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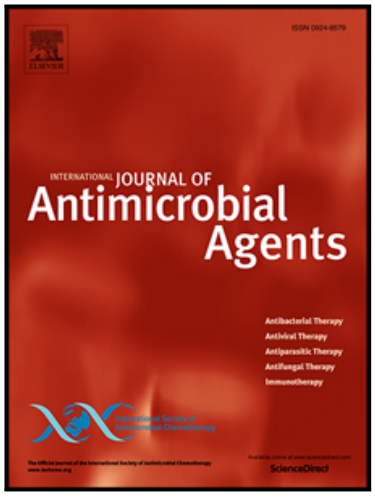

Comparative efficacy and safety of systemic antifungal agents for candidemia: A systematic review with network meta-analysis and multicriteria acceptability analyses

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HIGHLIGHTS

- Caspofungin and micafungin remain the most promising therapies for candidemia.
- Anidulafungin showed an inferior response compared to other drugs of the class.
- Rezafungin, a novel alternative for treating candidemia, should be further evaluated
- Amphotericin B and fluconazole should be used as second-line therapy for candidemia.

Comparative efficacy and safety of systemic antifungal agents for candidemia: A systematic review with network meta-analysis and multicriteria acceptability analyses

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ABSTRACT

Aim: Invasive candidiasis is the main fungal infection in patients attending health services and is associated with high mortality rates and prolonged hospital stay. We aimed to comparatively evaluate the efficacy and safety of antifungal agents for treating candidemia.

Methods: A systematic review with network meta-analysis (NMA), surface under the cumulative ranking analysis (SUCRA) and stochastic multicriteria acceptability analyses (SMAA) were performed (PROSPERO-CRD42020149264). Searches were conducted in PubMed and Scopus (Nov-2021). Randomised controlled trials evaluating the effect of oral antifungals (any dose or regimen) on mycological cure, discontinuation rates and adverse events were included.

Results: Overall, 13 trials (n=3,632) were analysed. No significant differences among therapies were found for the efficacy outcomes; however, caspofungin (50-150 mg), rezafungin (200-400mg) and micafungin (100-150 mg) were considered the most promising therapies, leading to higher rates of both clinical and mycological responses (SUCRA overall response over 60%). Fluconazole (400 mg) was rated as the last option for overall response (17%). Rezafungin (200-400mg) and micafungin (100 mg) were associated with lower discontinuation rates (<40%); conventional amphotericin B (0.6-0.7mg/kg) was more likely to be discontinued (OR 0.08 [95% CrI 0.00-0.95] vs. caspofungin 150 mg) and may impair liver function (87%).

Conclusion: Echinocandins should be listed as first-line treatments for invasive candidiasis following a priority order of caspofungin and micafungin. Rezafungin, an under development echinocandin, represents a potential option that should be further investigated. Azoles and liposomal amphotericin B can be used as second-line treatments in cases of fungal resistance or hypersensitivity.

Keywords: invasive fungal infection; invasive candidiasis; antifungal agents; systematic review; meta-analysis.

1. Introduction

In recent years, the incidence of fungal infections in healthcare services has significantly increased, probably related to the growth in medical and surgical procedures. The extensive use of more aggressive treatment approaches, such as stem cell transplantation, transplantation of solid organs and new immunomodulators has enhanced the number of immunocompromised individuals at risk of developing invasive fungal infections (IFI) [1].

IFI represent a leading cause of morbidity and mortality in immunocompromised patients, with rates exceeding 50%, depending on the pathogen and the underlying condition or disease. Invasive candidiasis, caused by the fungi species *Candida* spp*.*, is the fungal infection that most affects hospitalised patients or those undergoing solid organ transplants, with rates ranging from 50 to 60% [2]. Additionally, they are responsible for around 10% of haematological infections that occur in hospital environments. Candidiasis-related mortality and length of hospital stay may range from 10-55% and from 3 to 30 days, respectively, depending on patient clinical condition [3].

In recent decades, a variety of antifungal agents (i.e., polyenes, azoles and echinocandins) to prevent and treat IFI have been developed and are available in most countries [4]. However, because of the complexity of handling invasive candidiasis (e.g., infectious agents features, disease severity, patient characteristics) [5], and considering that these drugs have different pharmacological effects, costs and adverse events, establishing the best therapeutic option that provides high efficacy with low toxicity remains a challenge. In addition, recommendations for the management of these infections are often conflicting and controversial, which creates variability in clinical practice worldwide [6,7].

Several clinical trials evaluating the efficacy and safety of different antifungals are available in the literature [8,9]; however, they are usually restricted to pairs of direct comparisons. Systematic reviews with meta-analyses have the advantage of providing a higher level of evidence, converting scattered information into grounded knowledge. Network meta-analyses, an extension of pairwise meta-analyses, are particularly useful in this scenario because they enable multiple comparisons across studies. This tool simultaneously combines direct (i.e., based on existing comparative studies) with indirect evidence (i.e., based on common comparators) to obtain pooled effects for all pair of treatments in the network. Nonetheless, network meta-analysis evaluating the effect of antifungals for IFI are still scarce in the literature, most of which are limited by comparing only a few classes of drugs for a given clinical condition [10].

Thus, we aimed to update and synthesise the available evidence on the efficacy and safety of currently market antifungals for the treatment of IFI caused by

Candida spp. through a systematic review with network meta-analysis, and to quantitatively evaluate the benefit-risk ratio of each regimen by means of stochastic multicriteria acceptability analyses.

2. Methods

This systematic review with network meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses (PRISMA-NMA) and Cochrane Collaboration recommendations [11]. The PROSPERO registration number is CRD42020149264. The protocol is also available at the Open Science Framework platform (DOI 10.17605/OSF.IO/YD3R4). Two researchers performed all steps of study's selection and data extraction independently. Discrepancies were reconciled in consensus meetings, using a third author as a referee.

2.1 Search strategy and study selection

Systematic searches were conducted in PubMed and Scopus without limits for time-frame or language (updated in Nov-2021), using the search strategies depicted in the supplementary material. Trial registration databases (clinicaltrials.gov) and the reference lists of the included studies were manually searched. Titles and abstracts of the retrieved articles were screened for eligibility. Relevant registers were then read in full and studies that met the following inclusion criteria (PICOS' acronym) were included for extraction: (P) studies evaluating patients over 16 years old diagnosed with invasive candidiasis or candidemia (i.e., systemic infection by *Candida* spp.), (I) treatment with any antifungal agent for systemic use (any dose or regimen), (C) compared to placebo or other antifungal agent (any dose or regimen), (O) reporting data on efficacy (i.e., overall treatment response [defined as mycological eradication and clinical cure or improvement]; mycological response [defined as mycological eradication], disease recurrence [measured as patients who had a positive culture for *Candida* species or other fungal infection during follow-up]), or safety (adverse events and treatment discontinuation rates), (S) designed as randomised controlled trials. Studies were excluded if written in non-Roman characters.

2.2 Data extraction and quality assessment

The following data were independently extracted by two authors: (i) study characteristics and baseline information (author names, year of publication, country,

sample size, patient age, trial duration, previous treatments, patient comorbidities, *Candida* spp. species), evaluated treatments, (iii) study methodological features and clinical outcome results (efficacy and safety). The methodological quality of the included articles was evaluated according to the Cochrane Collaboration's revised tool for assessing risk of bias in randomized trials (RoB 2) and the Jadad scale.

2.3 Statistical analyses

Network meta-analyses were performed for each outcome of interest using a Bayesian framework based on the Markov Chain Monte Carlo simulation method (burn-in of 20,000 iterations and 50,000 iterations for estimation). Transitivity analyses were performed by comparing population, interventions, comparator, and outcome definitions among studies. A common heterogeneity parameter was assumed for all comparisons. We opted for a conservative analysis of non-informative priors. Consistency models were built for each network and effect size measures were defined as odds ratio (OR), expressed with 95% credibility intervals (CrI). Both fixed and random effect models were tested, and the one with the lowest deviance information criterion [11] was selected. Convergence was attained based on visual inspection of Brooks-Gelman-Rubin plots and a potential scale reduction factor (PSRF) ($1 < PSRF \leq 1.05$). Ranking probabilities were calculated via the surface under the cumulative ranking analysis (SUCRA) for each outcome to increase the estimated precision of the relative effect sizes of comparisons. The robustness of the networks was estimated by a node-splitting analysis, which depicts the inconsistency between the pooled direct and indirect evidence for a comparison (a p value < 0.05 reveals inconsistency in the network). Sensitivity analyses with the hypothetical removal of the studies were conducted when discrepancies were identified or to allow further interpretation of the network meta-analyses. All analyses were performed using software Addis version 1.17.6 (Aggregate Data Drug Information System; http://drugis.org/software/index). Visual schemas were built in R/R Studio (https://rstudio.com).

2.4 Multicriteria analysis

A stochastic multicriteria acceptability analysis (SMAA) is an extension of the multicriteria decision analysis (MCDA), which is a decision-making tool that estimates the benefit/risk ratio (BR) of healthcare interventions. 'Benefit' is described as the effect that takes the patient from the disease condition to health, while 'risk' refers to an effect that leads the patient from health to disease. Thus, this technique simultaneously

evaluates multiple therapeutic efficacy and safety attributes finally providing a 'rank' of the technologies, ranging from the worst to the best clinical option.

We used the SMAA to determine the BR of antifungal agents on the treatment of invasive candidiasis or candidemia using evidence from the network meta-analysis of clinical trials with unknown or partially known preferences. Two benefit criteria (i.e., overall response to treatment and recurrence) and one risk criterion (i.e., treatment discontinuation) were initially considered (scenario I). A model containing all therapies was built with missing preferences (i.e., without a previously established order of importance for the three outcomes) to provide a brief overview of the evidence. In a following step, additional models considering preferred order for the outcomes to occur were built as part of the sensitivity analyses. Caspofungin 150 mg was considered the baseline treatment as it is the most recommended drug for these patients according to the current clinical practice guidelines [6,12,13]. Other scenarios, considering different risk criteria (abnormal liver function; scenario II) were also performed. Models were generated using Monte Carlo iterations (Addis version 1.17.6).

3. Results

The search strategy retrieved 2,689 registers after duplicates removal, of which 2,598 were excluded during the screening process (titles and abstracts reading). Seventy-seven studies were excluded after full-text appraisal, remaining 14 registers referring to 13 randomised controlled trials [14-26] for data extraction and analyses (see Figure 1). The complete list of included and excluded studies after full-text reading are available in Tables S1 and S2 of the supplementary material.

These 13 trials (n = 3,632 patients) were published between 1996 and 2020, with most of them (69.2%) designed as international multicentric studies conducted in several countries. The median duration of the studies was 18.2 months (interquartile range [IQR] 5-44 months). Most patients were male (57%), with a median age of 63.4 years (IQR 16-97 years). Almost all trials directly compared active drugs; only one study had placebo as the main comparator. The evaluated antifungals were anidulafungin, caspofungin, conventional amphotericin-B, liposomal amphotericin B, fluconazole, isavuconazole, micafungin and rezafungin at different doses and regimens. The main characteristics of the included studies are presented in Table 1.

Some patients diagnosed with invasive candidiasis had previous exposure to risk factors such as use of antibiotics (n = 1,437; 39.6%) or use of a central venous catheter (n = 1853; 51%). The most reported comorbidities were neutropenia (n = 611; 16.8%), cancer in solid organs (n = 556; 15.3%) and diabetes (n = 502; 13.8%).

Overall, n = 2,391 patients (65.8%) had spread of the infection and were diagnosed with candidemia. The most common species causing IFI was *C. albicans* (around 41%), followed by *C. tropicalis* (15%), *C. parapsilosis* (around 12%), *C. glabrata* (11%) and C. *krusei* (<5%) (see Figure S1 of the supplementary material).

The overall methodological quality of the studies was judged as moderate with a mean Jadad score of 3.31 (IQR 2-5), with only three studies (23.1%) scoring 2. All trials were randomised, although the randomisation process and allocation concealment were properly described in seven studies (53.8%). One study was designed as open label and was judged as with a high risk of bias for the domain of blinding of participants and personnel. Seven trials (53.8%) were unclear regarding the blinding process. Few concerns were observed for the domains of incomplete outcome data and selective reporting. Almost all trials (n=12; 92,3%) were classified as having a high risk of bias (other bias domain) due to funding from pharmaceutical companies or presence of conflict of interest (see Figure S2 and S3 of the supplementary material).

We were able to build five network meta-analyses for the outcomes of: overall response to treatment (clinical and microbiological), microbiological response, disease recurrence, treatment discontinuation due adverse events and abnormal liver function (most reported adverse event) (see Figure 2). All networks were found to be robust with no significant discrepancy between direct and indirect evidence for all pairs of treatments (see the supplementary material).

Overall response to treatment (both clinical and microbiological) was reported by 11 trials (n=3,295 patients), enabling the comparison of 13 treatments: conventional amphotericin B (0.6-0.7 mg/kg), liposomal amphotericin B (3 mg/kg), anidulafungin (50 mg, 75 mg and 100 mg), caspofungin (50 mg and 150 mg), fluconazole (400 mg), isavuconazole (200 mg), micafungin (100 mg and 150 mg) and rezafungin (200 mg and 400 mg/week). The outcome of microbiological response was evaluated by five trials (n=1,898) and compared caspofungin (50 mg and 150 mg), isavuconazole (200 mg), liposomal amphotericin B (3 mg/kg), micafungin (100 mg) and rezafungin (200 mg/week and 400 mg/week). The article by Dupont [17] reported separate data for patients admitted to the intensive care unit and for those admitted to the common ward. Although no significant differences among therapies were found in the consistency analyses of these outcomes (see the supplementary material), SUCRA revealed caspofungin (150 mg) as the most promising therapy for both overall (clinical and microbiological) and microbiological responses with probabilities of 72% and 75%, respectively, followed by rezafungin 400 mg in the first week plus 200 mg in the following weeks (65% and 54%, respectively) and micafungin 100 mg (65% and 75%, respectively). Fluconazole (400 mg) was rated as the last option for overall response

(17% in SUCRA), while isavuconazole (200 mg) lead to the worst microbiological response (8%) (see Figure 3).

The networks of disease recurrence (four included studies; six evaluated treatments) and discontinuation due adverse events (eight included studies; nine treatments) also did not present statistical differences among therapies. Lower doses of micafungin (100 mg) and caspofungin (50 mg) were probably more related to recurrences (SUCRA values of 74% and 73%, respectively); conversely, higher doses of rezafungin (400 mg in the first week plus 200 mg in the following weeks) and caspofungin (150 mg) were the safest options (5% and 27% chance of recurrence). Amphotericin B and fluconazole (400 mg) were highly associated with discontinuation (88% and 65%, respectively), while rezafungin was the most tolerable alternative.

Finally, in the network of abnormal liver function (four studies; five treatments), conventional amphotericin B (0.6-0.7mg/kg) was found to be significantly more related to the incidence of this event when compared to caspofungin 150 mg (OR 0.08 [95% CrI 0.00-0.95]). No further differences among therapies were found in the consistency analyses (see the supplementary material for complete analyses). SUCRA demonstrated that amphotericin B and fluconazole (400 mg) had the highest probabilities of causing abnormal liver function (87% and 68%, respectively), while caspofungin 150 mg was the safest alternative (Figure 3).

The correlation between the outcome of the general response to treatment and the discontinuation due to adverse events are shown in Figure 4. Overall, caspofungin, micafungin, and rezafungin were related to both better efficacy (>60%) and a manageable safety profile (discontinuation under 45%). Although having moderate-high efficacy (around 50%), regimens containing amphotericin led to more discontinuation due adverse events. Drugs such as anidulafungin and isavuconazole seem to have moderate efficacy and a fairly good safety profile.

The sensitivity analyses of the networks with the hypothetical removal of the most recent therapy (i.e., rezafungin), which has not been approved for general use by regulatory agencies, is depicted in supplementary material (Figures S7 and S8). The overall results are similar to the original analyses and highlight caspofungin (150mg) as the most promising drug with favorable overall and microbiological responses (72% and 77% in SUCRA), low recurrence rates (17%) and few adverse events on liver function (12%).

The SMAA results were analogous to the sensitivity analyses including only currently approved drugs. The acceptability classification of scenario I (overall response to treatment, recurrence and discontinuation related to medication with missing preferences; caspofungin 150 mg as baseline) is shown in Figures S9 and S10

in the supplementary material (with six therapeutic options). This scenario favoured caspofungin 150 mg (benefit-risk [BR] ratio of 60%). Conventional amphotericin B was rated as with the worst BR ratio. When performing sensitivity analyses by setting the ordinal preferences of the three criteria (overall response to treatment as the first important outcome, followed by recurrence and discontinuation), caspofungin 150 mg remained the best option (52%), followed by micafungin 150 mg and caspofungin 50 mg (20% and 30% respectively). Conventional amphotericin B remained as the worst alternative. Five therapeutic regimens were included in scenario II of the SMAA (overall response to treatment and abnormal liver function; see Figures S11 and S12 of the supplementary material). For both missing and ordinal preferences, caspofungin 150 mg remained the best alternative (BR ratio of 69% and 60%, respectively), followed by caspofungin 50 mg (53% and 51%, respectively). Fluconazole 400 mg was rated as the worst option (BR ratio of 53% and 61%, respectively).

4. Discussion

This systematic review with network meta-analyses and stochastic multicriteria acceptability analyses synthesised the available evidence on the efficacy and safety profile of eight therapies at different doses and regimens (resulting in 13 approaches) used for treating invasive candidiasis and candidemia. *Candida* species are the fourth most common cause of hospital-acquired infections, especially in patients admitted to intensive care units. *Candida* spp. can colonise, invade, and spread through a patient's organs without causing specific signs and symptoms that could be related to the infection. Consequently, invasive infections are responsible for extending the mean length of hospital stay and are associated with a mortality rate of over 50% [27].

We found that most patients were infected by *C. albicans*, followed by the species *C. tropicalis*, *C. parapsilosis*, *C. glabrata* and *C. krusei*, which agrees with previous reports on the widespread distribution and emergence of *Candida* strains. Additionally, a recent meta-analysis indicated that critically ill patients with sepsis who are colonised with *Candida* are more likely to develop invasive candidiasis with an estimated magnitude of association of OR 3.32 (95% confidence interval 1.68-6.58) compared to non-colonised patients [28]. In this context, the prior documentation of *Candida* colonisation and correct identification of the species is extremely important for choosing the therapy and for predicting the potential risk of antifungal resistance.

Although several scientific publications approach the comparative efficacy of antifungals as primary prophylaxis in preterm or neonatal infants with invasive infections [29] or in immunosuppressed patients (*e.g.* haematological disease, cancer)

[30], the synthesised evidence on the clinical effect of these drugs for treating invasive *Candida* infections is still conflicting. The systematic review with pairwise meta-analysis published by Osa et al (2020) compared solely the class of azoles vs. conventional amphotericin B (only n=3 included trials) for candidemia and showed the superiority of the latter over azoles in terms of efficacy, but with a higher risk of causing renal disorders [31]. Tashiro et al. (2020) [32] directly compared the class of echinocandins with non-echinocandins (n=5 trials) and concluded that echinocandins were more associated with improved clinical success than azoles (Risk Ratio [RR] 1.20 [95% CI 1.08-1.34] p=0.001), whereas no significant differences were observed between echinocandins and polyenes. Regarding adverse events, there was no significant difference between treatment groups. For children and neonates with invasive candidiasis, Chen et al. (2019) [33] found no significant differences in using echinocandins or amphotericin B (n=5 trials) regarding clinical response rates (OR 1.38 [95% CI 0.68-2.80]). However, 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]).

We were able to produce different networks of treatment comparisons (n=13 included trials) accounting for different drug dosages. This broader overview of the effect of all the available alternatives may guide more assertive clinical decisions and the initiation of further well-designed clinical trials for invasive candidiasis and candidemia. Although no statistical differences were found among treatments, the class of echinocandins stands out given its combined slightly greater effectiveness and tolerability, which is in accordance with the pairwise meta-analyses of Tashiro et al. and Chen et al. [32, 33]. International clinical guidelines also recommend the use of echinocandins for managing different invasive fungal infections [6, 7, 13] . This can be due to the broad spectrum of action of echinocandins against most *Candida* species, with lower minimum inhibitory concentrations (MIC) and resistance when compared to other classes [8, 34].

In our study, caspofungin 150 mg was ranked as the most promising approved and market option for treating IFI caused by *Candida* spp. with higher probabilities (SUCRA 72%) of leading to both clinical and microbiological responses and with low discontinuation rates (SUCRA around 48% probability). The BR in the SMAA (scenario I) was of 60%. Next to this alternative, we found lower doses of caspofungin (50 mg) and both doses of micafungin of 50 and 150 mg (SUCRA probabilities of around 60% for efficacy and 40% for safety) (Figure 4, upper-left quadrant). Although the 2016 Clinical Practice Guideline for the Management of Candidiasis of the Infection Disease Society of America (ISDA) [7], and others guidelines [6, 12, 13], affirm that

echinocandins are similarly effective for treating IFI, we demonstrated slightly differences in their profile that may impact on clinical decisions and should be further investigated. Anidulafungin showed an inferior response compared to the other drugs of the class with probabilities of leading to overall response of under 45%. This may be justified by the difference in the ratio between the area under the curve and minimum inhibitory concentration (AUC:MIC) and volume of distribution of these drugs [34-36].

Scientific literature shows that, for true treatment effectiveness, with reduced mycological load as an outcome, the different doses of echinocandins must reach the AUC:MIC threshold of 3000 [36]. This is probably not achieved with the current concentrations of anidulafungin used in the studies included in this review. Bader et al. (2018) [73] demonstrated in a study with simulated patients that, after daily administration of 100 mg of anidulafungin for the treatment of candidemia caused by C. glabrata, the AUC:MIC ratio of the free drug in plasma was less than the minimum threshold required to reach the therapeutic target. Anidulafungin VD values also allowed us to assume that the drug has a lower plasma concentration and, consequently, less availability at the site of action [35]. Thus, antifungal pharmacokinetics and pharmacodynamics play a fundamental role in therapeutic decisions, favouring faster clinical and microbiological improvements while minimising the risk of adverse events [11].

Nonetheless, one should be aware that caspofungin and micafungin were applied at higher doses in the included studies (three times the recommended standard dose of caspofungin; micafungin at the dose recommended for esophageal candidiasis only), whereas anidulafungin had been administered at standard dose. Differences in plasma protein binding, which is lowest for caspofungin, might also play a role in these results. Moreover, it is important to highlight that micafungin has a restricted indication in Europe due to potential hepatotoxicity and risk of liver tumours, being, therefore, usually used when other antifungals are not appropriate. Although this warning is largely based on preclinical observations, its clinical relevance and need for further investigation in well-designed trials should not be ignored [6, 12, 13].

We also identified rezafungin, a novel once weekly echinocandin that is under development (i.e., currently not approved by regulatory agencies), as a potential alternative for treating IFI. Recent studies show that rezafungin has an exceptional stability and solubility and a uniquely long half-life allowing for front-loaded drug exposure with once-weekly dosing. This drug has been shown comparable to other echinocandins, with activity against *Candida spp*. and *Aspergillus spp*. including subsets of echinocandin-resistant *Candida auris* and azole-resistant Aspergillus

isolates. Phase III trials still need to be performed to confirm these findings and further allow the implementation of rezafungin in clinical practice [37].

The 'ideal' antifungal agent should have a broad spectrum of action, present fungicidal action at low concentrations and have favourable pharmacokinetics and pharmacodynamics, as well as an acceptable safety profile (e.g., no toxicity, side effects, resistance) [38]. Echinocandins have fungicidal activity against most species [8] and lead to less discontinuation (probability of 42.5% [IQR 35 - 45%]) and fewer adverse events, most of them considered mild (e.g. fever, nausea, vomiting, changes in liver enzymes, dizziness, tachycardia). Additionally, echinocandins are more active and effective than azoles in cases of *Candida* infections associated with the frequent use of venous catheters, which favour the entry of fungi and the formation of biofilms [7].

Similar to what was demonstrated by the direct comparison of Osa et al. [31] and by previous studies on the profile of amphotericin B formulations [39], we confirmed that conventional amphotericin B was associated with higher discontinuation rates and other adverse events such as abnormal liver function. This formulation, applied as intermittent infusion (>4h) has already proven to have low solubility and high toxicity; its use should be avoided in current practice. Instead, continuous infusion, lipid formulations or the infusion of amphotericin B with intralipid are recommended as safer alternatives to mitigate amphotericin-related nephrotoxicity [10, 39]. Both liposomal amphotericin B and azoles demonstrated an intermediate profile in the network meta-analyses (probabilities of efficacy and safety of around 50%). The intermediate efficacy of fluconazole and isavuconazole was directly associated to the dose used in the included clinical trials (under-dosage). According to Chen et al. [12], the dose of 400 mg/day of fluconazole may be insufficient to reach the goal of the AUC:MIC ratio, which is necessary for the improvement of clinical signs and mycological eradication in laboratory tests. Yet, as some *Candida* species have developed resistance to fluconazole, treatment with this drug can be challenging in IFI [7]. In this case, liposomal amphotericin B or other azoles can be an alternative to species-specific therapies against IFIs caused by *C. glabrata* and *C. parapsilosis* [40]. These drugs could be classified as 'second-line therapies' for invasive candidiasis, especially in cases of previous resistance to antifungals and cases of hypersensitivity to other drugs.

This study has some limitations. We selected only two databases (PubMed and Scopus) to perform the literature search. Nonetheless, these databases cover mostly biomedical literature, and no additional studies were found during manual searches, additionally confirming that our strategies were sensible and specific. We are also aware of the potential introduction of bias caused by the small number of included

studies that hampered further statistical analyses. Furthermore, the low reporting quality of some trials and the variance between efficacy endpoints narrow the performance of other networks. We analysed some of the most common and reported outcomes; however, important heterogeneity among studies exists (e.g., variations in terms of drugs doses, treatment duration and measurement of adverse events) and should not be ignored during decision-making processes. The safety profile of different type of drugs may vary according to the drug class (e.g., amphotericin B is associated with a higher rate of hepatotoxicity, while echinocandins and triazoles were associated with lower rates of adverse events overall, most commonly electrolyte disturbances). Similar to other methods, network meta-analysis is not free of limitations. The validity of this technique depends on the distribution of relative treatment effect modifiers across comparisons. The included randomized trials that differed in terms of size, risk of bias and external validity. We tried to avoid systematic errors by performing transitivity and sensitivity analyses whenever possible. Treatment rankings should not be interpreted in isolation from the relative treatment effects.

6. Conclusions

Considering these results of the network meta-analyses, echinocandins were demonstrated to be promising as first-line treatment for invasive candidiasis following a priority order of caspofungin, micafungin and finally anidulafungin. Rezafungin, a novel under development echinocandin, represents a potential option that should be further investigated in clinical trials. Azoles and liposomal amphotericin B can be used as second-line treatments in case of fungal resistance. This evidence should be further investigated in well-designed clinical trials with standard outcomes. Economic evaluations should be performed to strengthen the evidence on the benefits of these drugs and guide the decision-making process.

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Authors' Contributions

All authors contributed to the study elaboration and design. Eric L Domingos and Fernanda S Tonin conceived and designed the study. Eric L Domingos and Fernanda S Tonin conduct the meta-analysis and drafted the paper. Raquel O Vilhena and Josiane M M F Santos performed all steps of study's selection and data extraction independently. Mariana M Fachi, Livia M Adam, Beatriz Böger and Roberto Pontarolo revised the manuscript and gave the final approval of the manuscript. This study was supervised by Roberto Pontarolo. All authors read and approved the final manuscript.

Disclosures

Eric L Domingos, Raquel O Vilhena, Josiane M M F Santos, Mariana M Fachi, Beatriz Böger, Livia M Adam, Fernanda S Tonin and Roberto Pontarolo declare that they have no conflict of interest

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Figures captions

Figure 1. Flowchart of the systematic review process

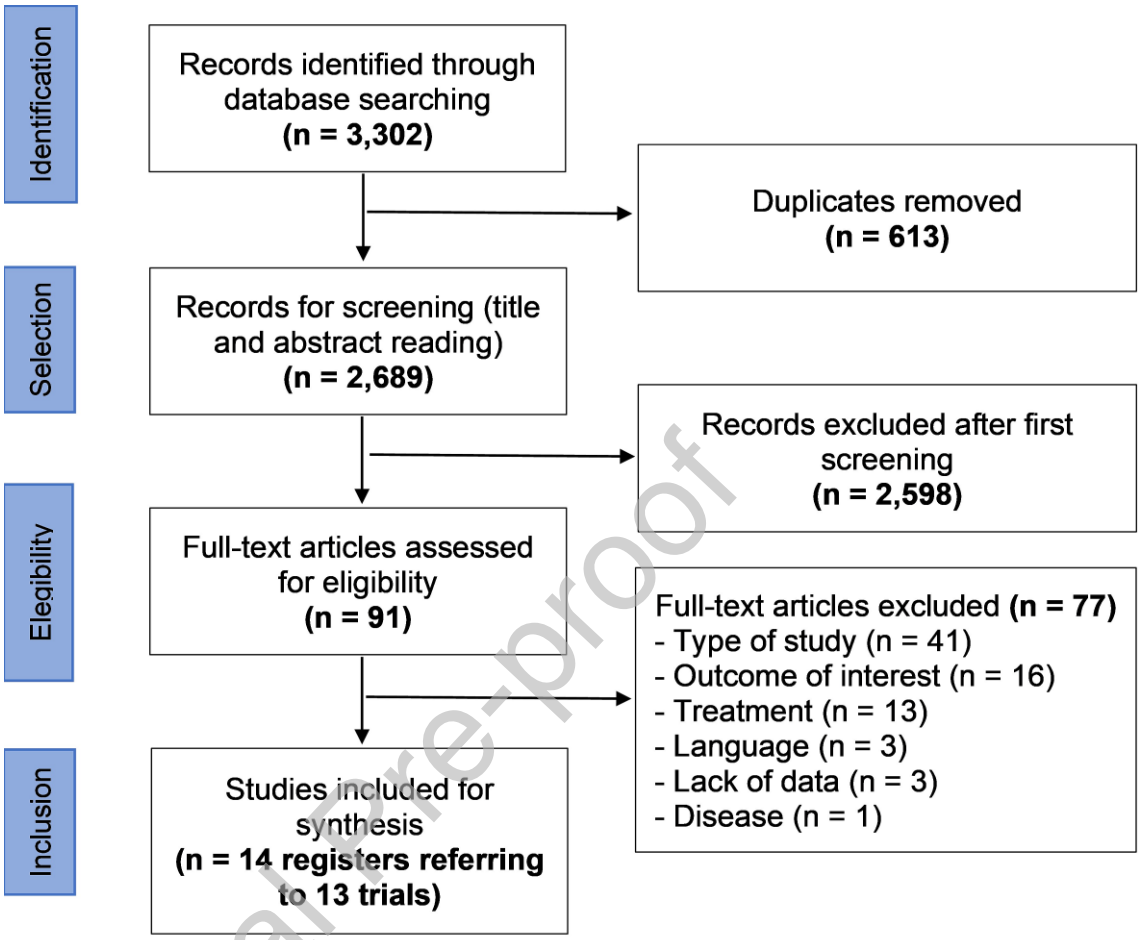

Figure 2. Network plots of treatment comparisons for each outcome of interest

Note: Directly comparable interventions are linked with a line. The thickness of the line is proportional to the number of trials for each comparison.

Legend: AMB: conventional amphotericin-B; ANI: anidulafungin; CAS: caspofungin; FLU: fluconazole; ISA: isavuconazole; L-AMB: liposomal amphotericin B; MIC: micafungin; RZF: rezafungin

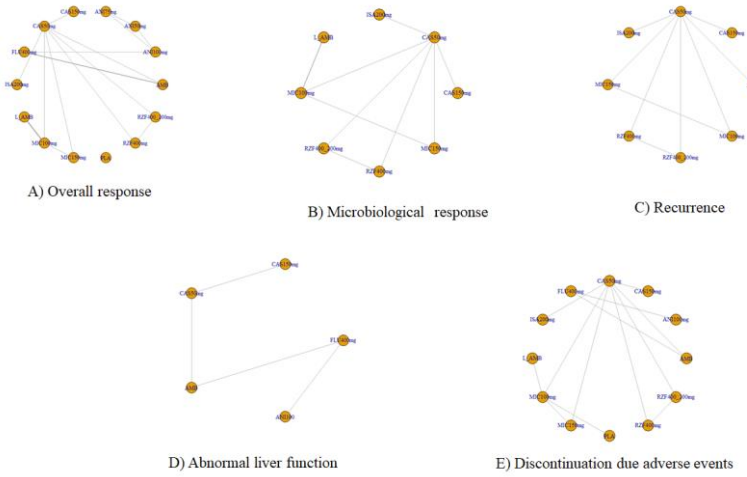

Figure 3. Surface under the cumulative ranking curve analysis (SUCRA) for each outcome of interest

Note: Values ranging from 0% (i.e., therapy less associated with the outcome) to 100% (i.e. therapy more associated with the outcome).

Legend: AMB: conventional amphotericin-B; ANI: anidulafungin; CAS: caspofungin; FLU: fluconazole; ISA: isavuconazole; L-AMB: liposomal amphotericin B; MIC: micafungin; RZF: rezafungin

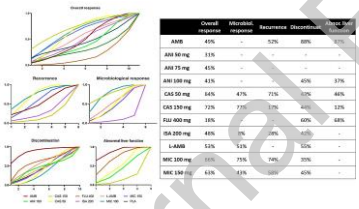

Figure 4. Ranking plot based on the surface under the cumulative ranking curve analysis (SUCRA) for the two main outcomes.

Note: Values of overall response (clinical and microbiological) overall safety as discontinuation due to adverse events. Treatments lying in the upper-left corner are more effective and safer than the other treatments. There is no available data for medication discontinuation for ANI 75 mg and ANI 50 mg.

Legend: AMB: conventional amphotericin-B; ANI: anidulafungin; CAS: caspofungin; FLU: fluconazole; ISA: isavuconazole; L-AMB: liposomal amphotericin B; MIC: micafungin; RZF: rezafungin

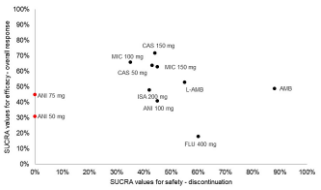

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Table 1 Characteristics of the included studies

Author, year	Country	Drugs	Dose (mg/day)	N	Mean age (years)	Treatment duration (days)	Males N (%)	Jadad Score
ABELE-HORN, 1996 [28]	Germany	FLU	200	36	58.3	14.9 (± 8.9)	26 (72.2)	2
		AMB/5-FL	1.0-1.5*/2500	36	59.7	15.4 (± 9.4)	25 (69.4)	
ANAISSIE, 1996 [29]	USA	FLU	400	75	62.0	11.0 (± NR)	46 (61.0)	2
		AMB	250	67	58.0	11.0 (± NR)	42 (63.0)	
BETTS, 2009 [30]	International	CAS	50	104	56.0	14.5 (1-49)	54 (51.9)	3
		CAS	150	100	57.8	14.2 (1-51)	60 (60.0)	
DUPONT, 2009 [31]	International	MIC	100	127	53.1	NR	79 (62.2)	3
		L-AMB	3*	136	52.4	NR	79 (58.1)	
	International	MIC	100	120	53.7	NR	76 (63.3)	
		L-AMB	3*	110	53.4	NR	68 (61.8)	
KNITSCH, 2015 [32]	International	PLA	NA	127	63.0	NR	42 (33.1)	3
		MIC	100	125	61.6	NR	53 (42.7)	
KRAUSE, 2004 [33]	USA	ANI	50	42	52.0	NR	13 (33.0)	2
		ANI	75	40	54.0	NR	21 (53.0)	
		ANI	100	41	59.0	NR	18 (45.0)	
KULLBERG, 2019 [34]	International	ISA	200	221	58.0	11.0 (1-56)c	143 (64.7)	5
		CAS	50	219	57.9	12.0 (1-56)	126 (57.6)	
KUSE, 2007 [81]	International	MIC	100	264	54.5	15.0 (± NR)	165 (63.0)	5
		L-AMB	3*	267	56.0	15.0 (± NR)	160 (60.0)	
MORA-DUARTE, 2002 [35]	International	CAS	50	114	56.0	12.1 (1-28)	56 (51.4)	4
		AMB	0.6-0.7*	125	55.0	11.7 (1-28)	69 (60.0)	
PAPPAS, 2007 [36]	International	MIC	100	191	56.6	14.0	107 (56.0)	3
		MIC	150	199	55.4	14.0	117 (58.8)	
		CAS	50	188	55.8	14.0	112 (59.6)	
PHILLIPS, 1997 [37]	Canada	FLU	400	53	65.0	21.0	26 (52.0)	3
		AMB	0.6-0.7*	53	58.0	15.0	32 (60.5)	
REBOLI, 2007 [82]	Canada and USA	ANI	100	127	57.0	13.5	65 (51.0)	4
		FLU	400	118	59.2	12.1	60	

							(51.0)	
THOMPSON, 2020[26]	International	RZF	400**	138	60.0	28.0	44 (54.3)	4
		CAS	50	69	59.0	28.0	38 (55.1)	

Note: 5-FL: flucytosine; AMB: conventional amphotericin-B; ANI: anidulafungin; CAS: caspofungin; FLU: fluconazole; ISA: isavuconazole; L-AMB: liposomal amphotericin B; MIC: micafungin; RZF: Rezafungin; PLA: placebo; NR: not reported.

*dose reported as mg/kg/day

**dose reported as mg/once week