Systematic review with network meta-analysis and multicriteria acceptability analyses on the effects of systemic antifungal agents for candidemia

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INTRODUCTION

High mortality rates and prolonged hospital stay are directly associated with invasive candidiasis, a leading fungal infection in hospitalised patients or in those undergoing solid organ transplants. We aimed compare the efficacy and safety of antifungal agents for treating invasive fungal infections caused by *Candida* spp.

METHODS

A systematic review with Bayesian network meta-analysis (NMA), surface under the cumulative ranking analysis (SUCRA) and stochastic multicriteria acceptability analyses (SMAA) were performed: PROSPERO register CRD42020149264. Searches were conducted in PubMed and Scopus (May-2021) and complemented by manual search. We included randomized controlled trials evaluating the effect of any dose or regimen of oral antifungals on the outcomes: mycological cure, discontinuation rates and adverse events. Networks meta-analysis were built for each outcome of interest. Results were reported as odds ratios (OR) with 95% credibility intervals (CrI) (Addis-v.1.17.6).

RESULTS

Thirteen trials (n=3,632) were included (**Figure 1**). No significant differences among therapies were found for the efficacy outcomes; however, caspofungin (50-150 mg), rezafungin (200-400mg) and micafungin (100-150 mg) led to higher rates of both clinical and mycological responses (SUCRA values over 60%). Fluconazole (400 mg) was rated as the last option for overall response (17%). Regarding treatment discontinuation and abnormal liver function, caspofungin 150 mg was considered the safest therapy. Rezafungin (200-400mg) and micafungin (100 mg) were associated with lower discontinuation rates (<40%) while conventional amphotericin B (0.6-0.7mg/kg) was more likely led to this outcome (OR 0.08 [95% CrI 0.00-0.95] vs. caspofungin 150 mg) and to liver function impairment. Caspofungin had the highest benefit-risk ratio (SMAA).

RESULTS

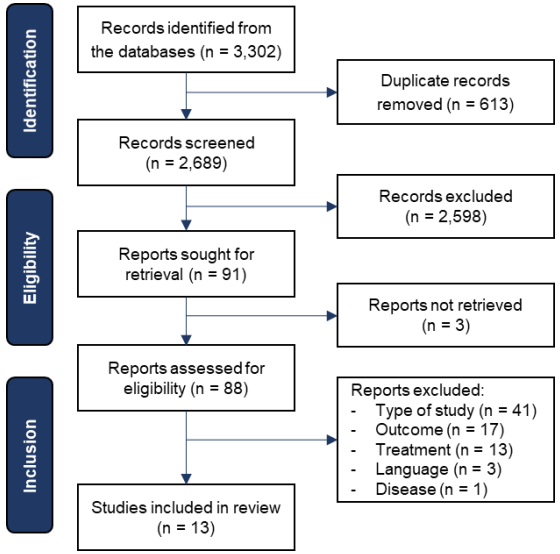


Figure 1. Flowchart of the systematic review

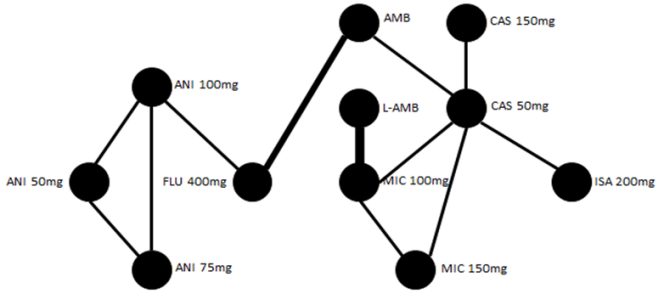


Figure 2. Network plot for the main efficacy outcome – overall response

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

RESULTS

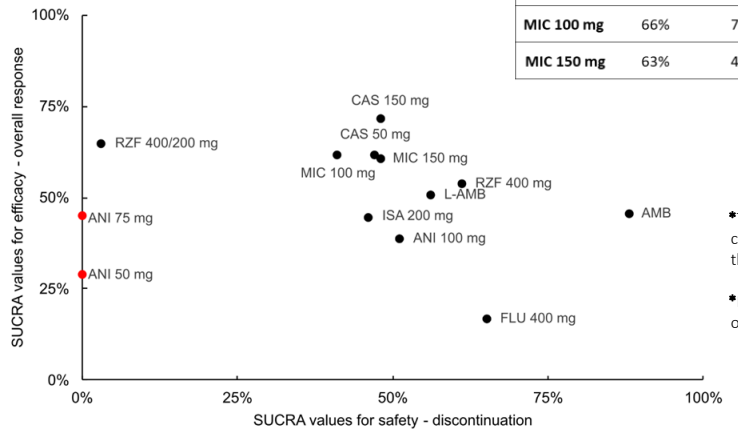
See the main network plot for the outcome of overall response (accounting for both clinical and microbiological responses) in **Figure 2.** The results obtained in SUCRA for all the individual outcomes are available in **Table 1**. The ranking plot on the two main outcomes (efficacy as overall response and safety as discontinuation due to adverse events) is depicted in **Figure 3.**

Table 1. SUCRA probabilities for each outcome

	Overall response	Microbiol. response	Recurrence	Discontinuat	Abnor. liver function
AMB	49%	-	52%	88%	87%
ANI 50 mg	31%	-	-	-	-
ANI 75 mg	45%	-	-	-	-
ANI 100 mg	41%	-	-	45%	37%
CAS 50 mg	64%	47%	71%	43%	46%
CAS 150 mg	72%	77%	17%	44%	12%
FLU 400 mg	18%	-	-	60%	68%
ISA 200 mg	48%	8%	28%	42%	-
L-AMB	53%	51%	-	55%	-
MIC 100 mg	66%	75%	74%	35%	-
MIC 150 mg	63%	43%	58%	45%	-

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

Figure 3. Ranking plot based on SUCRA



*Treatments lying in the upper-left corner are more effective and safer than the other treatments

*Red spots: no available data for the outcome

CONCLUSIONS

Echinocandins should be used as first-line treatments for invasive candidiasis following a priority order of caspofungin and micafungin. Rezafungin, an under development echinocandin, is an 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.