = 77)
C. albicans	11 (73.3)	13 (76.4)	18 (40.0)	13 (26)	8 (40)	5 (50)	37 (44.6)	31 (40.3)
C. parapsilosis	3 (20.0)	2 (11.8)	13 (28.9)	17 (34)	9 (45)	2 (20)	13 (15.6)	21 (27.3)
C. tropicalis	1 (6.7)	2 (11.8)	11 (24.4)	14 (28)	1 (5)	1 (10)	13 (15.6)	17 (22.1)
C. glabrata	0 (0)	0 (0)	1 (2.2)	1 (2)	0 (0)	2 (20)	1 (1.2)	3 (3.9)

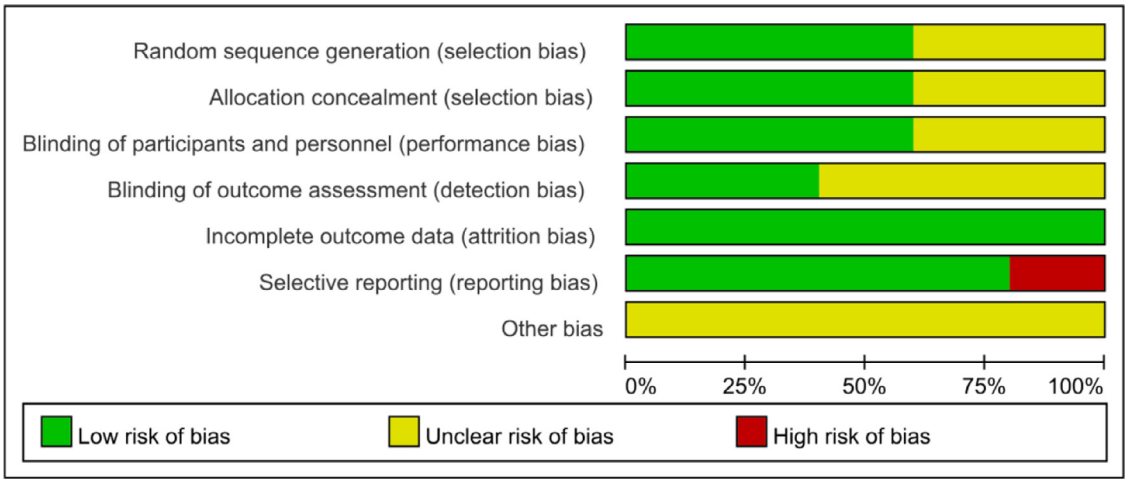

Fig. 2. Summary of risk of biases.

(OR, 1.38; 95% CI, 0.68-2.80; $I^2 = 39\%$, Fig. 4). Sensitivity analysis after deleting individual studies each time to determine the influence of a single dataset on the pooled OR showed similar findings. In the subgroup analysis, clinical responses were similar between micafungin or caspofungin and amphotericin B (micafungin vs. amphotericin B: OR, 0.92; 95% CI, 0.35-2.44; $I^2 = 0\%$; caspofungin vs. amphotericin B: OR, 1.89; 95% CI, 0.63-5.67; $I^2 = 62\%$, Fig. 5). Similar results were observed in the high-risk group (OR, 3.10; 95% CI, 0.10-97.23; $I^2 = 76\%$), the low-risk group (OR, 1.29; 95% CI, 0.36-4.62; $I^2 = 21\%$) and the neutropenia group (OR, 1.56; 95% CI, 0.75-3.26; $I^2 = 0\%$). Subgroup analysis of targeted treatment for proven invasive candidiasis and empirical treatment for suspected invasive candidiasis showed similar findings (targeted treatment: OR, 1.41; 95% CI, 0.33-5.93; $I^2 = 66\%$, empirical treatment: OR, 1.58; 95% CI, 0.73-3.38; $I^2 = 0\%$).

Two studies [18,19] provided data on mycological eradication and there were no significant differences between echinocandins and amphotericin B (OR, 0.67, 95% CI, 0.22-2.01; $I^2 = 14\%$). Three studies [18-20] assessed the risk of recurrence of candida infections, and no significant differences were found between echinocandins and amphotericin B (OR, 0.86, 95% CI, 0.72-1.04; $I^2 = 62\%$). Three studies [16,19,20] included mortality data.

Fig. 3. Risk of bias per study and domain.

Although echinocandins were associated with lower mortality than amphotericin B, the difference did not reach statistical significance (OR, 0.30, 95% CI, 0.09-1.06; $I^2 = 0\%$).

3.3. Adverse effects

Total adverse effects were reported in three studies [16,17,19]: echinocandins were associated with a lower risk of adverse effects than amphotericin B, but the difference did not reach statistical significance (OR, 0.70, 95% CI, 0.39-1.26; $I^2 = 0\%$). Regarding other specific adverse effects, there were no significant differences between echinocandins and amphotericin B in terms of fever (OR, 0.72; 95% CI, 0.32-1.63; $I^2 = 0\%$), hypokalaemia (OR, 0.46; 95% CI, 0.17-1.24; $I^2 = 0\%$), vomiting (OR, 0.90; 95% CI, 0.33-2.51; $I^2 = 6\%$), and infusion-related events (OR, 0.79; 95% CI, 0.40-1.55; $I^2 = 10\%$). All studies [16-20] reported the risk of discontinuing drug treatment due to adverse effects, with the risk significantly lower in the echinocandins group than in the amphotericin B group (OR, 0.30; 95% CI, 0.12-0.76; $I^2 = 0\%$, Fig. 6).

4. Discussion

This meta-analysis was based on five RCTs of 351 paediatric patients with proven or suspected invasive candidiasis and showed that echinocandins produced a similar clinical response to amphotericin B. Similar findings were also noted in other comparisons, such as mycological response, mortality and recurrence of candida infection. In addition, these results were not affected by different forms of echinocandin (micafungin or caspofungin), different risk groups (high-risk, low-risk, or neutropenic groups), and different usage of echinocandins (targeted treatment or empirical use). These findings are consistent with a recent meta-analysis by Tsekoura et al [21] of four RCTs with 324 children in which there were no significant differences in treatment success between echinocandins and amphotericin B (OR=1.61, 95% CI 0.74-3.50). However, in contrast to the analysis by Tsekoura et al [21], the present meta-analysis extracted more clinical and mycological outcomes from more subgroup analyses. Overall, this meta-analysis confirmed that the role of echinocandins in the treatment of invasive candidiasis in paediatric patients is comparable with that of amphotericin B.

In addition to the assessment of clinical efficacy, safety issues are another important concern in the treatment of invasive candidiasis. In this meta-analysis, lower risk of adverse effects, including total adverse effects, fever, hypokalaemia, vomiting and infusion-related events, was observed for echinocandins compared with amphotericin B; however, these differences did not reach statistical significance because of the limited number of cases. However, echinocandins were associated with a significantly lower risk of discontinuing drug treatment because of adverse effects than amphotericin B (OR, 0.30, 95% CI, 0.12-0.76). All these findings indicate that echinocandins may be a safer option than amphotericin B in treatment of invasive candidiasis in paediatric patients.

In this analysis, *C. parapsilosis* was the second most common pathogen, which is consistent with previous studies [1,2,4]. This finding indicates that *C. parapsilosis* is an important pathogen in paediatric patients. However, the in vitro efficacy of all the echinocandins against *C. parapsilosis* has been shown to be low [22]. Even in a clinical study of adult patients with a *C. parapsilosis* bloodstream infection, the survival rate of patients receiving echinocandins was lower than that of patients receiving fluconazole [23]. Therefore, it is possible that the efficacy of echinocandins in this analysis of many *C. parapsilosis* cases could be affected. Further study is warranted to clarify this issue.

This meta-analysis has several limitations. First, the differences in study subjects, disease severity, setting, candida species, and

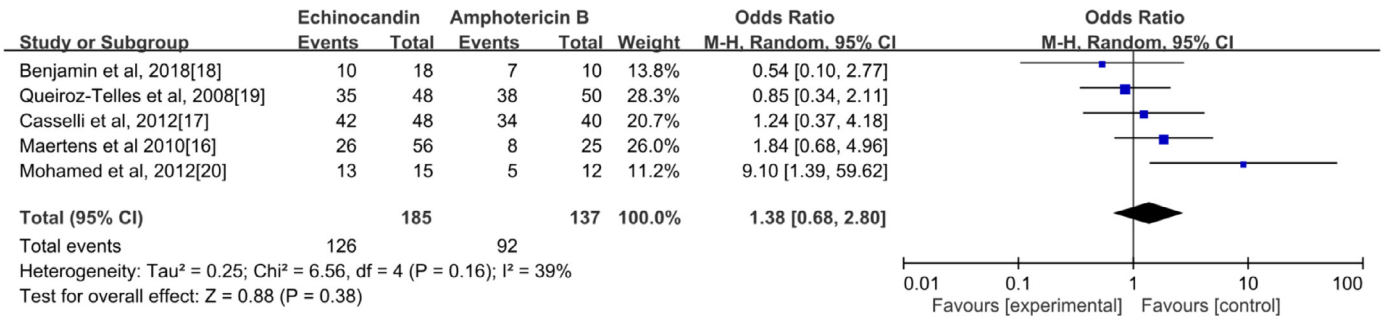

Fig. 4. The overall clinical response rate between the echinocandins group and the amphotericin B group in the treatment of invasive candidiasis in paediatric patients.

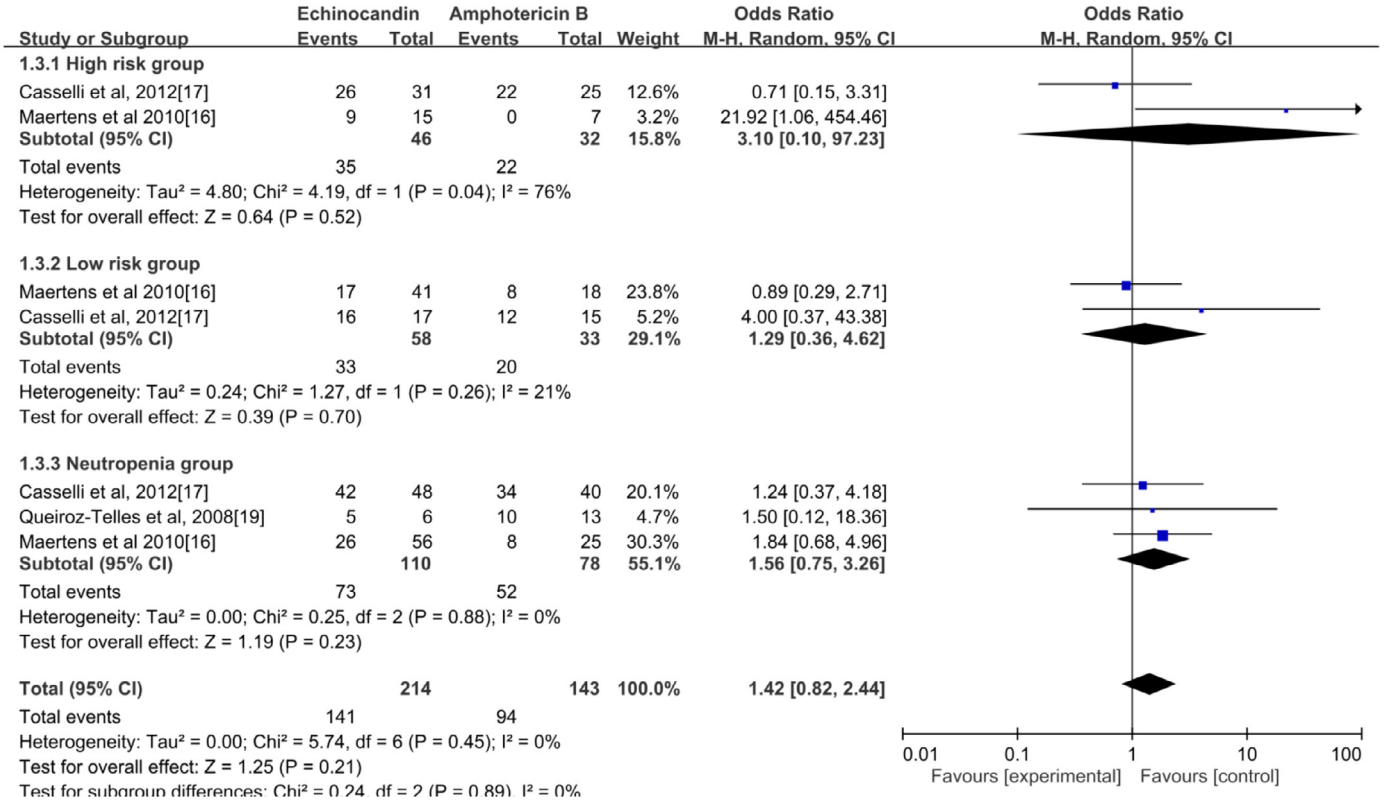

Fig. 5. Subgroup analysis of the clinical response rate between the echinocandins group and the amphotericin B group in the treatment of invasive candidiasis in paediatric patients.

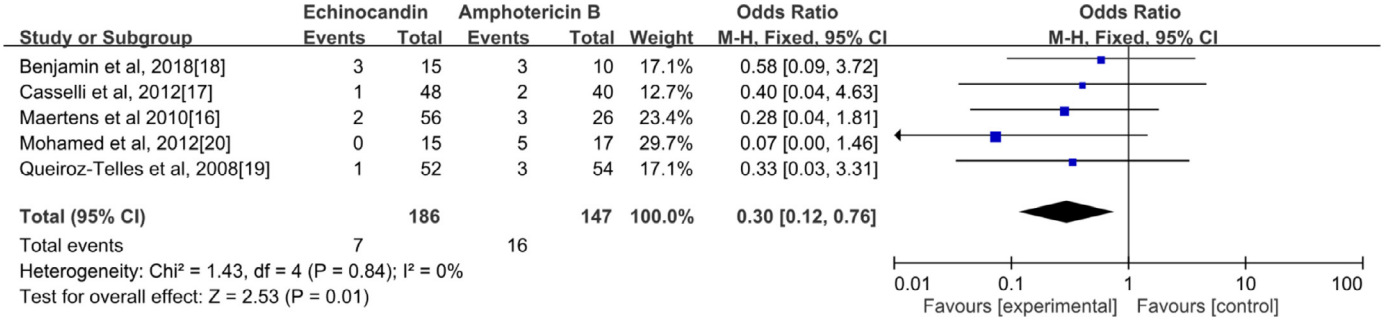

Fig. 6. The risk of discontinuation of drug treatment due to adverse effects between the echinocandins group and the amphotericin B group in the treatment of invasive candidiasis in paediatric patients.

type of infections between individual studies made the study population heterogeneous. Second, the numbers of included RCTs and study subjects were limited. Further large-scale studies are warranted. Third, all the enrolled studies in this meta-analysis did not report the antifungal susceptibility of candida. Thus, we cannot evaluate the association between in vitro activity and in vivo response.

In conclusion, based on the analysis of five RCTs, there were no differences in efficacy between echinocandins and amphotericin B in the treatment of invasive candidiasis in paediatric patients. However, the echinocandins group had a significantly lower risk of treatment discontinuation because of adverse effects than the amphotericin B group.

Declarations

Funding

No funding

Competing Interests

None

Ethical Approval

Not required

Appendix 1. List of Terms of the Search Strategy

PubMed

1 “echinocandins” [24]
2 “echinocandins” [All Fields]
3 “caspofungin” [All Fields]
4 “micafungin” [All Fields]
5 1 OR 2 OR 3 OR 4
6 “amphotericin b”
7 “amphotericin b” [All Fields]

8 “liposomal amphotericin B” [All Fields]
9 “liposomal amphotericin B“
10 6 OR 7 OR 8 OR 9
11 “neonates” [All Fields]
12 “newborn” [All Fields]
13 “infant” [All Fields]
14 “child” [All Fields]
15 “adolescent” [All Fields]
16 11 OR 12 OR 13 OR 14 OR 15
17 “randomized” [All Fields]
18 “randomised” [All Fields]
19 17 OR 18
20 5 AND 10 AND 19

Embase

1 “echinocandins”
2 “caspofungin”
3 “micafungin”
4 1 OR 2 OR 3
5 “amphotericin b”
6 “liposomal amphotericin B”
7 5 OR 6
8 “neonates”
9 “newborn”
10 “infant”
11 “child”
12 “adolescent”
13 8 OR 9 OR 10 OR 11 OR 12
14 4 AND 7 AND 13

Cochrane

1 “echinocandins”
2 “caspofungin”
3 “micafungin”
4 1 OR 2 OR 3
5 “amphotericin b”
6 “liposomal amphotericin B”
7 5 OR 6
8 “neonates”
9 “newborn”
10 “infant”
11 “child”
12 “adolescent”
13 8 OR 9 OR 10 OR 11 OR 12
14 4 AND7 AND 13

References

[1] Steinbach WJ. Pediatric invasive candidiasis: epidemiology and diagnosis in children. J Fungi (Basel) 2016;2.
[2] King J, Pana ZD, Lehrnbecher T, Steinbach WJ, Warris A. Recognition and clinical presentation of invasive fungal disease in neonates and children. J Pediatric Infect Dis Soc 2017;6:S12–21.
[3] Warris A. The European Paediatric Mycology Network (EPMyN): Towards a better understanding and management of fungal infections in children. Curr Fungal Infect Rep 2016;10:7–9.
[4] Zaoutis TE, Argon J, Chu J, Berlin JA, Walsh TJ, Feudtner C. The epidemiology and attributable outcomes of candidemia in adults and children hospitalized in the United States: a propensity analysis. Clin Infect Dis 2005;41:1232–9.
[5] Zaoutis TE, Prasad PA, Localio AR, Coffin SE, Bell LM, Walsh TJ, et al. Risk factors and predictors for candidemia in pediatric intensive care unit patients: implications for prevention. Clin Infect Dis 2010;51:e38–45.
[6] Cornely OA, Bassetti M, Calandra T, Garbino J, Kullberg BJ, Lortholary O, et al. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. Clin Microbiol Infect 2012;18(Suppl 7):19–37.
[7] Bassetti M, Marchetti M, Chakrabarti A, Colizza S, Garnacho-Montero J, Kett DH, et al. A research agenda on the management of intra-abdominal candidiasis: results from a consensus of multinational experts. Intensive Care Med 2013;39:2092–106.
[8] Scudeller L, Viscoli C, Menichetti F, del Bono V, Cristini F, Tascini C, et al. An Italian consensus for invasive candidiasis management (ITALIC). Infection 2014;42:263–79.
[9] Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 2016;62:e1–50.
[10] Kung HC, Huang PY, Chen WT, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. 2016 guidelines for the use of antifungal agents in patients with invasive fungal diseases in Taiwan. J Microbiol Immunol Infect 2018;51:1–17.
[11] Viscoli C, Bassetti M, Castagnola E, Cesaro S, Menichetti F, Ratto S, et al. Micafungin for the treatment of proven and suspected invasive candidiasis in children and adults: findings from a multicenter prospective observational study. BMC Infect Dis 2014;14:725.
[12] Kobayashi C, Hanadate T, Niwa T, Yoshiyasu T, So M, Matsui K. Safety and effectiveness of micafungin in Japanese pediatric patients: results of a postmarketing surveillance study. J Pediatr Hematol Oncol 2015;37:e285–91.
[13] Mori M, Imaizumi M, Ishiwada N, Kaneko T, Goto H, Kato K, et al. Pharmacokinetics, efficacy, and safety of caspofungin in Japanese pediatric patients with invasive candidiasis and invasive aspergillosis. J Infect Chemother 2015;21:421–6.
[14] Zaoutis TE, Jafri HS, Huang LM, Locatelli F, Barzilai A, Ebell W, et al. A prospective, multicenter study of caspofungin for the treatment of documented candida or aspergillus infections in pediatric patients. Pediatrics 2009;123:877–84.
[15] Higgins JP, Altman DG, Gotzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
[16] Maertens JA, Madero L, Reilly AF, Lehrnbecher T, Groll AH, Jafri HS, et al. A randomized, double-blind, multicenter study of caspofungin versus liposomal amphotericin B for empiric antifungal therapy in pediatric patients with persistent fever and neutropenia. Pediatr Infect Dis J 2010;29:415–20.
[17] Caselli D, Cesaro S, Ziino O, Ragusa P, Pontillo A, Pegoraro A, et al. A prospective, randomized study of empirical antifungal therapy for the treatment of chemotherapy-induced febrile neutropenia in children. Br J Haematol 2012;158:249–55.
[18] Benjamin DK Jr, Kaufman DA, Hope WW, Smith PB, Arrieta A, Manzoni P, et al. A phase 3 study of micafungin versus amphotericin B deoxycholate in infants with invasive candidiasis. Pediatr Infect Dis J 2018;37:992–8.
[19] Queiroz-Telles F, Berezin E, Leverger G, Freire A, van der Vyver A, Chotpitayasunondh T, et al. Micafungin versus liposomal amphotericin B for pediatric patients with invasive candidiasis: substudy of a randomized double-blind trial. Pediatr Infect Dis J 2008;27:820–6.
[20] Mohamed WA, Ismail M. A randomized, double-blind, prospective study of caspofungin vs. amphotericin B for the treatment of invasive candidiasis in newborn infants. J Trop Pediatr 2012;58:25–30.
[21] Tsekoura M, Ioannidou M, Pana ZD, Haidich AB, Antachopoulos C, Iosifidis E, et al. Efficacy and safety of echinocandins for the treatment of invasive candidiasis in children: A meta-analysis. Pediatr Infect Dis J 2019;38:42–9.
[22] Xu G, Zhu L, Liao S, Ge T, Yang J. Assessment of echinocandin regimens by pharmacokinetic/pharmacodynamic analysis against Candida spp. in paediatric patients. Int J Antimicrob Agents 2015;46:631–41.
[23] Lin CC, Liu CP, Hsieh FC, Lee CM, Wang WS. Antimicrobial susceptibility and clinical outcomes of Candida parapsilosis bloodstream infections in a tertiary teaching hospital in Northern Taiwan. J Microbiol Immunol Infect 2015;48:552–8.