REVIEW ARTICLE

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Breakthrough invasive fungal infections in liver transplant recipients exposed to prophylaxis with echinocandins vs other antifungal agents: A systematic review and meta-analysis

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Abstract

Introduction: Although echinocandins are recommended as first-line prophylaxis for high-risk orthotopic liver transplant (OLT) recipients, occurrence of breakthrough-invasive fungal infections (IFIs) remains a serious concern. We aim to assess the risk of breakthrough IFIs among OLT recipients exposed to prophylaxis with echinocandins compared to other antifungals.

Materials and methods: Two authors independently searched PubMed-MEDLINE, Embase, study registries and reference lists from inception to March 2021, to retrieve randomised controlled trials (RCTs) or observational studies comparing efficacy and safety of echinocandins vs other antifungals for prophylaxis in OLT recipients. Data were independently extracted from two authors, and the quality of included studies was independently assessed according to ROB 2.0 tool for RCTs and ROBINS-I tool for observational studies. The primary outcome was occurrence of breakthrough IFI at the end of prophylaxis (EOP).

Results: 698 articles were screened, and ten studies (3 RCTs and 7 observational) were included. No difference between echinocandins and other antifungals in terms of breakthrough IFIs at the EOP emerged both from RCTs (odds ratio [OR] 0.85, 95% CI 0.24–2.99) and observational studies (OR 1.43, 95% CI 0.28–7.40). No difference emerged also for secondary outcomes. In the subgroup comparison between echino-candins and polyenes, a trend for higher risk of breakthrough IFI at the EOP (OR 4.82, 95% CI 0.97–24.03) was noted.

Conclusions: Echinocandins do not seem to be associated with increased risk of breakthrough IFIs in OLT recipients. However, the large diversity in the comparator group hinders a definitive interpretation. Further studies exploring the relationship between echinocandin use and breakthrough IFIs according to specific comparators are warranted.

1 | INTRODUCTION

Invasive fungal infections (IFI) are burdened by high morbidity and mortality rates among orthotopic liver transplant (OLT) recipients, even if their incidence was shown to be decreased over the last two decades.[1]

International guidelines recommend the application of antifungal prophylaxis only as targeted (TAP) when in presence of specific risk factors rather than universally.[2,3] However, since the incidence of breakthrough IFI in OLT recipients receiving TAP is quite remarkable, which antifungal agent could be the most suitable for TAP is still a matter of debate.[4] Previous meta-analysis and randomised controlled trials (RCTs) did not report differences in terms of efficacy and safety between fluconazole, amphotericin B and echinocandins in OLT recipients.[5–7] Conversely, real-world data showed that in patients receiving echinocandins as TAP there was a trend towards higher risk of breakthrough IFI,[8] as previously reported in haematological setting as well.[9,10]

In high-risk OLT recipients, TAP is more widely based on echinocandins rather than on azoles and polyenes, thanks to reduced risk of clinically relevant drug–drug interactions with immunosuppressive agents and low toxicity risk.[11] However, various concerns about echinocandins emerged in terms of optimal peritoneal penetration and/or development of resistance (especially with *Candida glabrata*).[11–13]

The aim of this study was to conduct a systematic review with meta-analysis in order to assess the risk of breakthrough IFI in OLT recipients who received TAP with echinocandins compared to other antifungal agents.

2 | MATERIALS AND METHODS

A systematic review and meta-analysis investigating the risk of breakthrough IFI in OLT recipients managed with echinocandins as antifungal prophylaxis compared to other antifungal agents were performed. The meta-analysis is registered in the PROSPERO database, number CRD42020199132, and was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines.[14]

2.1 | Literature search

Two authors (MiGa and MR) independently searched PubMed-MEDLINE and Embase, from inception to 31 March 2021. The following search string was developed ('liver transplant' OR 'liver transplantation' OR 'orthotopic liver transplant' OR 'orthotopic liver transplantation') AND ('antifungal prophylaxis' OR 'targeted prophylaxis' OR 'echinocandin' OR 'echinocandins' OR 'anidulafungin' OR 'micafungin' OR 'caspofungin'). Reference lists of included studies were screened to identify any potentially relevant article. The ClinicalTrials.gov website of the US National Library of Medicine (http://clinicaltrials.gov; search performed on 31 March 2021) was also searched for completed and ongoing trials.

2.2 | Study selection

Randomised controlled trials or prospective/retrospective observational studies investigating the comparative efficacy and safety of echinocandins vs other antifungal agents (azoles or polyenes) as prophylaxis in OLT recipients were included. Studies were excluded if echinocandins were not administered in one of the two arms, no comparator group was provided, or quantitative target outcome results were lacking. Additionally, conference abstracts or studies published in languages other than English were also not eligible.

Primary outcome was the rate of breakthrough IFI at the end of prophylaxis (EOP) in each of the two groups (intervention and comparator). Breakthrough IFI was defined by the first sign, symptom or findings of IFI that occurs during antifungal prophylaxis according to the latest definitions stated by Mycoses Study Group Education and Research Consortium and the European Confederation of Medical Mycology.[15]

Secondary outcomes included rate of IFI defined according to the EORTC criteria[16] at the end of study (EOS), breakthrough IFI caused by *Candida* spp. at EOP, breakthrough IFI caused by mould at EOP, mortality rate at EOP and EOS, overall adverse events (AEs).

Two authors (MiGa and MR) independently screened titles and abstracts for potential relevance and assessed eligibility of relevant full texts. Discrepancies were resolved by a third author (MaGi).

2.3 | Data extraction

Two authors (MiGa and MR) independently extracted data in a prespecified form. The following data were extracted for each included study: (a) study author and year of publication, as well as the country in which the study was conducted; (b) study characteristics including study design, time period, sample size, exclusion criteria and funding; (c) features of the patients including age, sex, underlying liver diseases, Model for End-Stage Liver Disease [MELD] at transplantation, CMV mismatch, risk factors for IFI; (d) characteristics of the treatment including dosage of echinocandins and duration; (e) characteristics of the control group including dosage of azoles or polyenes and duration; (f) types of outcome measurements.

Corresponding authors of publications that reported unclear data that may lead to misinterpretations were contacted by email for clarification and/or for requesting supplemental information of the included studies.

2.4 | Risk of bias assessment

Two authors (MiGa and MR) independently assessed the risk of bias of the included studies. The Cochrane Risk of Bias Tool (RoB 2.0)[17] and the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I)[18] were used to assess the risk of bias in RCTs and observational studies, respectively. Any disagreement was resolved by means of discussion or consultation with a third reviewer (MaGi).

2.5 | Data analysis

Data retrieved from RCTs and observational studies were analysed separately. In regard to RCTs, when outcome data were provided for both the intention-to-treat (ITT) and the per-protocol populations were taken into consideration. Quantitative analysis of research question was implemented by combining efficacy estimates on the selected outcome for each intervention against any comparator.

For both RCTs and observational studies, treatment effects were calculated as odds ratio (OR), with 95% confidence interval (CI) for dichotomous data, using a fixed- or random effects model according to heterogeneity among studies. Statistical heterogeneity among studies was assessed by χ^2 test ($p < .10$ indicated significant heterogeneity) and I^2 (degree of heterogeneity). An I^2 of >50% was considered indicative of statistically significant heterogeneity. If heterogeneity was <50%, results were quantitatively synthesised by means of fixed-effect meta-analysis, if between 50% and 75% by random effects meta-analysis, if >75% no quantitative synthesis was performed. Subgroup analysis was prespecified according to the comparator agent (azoles or polyenes). Sensitivity analyses

were also conducted by excluding each study and according to the risk of bias in order to investigate the confidence of the outcomes. Publication bias was assessed by visual inspection of the funnel plot and Egger's test.[19]

Statistical analysis was performed using ProMeta for Windows (ProMeta software version 3.0, Internovi).

3 | RESULTS

Electronic and manual search identified 698 potential studies, and among these 150 were removed as being duplicates. After initial screening of titles and abstracts, 533 studies were excluded, and two additional records were identified through search on *ClinicalTrials. gov*. Overall, 17 full-text articles were assessed for eligibility, and finally, ten studies met the inclusion criteria. Seven studies were excluded according to the following criteria: abstract conference (4 studies); lack of comparator group (2 studies); no available results (one study; Figure 1).

3.1 | Characteristics of the included studies

Features of the ten included studies are shown in Table 1. Overall, 1725 enrolled patients were included. Three RCTs[6,7,20] and seven observational studies (two prospective and five retrospective) were included.[8,21–26] Half of the studies were multicentric. Among the 10 included studies, five were conducted in USA, four in Europe and one in Asia. Mean or median patient age ranged from 50.5 to 60 years, with male preponderance (from 55.6% to 92.9%). Mean or median MELD at time of transplantation was above 25 in half of studies. Viral hepatitis, mostly due to HCV, represented the most frequent underlying disease responsible for liver transplant in eight out of ten studies.

Micafungin, caspofungin and anidulafungin were investigated in five, four, and three studies, respectively (in two studies different echinocandins were allowed for prophylactic use[8,21]). Comparators were fluconazole in four studies fluconazole or amphotericin B in

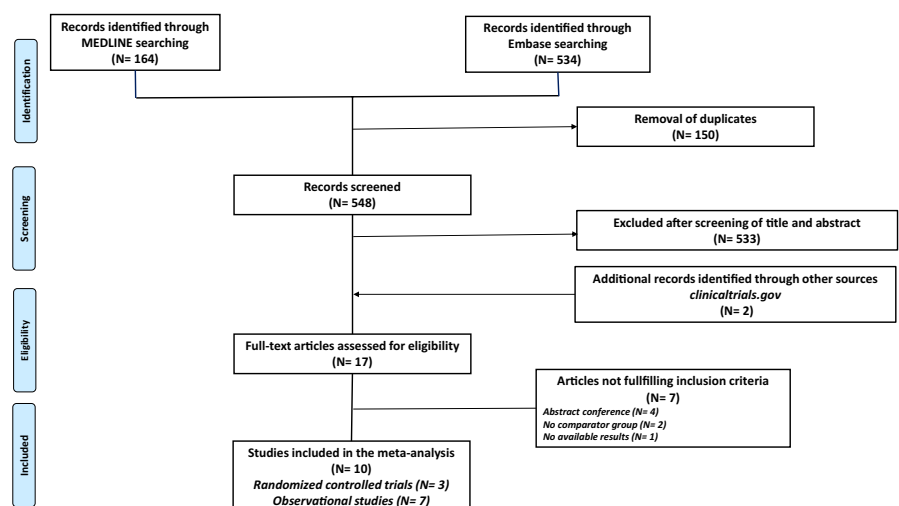**FIGURE 1** PRISMA flow diagram for study selection

TABLE 1 Main features of included studies

Study reference	Stud design	Country	Time period	No. of enrolled patients	Age/sex	Liver disease	MELD
Saliba et al., 2015	RCT, open-label, multicentric, non-inferiority	Europe	2009–2012	344	51.9 ± 10.5 vs 50.5 ± 11.8 Male 67.4%	Cirrhosis 67.5% HCC 16.2%	19.9 ± 10 vs 21.1 ± 10
Kang et al., 2020	RCT, open-label, multicentric	South Korea	2012–2015	172	54.2 ± 8.0 Male 76.2%	NA	16.5 ± 5.3
Winston et al., 2014	RCT, double-blind, multicentric	USA	2010–2011	200	58 (27–74) vs 58 (19–75) Male 69.5%	HCV 44% Alcoholic cirrhosis 35.5% HCC 20.5%	NA
Sun et al., 2013	Retrospective cohort observational, monocentric	USA	1997–2009	42	60 (56–61) vs 54 (49–57) Male 92.9%	HCV 64.3% Alcoholic cirrhosis 38.1% HCC 21.4%	29.5 (22–40) vs 29 (22-40)
Amin et al., 2020	Retrospective cohort observational, monocentric	USA	2010–2015	27	56 (33–68) Male 55.6%	HCV 44.4% Alcoholic cirrhosis 11.1% HCC 7.4%	39 (20–46)
Doria et al., 2011	Retrospective cohort observational, monocentric	USA	2003–2007	82	55 (27–72) Male 68.3%	Viral hepatitis 64.6% Alcoholic cirrhosis 28.0% HCC 14.6%	26
Fortun et al., 2016	Retrospective cohort observational, multicentric	Spain	2005–2012	195	55 (19–75) vs 58 (20–74) Male 73.3%	HCV 47.2% Alcoholic cirrhosis 33.8% HCC 21.5%	>25 (52.8%)
Perrella et al., 2015	Prospective observational, monocentric	Italy	2006–2012	54	55 ± 3 vs 58 ± 4 Male 64.8%	Viral hepatitis 79.6% HCC 29.6%	23 vs 21
Neyra et al., 2019	Retrospective cohort observational, monocentric	USA	2010–2014	124	56 ± 11 Male 68.0%	HCV 31.8% Alcoholic cirrhosis 19.3% HCC 28.1%	25 ± 7
Rinaldi et al., 2021	Prospective observational, multicentric	Italy	2015–2018	485	56 (49–61) Male 73%	Viral hepatitis 49.5% HCC 47.4% Alcoholic cirrhosis 24.7%	17 (12–25)

Abbreviations: ABLC, amphotericin B lipidic complex; d-AmB, amphotericin B deoxycholate; HCC, hepatocellular carcinoma; L-AmB, liposomal amphotericin B; LD, loading dose; MD, maintenance dose; NA, not available; RCT, randomised controlled trial.

three studies, voriconazole, liposomal amphotericin B (L-AmB, and amphotericin B lipidic complex (ABLC) in one study each. Mean or median duration of antifungal prophylaxis ranged from 12 to 22 days and from 12 to 27 days for intervention and comparator group, respectively.

3.2 | Outcome assessment

A summary of the results of meta-analysis for primary and secondary outcomes for RCTs and observational studies is shown in Tables 2 and 3, respectively.

3.3 | Breakthrough IFI at EOP

A total of eight studies (three RCTs and five observational studies; 1255 patients) provided data for breakthrough IFI at EOP.[6–8,20,23–26] Overall, antifungal prophylaxis with echinocandins was not associated with higher risk of breakthrough IFI compared to other antifungal agents in RCTs (OR 0.85; 95% CI 0.24–2.99; Figure 2). Heterogeneity was not observed ($p = .37, I^2 = 0.56\%$). The funnel plot and Egger's test ($p = .17$; Table 2) showed no evidence of publication bias. Similarly, no association with higher risk of breakthrough IFI was found with echinocandins compared to other antifungal agents in observational studies, as well (OR 1.43; 95% CI 0.28–7.40; Figure 3).

Intervention group				Comparator group			
Agent	No. patients	Dose	Duration (days)	Agent	No. patients	Dose	Duration (days)
Micafungin	172	100 mg/day	16.7 ± 7.0	Fluconazole or L-AmB or Caspofungin	172	200–400 mg/day 1–3 mg/kg/day 70 mg LD 50 mg MD	17.1 ± 8.0
Micafungin	86	100 mg/day	20	Fluconazole	86	100–200 mg/day	21
Anidulafungin	100	200 mg LD 100 mg LD	21 (5–46)	Fluconazole	100	400 mg/day	21 (5–43)
Micafungin	18	100 mg/day	20 (12–32)	ABLC	24	5 mg/kg/day	27 (16–47)
Caspofungin or Anidulafungin	5	NA	NA	Voriconazole	22	NA	NA
Caspofungin	16	70 mg LD 50 mg MD	NA	Fluconazole or d-AmB	62	NA	NA
Caspofungin	97	70 mg LD 50 mg MD	22 (14–26)	Fluconazole	98	200 mg/day (100–400)	24 (17–28)
Caspofungin	26	70 mg LD 50 mg MD	NA	L-AmB	28	3 mg/kg/day	NA
Micafungin	33	NA	12	Fluconazole	91	NA	12
Caspofungin or Micafungin or Anidulafungin	110	70 mg LD 50 mg MD 100 mg/day 100 mg/day	13 (7–20) overall	Fluconazole or L-AmB	22 88	400 mg/day 3 mg/kg/day or 10 mg/kg/week	13 (7–20) overall

Substantial heterogeneity was observed ($p = .07$, $I^2 = 53.73\%$). The funnel plot and Egger's test ($p = .72$; Table 3) showed no evidence of publication bias.

3.4 | Secondary outcomes

In RCTs, echinocandins were not associated with increased risk of IFI at EOS (OR 0.84; 95% CI 0.41–1.70), with higher occurrence of breakthrough IFI caused by mould (OR 0.62; 95% CI 0.12–3.25) or *Candida* spp. (OR 0.62; 95% CI 0.20–1.92), with higher mortality rate at EOP (OR 1.31; 95% CI 0.64–2.69) or EOS (OR 1.20; 95%

CI 0.74–1.96), and with higher occurrence of AEs (OR 0.75; 95% CI 0.46–1.22). For each outcome, heterogeneity was not observed, and the funnel plot and Egger's test showed no evidence of publication bias (Table 2).

In observational studies, echinocandins were not associated with increased risk of IFI at EOS (OR 0.53; 95% CI 0.23–1.22), with higher occurrence of breakthrough IFI caused by mould (OR 0.94; 95% CI 0.30–2.92) or *Candida* spp. (OR 1.24; 95% CI 0.44–3.48), and with higher mortality rate at EOS (OR 1.24; 95% CI 0.69–2.24). For each outcome, heterogeneity was not observed, and the funnel plot and Egger's test showed no evidence of publication bias (Table 3).

TABLE 2 Results of meta-analysis for primary and secondary outcomes in randomised controlled trials

Outcome	Studies	No. of patients (Echinocandins vs comparators)	No. of events in intervention group	No. of events in comparator group	Odds ratio (95% CI)	Heterogeneity (I²; p value)	Publication bias (p value Egger's test)
Primary outcome							
Breakthrough IFI at EOP	3	620 (307 vs 313)	5/307 (1.6%)	6/313 (1.9%)	0.85 (0.24–2.99) p = .80	0.56%; p = .37	p = .17
Secondary outcome							
IFI at EOS	3	687 (339 vs 348)	15/339 (4.4%)	18/348 (5.2%)	0.84 (0.41–1.70) p = .62	0.0%; p = .79	p = .94
Breakthrough IFI caused by mould	2	541 (270 vs 271)	2/270 (0.7%)	4/271 (1.5%)	0.62 (0.12–3.25) p = .57	0.0%; p = .38	Not applicable
Breakthrough IFI caused by Candida spp.	2	541 (270 vs 271)	5/270 (1.9%)	8/271 (3.0%)	0.62 (0.20–1.92) p = .41	0.0%; p = .92	Not applicable
Mortality at EOP	2	544 (272 vs 272)	18/272 (6.6%)	14/272 (5.1%)	1.31 (0.64–2.69) p = .47	0.0%; p = .97	Not applicable
Mortality at EOS	2	544 (272 vs 272)	41/272 (15.1%)	35/272 (12.9%)	1.20 (0.74–1.96) p = .46	0.0%; p = .61	Not applicable
Overall AEs	2	516 (257 vs 259)	90/257 (35.0%)	101/259 (39.0%)	0.75 (0.46–1.22) p = .25	0.0%; p = .59	Not applicable

Abbreviations: AEs, adverse events; CI, confidence interval; EOP, end of prophylaxis; EOT, end of study; IFI, invasive fungal infections.

TABLE 3 Results of meta-analysis for primary and secondary outcomes in observational studies

Outcome	Studies	No. of patients (Echinocandins vs comparators)	No. of events in intervention group	No. of events in comparator group	Odds ratio (95% CI)	Heterogeneity (I²; p value)	Publication bias (p value Egger's test)
Primary outcome							
Breakthrough IFI at EOP	5	635 (284 vs 351)	12/284 (4.2%)	11/351 (3.1%)	1.43 (0.28–7.40) p = .67	53.73%; p = .07	p = .72
Secondary outcome							
IFI at EOS	6	490 (195 vs 295)	7/195 (3.6%)	21/295 (7.1%)	0.53 (0.23–1.22) p = .14	0.0%; p = .82	p = .34
Breakthrough IFI caused by mould	5	635 (284 vs 351)	6/284 (2.1%)	7/351 (2.0%)	0.94 (0.30–2.92) p = .91	0.00%; p = .45	p = .39
Breakthrough IFI caused by Candida spp.	5	635 (284 vs 351)	9/284 (3.2%)	7/351 (2.0%)	1.24 (0.44–3.48) p = .69	0.92%; p = .40	p = .29
Mortality at EOP	0	–	–	–	–	–	–
Mortality at EOS	3	319 (131 vs 188)	29/131 (22.1%)	34/188 (18.1%)	1.24 (0.69–2.24) p = .48	0.0%; p = .46	p = .11
Overall AEs	1	82 (16 vs 66)	13/16 (81.3%)	33/66 (50.0%)	4.33 (1.13–16.63) p = .03	Not applicable	Not applicable

Abbreviations: AEs, adverse events; CI, confidence interval; EOP, end of prophylaxis; EOT, end of study; IFI, invasive fungal infections.
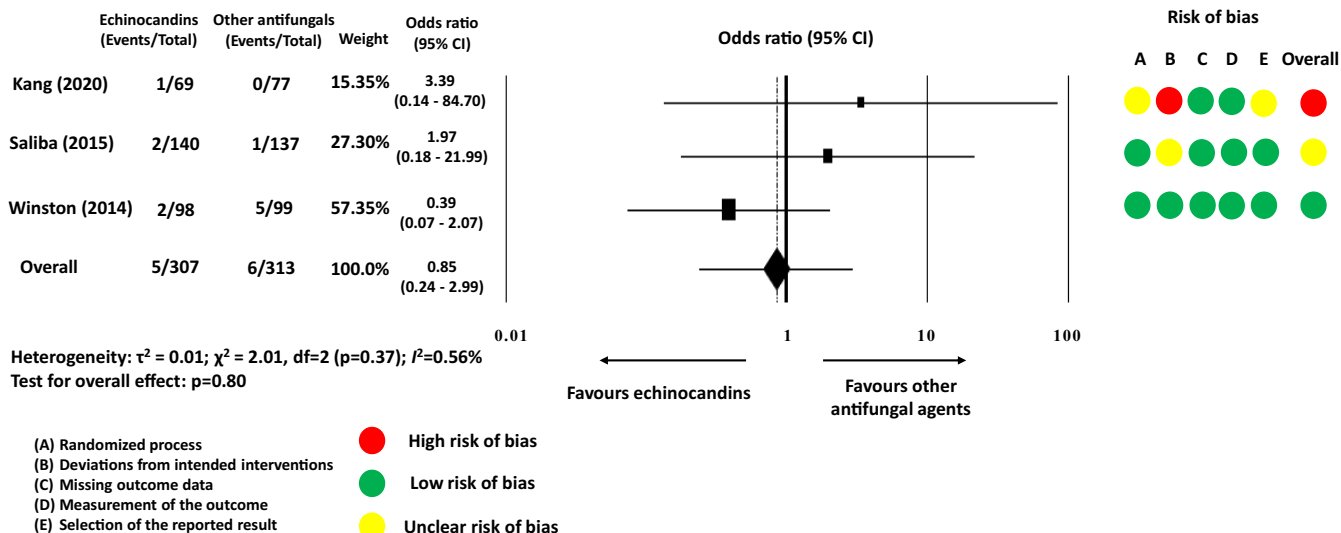
FIGURE 2 Forest plot of breakthrough IFI among OLT recipients receiving antifungal prophylaxis with echinocandins compared to other agents in randomised controlled trials
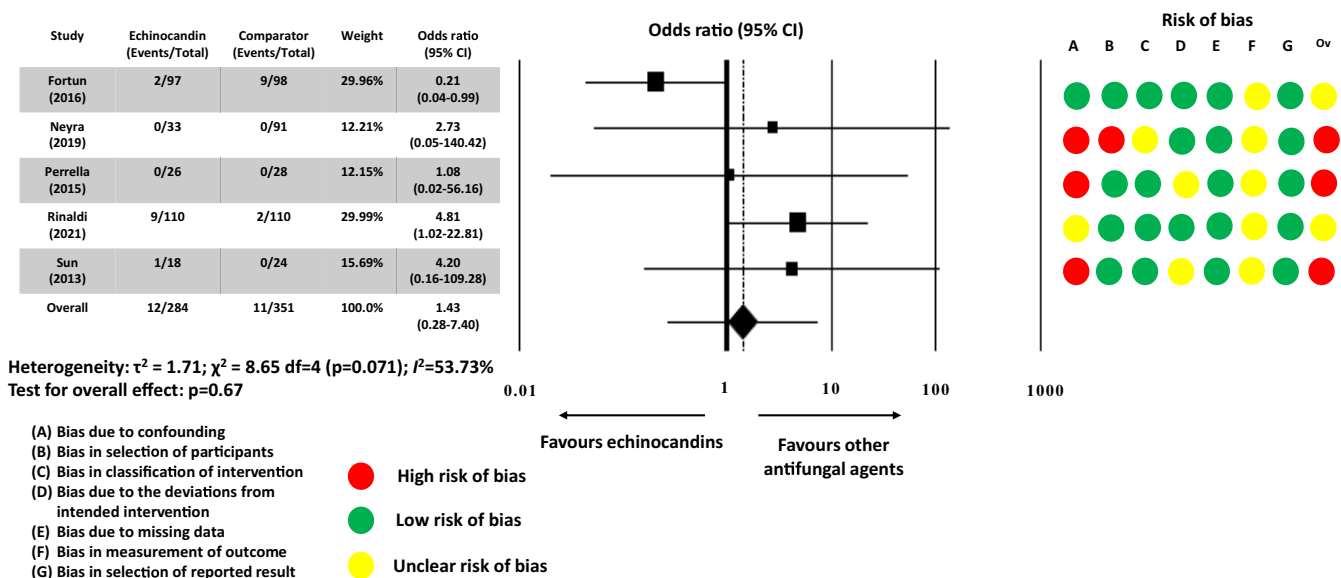

FIGURE 3 Forest plot of breakthrough IFI among OLT recipients receiving antifungal prophylaxis with echinocandins compared to other agents in observational studies

3.5 | Subgroup and sensitivity analysis

In RCTs, echinocandins were not associated with higher risk of breakthrough IFI at EOP or IFI at EOS compared to azoles. Assessment of other secondary outcomes was not performed due to lack of available data. Furthermore, comparison with polyenes was unfeasible as amphotericin B was administered as comparator in only one study (Table S1). In sensitivity analysis, after exclusion of each study, no significant association emerged for primary and secondary outcomes. Similarly, no significant association was found after exclusion of studies with high risk of bias (Table S1).

In observational studies, a trend towards higher risk of breakthrough IFI at EOP (OR 4.82, 95% CI 0.97–24.03; $p = .055$) with echinocandins compared to amphotericin B was noted. No significant association emerged in comparison with azoles (Table S2). In sensitivity analysis, after exclusion of the study performed by Fortún et al.,[23] a higher risk of breakthrough IFI at EOP (OR 3.83, 95% CI 1.09–13.43; $p = .036$) and a trend towards higher occurrence of breakthrough IFI caused by *Candida* spp. (OR 3.58, 95% CI 0.79–16.28; $p = .10$) were reported with echinocandins. No significant association was found after exclusion of studies with high risk of bias (Table S2).

3.6 | Quality of the included studies

Among RCTs, only in one study a high risk of bias in at least one domain was found (Table S3). Among observational studies, five out of the seven included articles showed serious risk of bias in at least one domain, and bias due to confounding was the most reported one. Consequently, only two studies were classified as being at moderate risk of bias (Table S4).

4 | DISCUSSION

Our meta-analysis found that echinocandins were not significantly associated with a higher risk of breakthrough IFI in OLT recipients compared to other antifungal agents, even if the large diversity in the comparator group hinders a definitive interpretation. A trend towards higher risk of breakthrough IFI with echinocandins compared to polyenes (L-AmB and ABLC) was found in subgroup analysis of observational studies. This emphasises the importance that selecting appropriate comparators may have in order to provide an accurate interpretation of retrieved findings.

In this regard, fluconazole, alone or in alternative to amphotericin B, was selected as comparator agent in most of the included studies. However, several concerns may arise with the administration of fluconazole as TAP in high-risk OLT recipients. Fluconazole is characterised by lack of activity against mould and some *Candida* spp. (namely *Candida glabrata* and *Candida krusei*).[11] Furthermore, major concerns may arise in OLT recipients affected by acute or chronic renal impairment and/or because of drug-drug interactions with immunosuppressive agents (namely calcineurin- and mTOR inhibitors).[11] Consequently, fluconazole could not represent the best comparator antifungal agent to investigate the risk of breakthrough IFI with echinocandins,[27] also considering that previous universal antifungal prophylaxis approach in OLT recipients led to a dramatic shift towards non-*albicans Candida* spp.[28–30]

Amphotericin B, by virtue of the broad spectrum of activity including non-*albicans Candida* spp. and *Aspergillus* spp., and the low risk of perpetrating clinically relevant drug interactions with immunosuppressive agents,[11] could represent a more appropriate comparator choice. High-dose weekly L-AmB was reported as an effective and safe prophylactic strategy in high-risk OLT recipients.[31] Notably, Rinaldi et al.[8] reported a trend towards higher rate of breakthrough IFI in OLT patients receiving antifungal prophylaxis with echinocandins. Similarly, a greater incidence of breakthrough IFI (5.9% vs 0.0%) with micafungin compared to ABLC was reported by Sun et al.[26] Although the overall risk of breakthrough IFI with echinocandins was not increased in our meta-analysis, the trend for higher risk of breakthrough IFI reported in subgroup analysis could reflect a suboptimal efficacy of echinocandins in OLT setting when appropriate comparators are selected.

In this regard, our sensitivity analysis found a significantly higher risk of breakthrough IFI with echinocandins after the exclusion of the study by Fortún et al.,[23] in which the proportion of breakthrough IFI with fluconazole was higher compared to caspofungin (9.2% vs 2.1%), especially in OLT recipients requiring renal replacement therapy (RRT). High variability in fluconazole exposure was reported among critically ill patients, with suboptimal concentrations in up to 33% of cases.[32,33] Furthermore, fluconazole dosage of 400 mg and 600–800 mg daily are required to achieve optimal concentrations in critically ill patients with poor/moderate renal function or receiving RRT, respectively.[34,35] Notably, fluconazole dosage in the study by Fortún et al.[23] ranged from 100 to 400 mg/day; thus, it is likely that implemented dosing regimen was inadequate for maximising fluconazole pharmacokinetic/pharmacodynamic (PK/PD) target. This issue may justify the higher incidence of breakthrough IFI reported with fluconazole compared to echinocandins in the studies by Fortún et al.[23] and Winston et al.[7] This further strengthens the importance of selecting the most appropriate comparators (both in terms of specific agent and PK/PD optimisation) for assessing the efficacy of antifungal prophylaxis among high-risk OLT recipients.

Several PK/PD concerns may arise with the use of when using the echinocandins for prophylaxis or treatment of invasive fungal abdominal infections, particularly in critically ill OLT recipients. The hydrophilic nature of echinocandins coupled with the high molecular weight and the high protein binding makes the achievement of effective concentrations at the infection sites challenging, especially in abdominal infections.[36,37] Several preclinical and clinical studies showed the limited efficacy of echinocandins in achieving adequate exposure at the recommended dosage for the treatment of invasive abdominal candidiasis.[12,38,39] Zhao et al.[38] found in a preclinical murine model a significantly lower reduction of fungal burden with micafungin compared to high-dose rezafungin. Additionally, no liver sterilisation was reported with micafungin.[38] Grau et al.[12] reported low-moderate micafungin penetration into the peritoneal fluid of ten post-surgical patients affected by severe peritonitis. The median area-under-curve peritoneal fluid/plasma ratio after the first dose and at steady state was 0.3.[12] Considering that critically ill patients usually exhibit lower serum echinocandin exposure compared to other populations, a more critical and suboptimal concentration are consequently expected in intrabdominal fungal infections. Furthermore, several evidence reported a remarkable echinocandin underexposure both in plasma and surgical site in critically ill patients.[40–43] This may favour the selection of fungi with less echinocandin susceptibility and/or the development of echinocandin resistance.[44] Indeed, invasive abdominal candidiasis was reported as a hidden reservoir for the development of echinocandin resistance, especially in case of prolonged echinocandin exposure and concomitant infections with multidrug-resistant bacteria (vancomycin-resistant *Enterococci* or extended-spectrum beta-lactamase- or carbapenemase-producing *Enterobacteriaceae*), which may promote the emergence of FKS mutant *Candida*.[39] Notably, emergence of echinocandin resistance in *Candida* isolates was reported in up to 8% of OLT recipients within one month of treatment.[13] Consequently, the concept of 'one size fits all' guiding dosing recommendations of echinocandins seems to be inappropriate in critically ill OLT recipients.[44] This may possibly explain the

trend towards higher risk of breakthrough IFI found in our analysis with echinocandins compared to amphotericin B. Echinocandin dosing adjustment (eg anidulafungin 150 mg/day, micafungin 150–200 mg/day or caspofungin 2 mg/kg loading dose followed by 1.25 mg/kg/day[40,42,43]) should be implemented in critically ill OLT recipients in order to maximise the achievement of optimal PK/PD target especially against *Candida* spp., representing a major issue in the immediate post-transplant period.[45]

Although a significantly higher number of AEs emerged with echinocandins in observational studies, safety data were only provided by one out of the seven included studies,[22] thus the retrospective design of this analysis could affect the retrieved findings. Notably, no significant difference between echinocandins and other antifungal agents in terms of overall AEs was found in the analysis of RCTs. Echinocandins are characterised by a favourable risk-benefit profile compared to azoles and polyenes, specifically concerning the lack of relevant drug-drug interactions and the negligible impact on renal and hepatic function.[11]

Limitations of our meta-analysis have to be addressed. No other subgroup analysis according to different clinical or demographics features (eg age, MELD score) was performed due to lack of available data. Although for most of outcomes no evidence of statistical heterogeneity existed, a certain degree of clinically meaningful heterogeneity between the included studies is expected (eg comparator agents). Finally, unmeasured confounders could bias findings retrieved even in observational studies with low or moderate risk of bias.

In conclusion, in our meta-analysis, no overall increased risk of breakthrough IFI with echinocandins was found, although the large diversity in the comparator group hinders a definitive interpretation. The trend towards higher risk of breakthrough IFI reported with echinocandins compared to amphotericin B in subgroup analysis could reflect a suboptimal efficacy of echinocandins due to PK/PD issues in the OLT setting when appropriate comparators are selected. Further studies are warranted for exploring the relationship between echinocandin use and breakthrough IFI in OLT recipients according to specific comparators.

CONFLICT OF INTERESTS
FP participated in speaker bureau for Angelini, Basilea Pharmaceutica, Gilead, Hikma, Merck Sharp & Dohme, Nordic Pharma, Pfzer and Sanof Aventis, and in advisory board for Angelini, Basilea Pharmaceutica, Correvio, Gilead, Hikma, Merck Sharp & Dohme, Nordic Pharma, Novartis, Pfzer, Shionogi and Thermo-Fisher. Other authors have none to declare.

AUTHOR CONTRIBUTION
Milo Gatti: Conceptualization (equal); Data curation (lead); Formal analysis (lead); Methodology (equal); Writing-original draft (lead).

Matteo Rinaldi: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Methodology (equal); Writing-review & editing (equal). **Giuseppe Ferraro:** Data curation (supporting). **Alice Toschi:** Data curation (supporting). **Natascia Caroccia:** Data curation (supporting). **Federica Arbizzani:** Data curation (supporting). **Emanuel Raschi:** Methodology (supporting); Writing-review & editing (equal). **Elisabetta Poluzzi:** Methodology (supporting); Writing-review & editing (equal). **Federico Pea:** Writing-review & editing (equal). **Pierluigi Viale:** Writing-review & editing (equal). **Maddalena Giannella:** Conceptualization (lead); Data curation (supporting); Formal analysis (supporting); Methodology (equal); Writing-review & editing (lead).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.