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Systemic antifungal therapy for oesophageal candidiasis – systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Introduction: Oesophageal candidiasis is a common infection among individuals with immunosuppression, associated with significant morbidity. Available guidelines recommend fluconazole as the preferred treatment; however, data regarding its effectiveness in an era of increased fluconazole resistance has not been systematically compiled.

Methods: A systematic review and meta-analysis of randomized controlled trials (RCTs) addressing systemic antifungal therapy for oesophageal candidiasis was undertaken. The primary outcome was clinical response. Subgroup analysis was planned based on immune status and *Candida* spp.

Results: Twelve RCTs were included, of which six compared fluconazole with other azoles, four compared fluconazole with echinocandins, and two compared amphotericin deoxycholate with echinocandins. Most RCTs mainly included human-immunodeficiency-virus-positive individuals. No significant differences were found between fluconazole and comparators for the outcomes of clinical response or combined clinical and endoscopic response [relative risk (RR) 1.02, 95% confidence interval (CI) 0.97–1.07 and RR 1.06, 95% CI 0.98–1.15, respectively]. No differences were found between fluconazole and other azoles for other outcomes; however, compared with echinocandins, fluconazole had significantly higher mycological response rates and lower early relapse rates (RR 1.09, 95% CI 1.02–1.17 and RR 0.42, 95% CI 0.26–0.68, respectively). No significant differences were demonstrated between fluconazole and comparators for overall or severe adverse events. Information required for the planned subgroup analyses was not available.

Conclusions: No differences in efficacy or safety were found between fluconazole and other azoles for the treatment of candida oesophagitis. The use of echinocandins resulted in lower mycological cure rates and higher relapse rates. Additional RCTs should evaluate these interventions among broader patient populations and a wider spectrum of *Candida* spp.

1. Background

The prevalence of oesophageal candidiasis has increased, and is reported to affect approximately 15% of individuals infected with human immunodeficiency virus (HIV) [1]. *Candida albicans* is the most common causative organism, accounting for approximately 80% of cases [2]. However, the emergence of non-*albicans* species and fluconazole resistance are well documented [3–7]. Oesophageal candidiasis also occurs in HIV-seronegative immunocompromised individuals, such as solid organ transplant recipients, patients with haematological malignancy, and patients treated with corticosteroids [8,9].

The diagnosis of oesophageal candidiasis is usually made by endoscopy. Clinical criteria may also be acceptable for initiating systemic antifungal therapy in high-risk populations [10]. Oesophageal candidiasis, occurring with or without oropharyngeal involvement, is associated with significant morbidity, including pain

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when swallowing, ulcers, erosions and fistulae. Among individuals with significant immunosuppression, oesophageal candidiasis may also cause dissemination. Accordingly, in this particular population, a prompt systemic antifungal treatment is required. Several guidelines recommend fluconazole as the preferred treatment for oesophageal candidiasis [11–13]. However, colonization with azole-resistant isolates represents an increasing problem, while concerns regarding higher rates of relapse with echinocandins have been raised [14]. A recent network meta-analysis evaluated various interventions for the management of individuals with concomitant oropharyngeal and oesophageal candidiasis. Only four trials comparing currently accepted systemic antifungal drugs were included in this meta-analysis [15]. Therefore, a systematic review and meta-analysis of randomized controlled trials (RCTs) addressing systemic antifungal therapy for oesophageal candidiasis was undertaken.

2. Methods

This review was conducted and reported according to PRISMA guidelines [16]. The protocol was registered in PROSPERO (CRD42021277409).

2.1. Inclusion criteria and outcomes

This review included RCTs that compared any systemic antifungal drug regimen with another systemic regimen, administered to adult (age ≥18 years) individuals diagnosed with oesophageal candidiasis. Any dosage of study drugs, any route of administration (i.e. oral or intravenous) and any duration were included. Monotherapy or combination therapy with any azole, echinocandin or amphotericin B (AmpB) formulation were allowed. Trials using placebo as a comparator were excluded, as well as those using monotherapy with ketoconazole, miconazole or flucytosine, as these comparators are not in routine use due to ineffectiveness or serious adverse events (AEs) in the presence of newer available drugs [17]. In addition, RCTs with differences in treatment durations between the study arms were excluded.

Clinical response at the end of therapy and at late follow-up were defined as primary outcomes. Secondary outcomes included combined clinical and endoscopic response, endoscopic cure/response alone, and mycological response, all as defined in the individual studies. In addition, mortality, duration of hospitalization, AEs and additional outcomes, as defined in individual trials, were documented.

2.2. Search strategy and selection criteria

PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and ClinicalKey were searched from inception to 14 August 2021 (last search date). The search term for PubMed included a combination of the term ‘candida OR candidal OR candidiasis OR candidiases) with the term ‘esophageal OR esophagitis’, combined with the Cochrane filter for RCTs. Unpublished data were searched in references of included trials, relevant conference proceedings, ClinicalTrials.gov and through personal contact with the investigators of the included studies. No language, publication status or date restrictions were applied.

2.3. Study selection and data extraction

Two reviewers independently performed the search, applied the inclusion criteria and conducted data extraction. For all outcomes, data were extracted preferentially for the intention-to-treat population; if not available, data were extracted for the per-protocol population. Risk of bias was assessed using the domain-based evaluation recommended by the Cochrane Collaboration [18]. The following domains were assessed: allocation sequence generation, allocation concealment, blinding, incomplete outcome data assessment, selective outcome reporting, and other potential biases. These were graded as low, high or unknown risk of bias, according to the criteria provided in the Cochrane handbook [18]. Sensitivity analysis was planned by allocation concealment and generation status, as well as blinding. The following subgroup analyses were also planned: HIV-positive individuals, individuals with haematological malignancy, and individuals infected with non-*albicans* spp. (specifically, *Candida glabrata* or *Candida krusei* oesophagitis). A funnel plot was planned to assess small study effects for outcomes reported by >10 trials.

2.4. Statistical analysis

For each individual study, relative risks (RR) and 95% confidence intervals (CI) were calculated. Heterogeneity was assessed using the χ^2 test for heterogeneity and the I^2 measure of inconsistency [19]. If no substantial heterogeneity was found (I^2<50%), meta-analysis was performed using the Mantel–Haenszel fixed-effects model (RevMan Version 5.3); otherwise, the random effect model was used. Comparisons were subcategorized by the type of drug (fluconazole vs. other azoles or vs. echinocandin; AmpB vs. echinocandin).

3. Results

The study flow chart is presented in Fig. 1. Twenty-one publications were retrieved for full-text assessment; of these, 12 met the inclusion criteria [20–32]. In 11 trials, the majority of participants (>75%) were HIV-positive individuals. In one trial [20], HIV-positive individuals accounted for 37% of the sample.

The comparisons included fluconazole vs. any other azole (six trials: four compared fluconazole with itraconazole, one compared fluconazole with voriconazole [25], and one compared fluconazole with isavuconazole [20]); fluconazole vs. echinocandin (four trials: two compared fluconazole with micafungin [26,27], one compared fluconazole with caspofungin [28], and one compared fluconazole with anidulafungin [29]); and echinocandin vs. amphotericin deoxycholate (two trials comparing AmpB with caspofungin (30,31)]. Details regarding included trials and comparisons are provided in Table 1.

Fluconazole was administered orally in most trials, and intravenously in three trials comparing fluconazole with an echinocandin [26–28]. The dosage of fluconazole was 200 mg/day in most trials; two studies used 200 mg as a loading dose, followed by 100 mg/day [20,29]. The duration of therapy was ≥2 weeks and up to 6–8 weeks [24,25] in all but two trials, using a 1–3-week regimen [28,31]. Trials using itraconazole as the comparator used capsules in three trials and solution in one trial [24] (see Table 1).

Five included trials were industry-sponsored; four of them compared fluconazole with an echinocandin and one compared fluconazole with isavuconazole [20,26–29]. All studies required endoscopic confirmation for the diagnosis of oesophageal candidiasis. All trials reported baseline *Candida* spp., with <5% *C. glabrata* or *C. krusei* in all but one trial which reported 19% of the total cohort with these species at baseline [28].

All included trials were considered to have unclear risk of bias for allocation concealment. Four trials were found to have unclear risk of bias for allocation generation [24,26,29,31], while the others had low risk of bias. Eleven studies were double blinded, while one large trial comparing fluconazole with itraconazole was unblinded [22]. Table S1 (see online supplementary material) shows detailed risk of bias assessment.

Table 1
Characteristics of included trials.

Study ID	Comparator drug	Route of administration and intervention	Underlying condition	Duration of treatment (weeks)	Number randomized	Primary outcome	Allocation generation	Allocation concealment	Blinding
Fluconazole vs. another azole									
Ally 2001 [25]	Voriconazole	PO, 200 mg x1/d	HIV 94%	2–6	391	Endoscopic cure	A	B	DB
Barbaro 1996 [22]	Itraconazole	PO (capsules), 100 mg twice daily	HIV 100%	2–5	2213	Endoscopic and clinical cure, and rate of treatment failure	A	B	Open
Barbaro 1995 [21]	Itraconazole	PO (capsules), 100 mg twice daily	HIV 100%	3	123	Endoscopic and clinical response	A	B	DB
Barbaro 1996 [23]	Itraconazole + flucytosine	PO (capsules), 3 mg/kg/day	HIV 100%	2–5	85 (60 intervention groups)	Endoscopic and clinical response	A	B	DB
Wilcox 1997 [24]	Itraconazole	PO (solution), 100–200 mg once daily	HIV 93%	3–8	110	Clinical response	B	B	DB
Viljoen 2015 [20]	Isavuconazole	PO, 200 mg on day 1 and then 100 mg once daily	37% HIV	2–3	160	Endoscopically confirmed clinical response	A	B	DB
Fluconazole vs. echinocandin									
de Wet 2004 [26]	Micafungin	IV, 200 mg/day	HIV 100%	2–3	245	Endoscopic cure	B	B	DB
de Wet 2005 [27]	Micafungin	IV, 200 mg/day	HIV 94%	2–6	523	Endoscopic cure	A	B	DB
Krause 2004 [29]	Anidulafungin	PO, 200 mg on day 1, followed by 100 mg/day	HIV 76%	2–3	601	Endoscopic cure	B	B	DB
Villanueva 2002 [28]	Caspofungin	IV, 200 mg/day	HIV 87%	1–3	177	Combined clinical and endoscopic response	A	B	DB
Amphotericin B vs. echinocandin									
Villanueva 2001 [30]	Caspofungin	IV Amphotericin B dexycholate 0.5 mg/kg/day	HIV 80%	2	128	Combined clinical and endoscopic response	A	B	DB
Arathoon 2002 [31]	Caspofungin	IV Amphotericin B dexycholate 0.5 mg/kg/day	HIV 98%	1–2	140	Combined clinical and endoscopic response	B	B	DB

A, low risk of bias; B, unclear risk of bias; DB, double blind; HIV, human immunodeficiency virus.

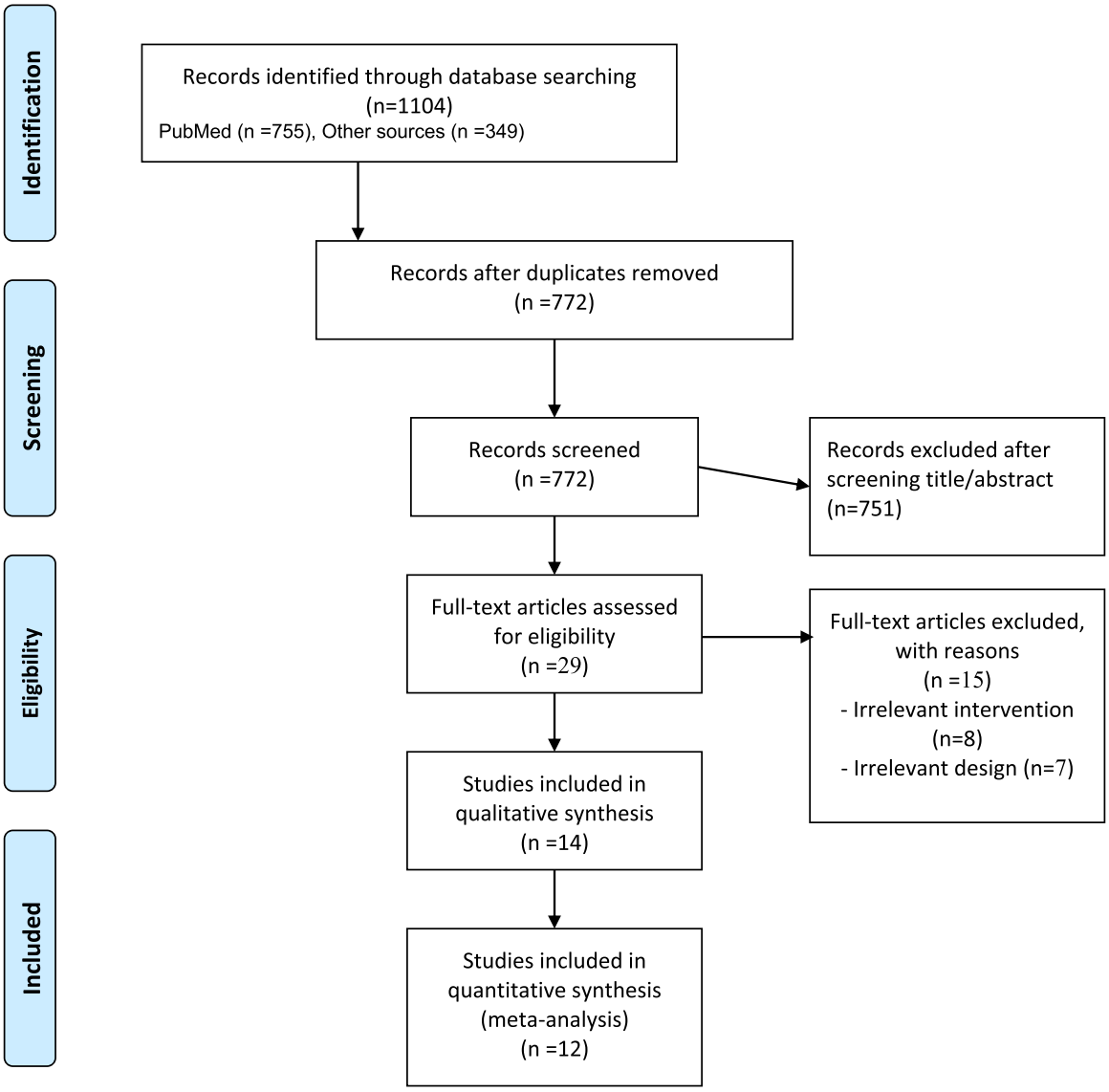

Fig. 1. Study flowchart.

3.1. Outcomes stratified by comparison

3.1.1. Fluconazole vs. other therapy

For the primary outcome of clinical response at the end of therapy, eight trials (3936 patients) were included; all but one [20] of these trials mainly evaluated HIV-positive individuals. Four compared fluconazole with another azole (mostly itraconazole), and four compared fluconazole with echinocandin. All comparisons demonstrated no difference between arms (fluconazole vs. others, RR 1.02, 95% CI 0.97–1.07), with substantial heterogeneity for this outcome (I^2=79%). This heterogeneity resolved after excluding the study by Barbaro *et al.*, comparing fluconazole with itraconazole [22]. However, this did not change the results (RR 1.01, 95% CI 0.99–1.02) (Fig. 2). No studies reported clinical response at late follow-up.

All eight trials had unknown risk of bias for allocation concealment. Five trials had low risk of bias for allocation generation, and demonstrated no significant difference between fluconazole and comparators (RR 1.01, 95% CI 0.96–1.06). Seven trials were double blinded, again with no difference between the arms compiling these trials (RR 1.01, 95% CI 0.99–1.02, without heterogeneity). Three trials administering intravenous fluconazole and reporting clinical response at the end of therapy demonstrated similar results to five trials using oral formulations. All but two trials [20,29] used a fluconazole dosage of 200 mg/day. None of the outcomes in the latter two trials, using fluconazole 100 mg/day, were demonstrated to be inferior.

Subgroup analysis for haematological malignancy was not available. Regarding HIV-positive individuals, excluding the one trial which had a population of <75% HIV-positive individuals [20], no difference in the primary outcome was observed. Only microbiological outcomes were reported by *Candida* spp. (see below). A funnel plot has not been presented due to the low number of included trials.

Combined clinical and endoscopic response was reported in two trials at the end of therapy [26,28], with no significant difference between fluconazole and echinocandin (RR 1.06, 95% CI 0.98–115, I^2=0%). At late follow-up, two trials reported no difference between fluconazole and other azoles (RR 1.03, 95% CI 0.97–1.10) [22,25]. One trial (452 patients), comparing fluconazole with

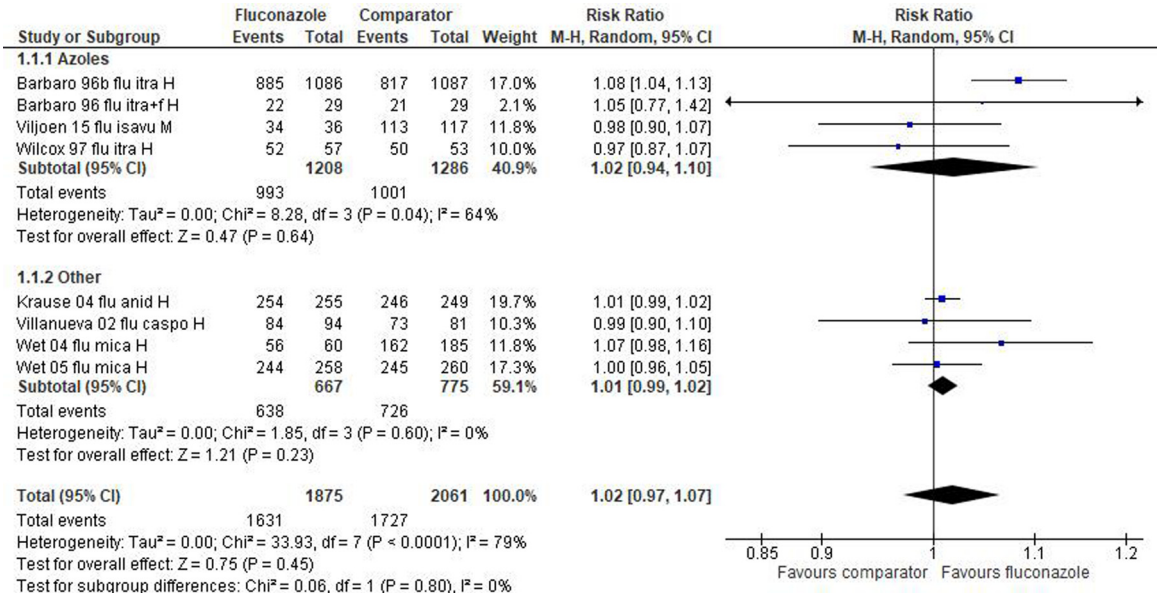

Fig. 2. Fluconazole vs. comparator – clinical response at end of therapy. CI, confidence interval.

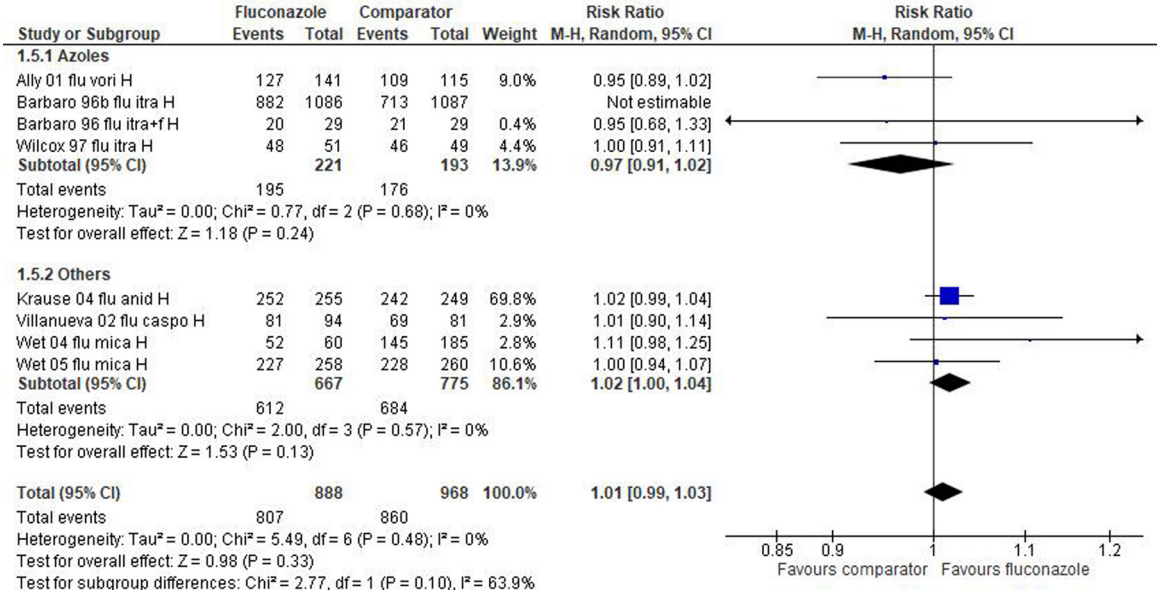

Fig. 3. Fluconazole vs. comparator – endoscopic response at end of therapy. CI, confidence interval.

anidulafungin in a mixed population, demonstrated a significantly higher response rate for fluconazole (RR 1.39, 95% CI 1.25–1.54) [29].

Eight trials (4029 patients) reported endoscopic cure rates at the end of therapy, with no significant difference between fluconazole and other azoles (RR 1.04, 95% CI 0.86–1.26) or between fluconazole and echinocandins (RR 1.02, 95% CI 1.0–1.04). Substantial heterogeneity was, again, resolved by excluding Barbaro *et al.* [20], without changing the results (Fig. 3). At late follow-up, three trials did not demonstrate any difference between fluconazole and other azoles (RR 0.98, 95% CI 0.96–1.01).

Five trials (1142 patients) reported mycological response at the end of therapy and none at late follow-up, with no significant difference between fluconazole and other azoles (two trials, RR 0.92, 95% CI 0.84–1.00, without heterogeneity). However, a significantly lower mycological response was reported for echinocandins compared with fluconazole (three trials, RR 1.09, 95% CI 1.02–1.17, without heterogeneity) (Fig. 4). Very few data were available on this outcome for the subgroup of patients with *C. krusei* or *C. glabrata* (36 patients), with no difference between fluconazole and voriconazole or caspofungin for *C. krusei* and *C. glabrata*, respectively.

No significant difference was demonstrated between fluconazole and any of the comparators for the outcome of 28-day mortality (four trials, 3033 patients, RR 1.10, 95% CI 0.75–1.6, without heterogeneity).

Early relapse was reported from seven trials (3509 patients) and demonstrated no difference between fluconazole and other azoles. However, early relapse was significantly more common with echinocandins compared with fluconazole (four trials, 1204 patients, RR 0.42, 95% CI 0.26–0.68, I^2=21%, Fig. 5). No significant difference in late relapse was demonstrated between fluconazole and other azoles (two trials, RR 1.15, 95% CI 0.78–1.69), or between fluconazole and echinocandins (two trials, RR 0.70, 95% CI 0.44–

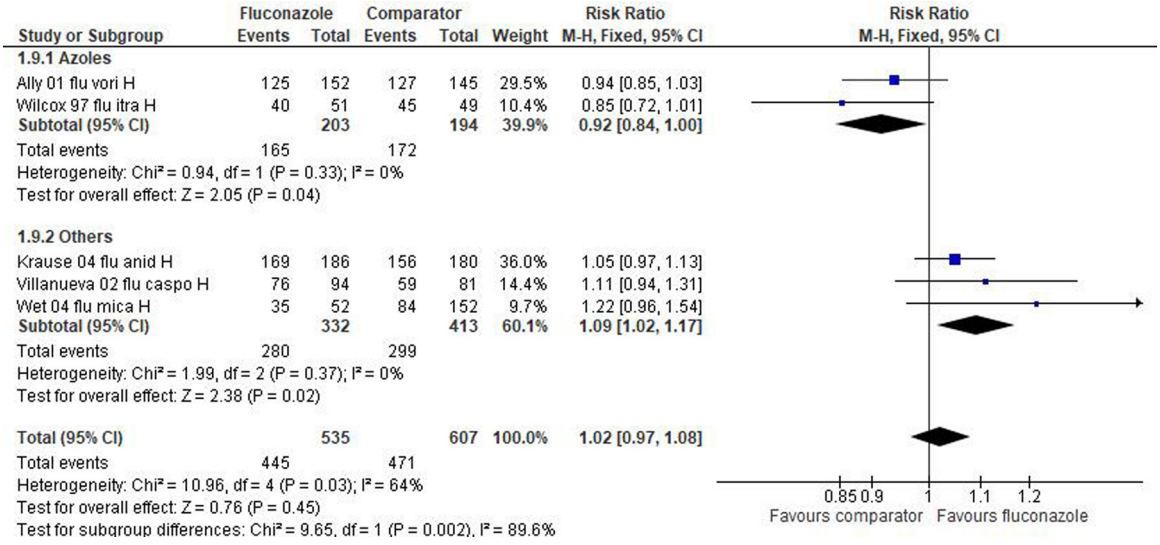

Fig. 4. Fluconazole vs. comparator – mycological response at end of therapy. CI, confidence interval.

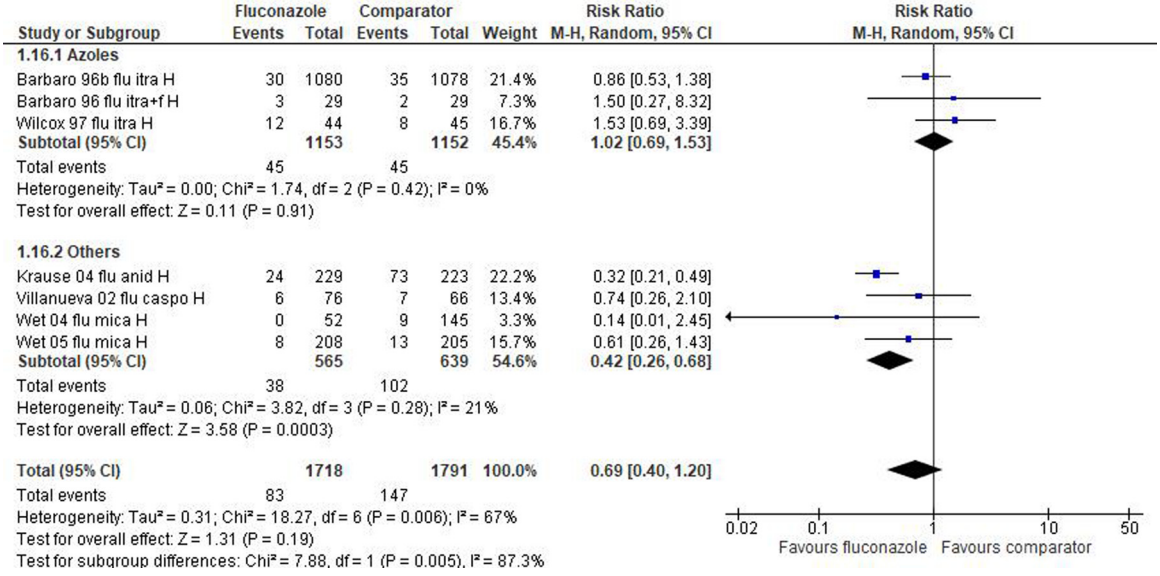

Fig. 5. Fluconazole vs. comparator – early relapse. CI, confidence interval.

1.10). Re-admissions and duration of hospitalization were not reported in any of the trials.

No significant difference between fluconazole and comparators was demonstrated for any AEs (six trials, RR 0.94, 95% CI 0.83–1.05, I^2=2%), severe AEs (two trials, RR 1.66, 95% CI 0.60–4.60, without heterogeneity), and AEs requiring drug discontinuation (seven trials, RR 0.72, 95% CI 0.42–1.25, without heterogeneity). No significant difference between fluconazole and comparators was demonstrated for laboratory AEs in general, and for liver function abnormality tests specifically. Regarding other AEs, no difference in diarrhoea and phlebitis rates was demonstrated between arms. In contrast, fever and rash were significantly less common with comparators compared with fluconazole (fever: five trials, RR 0.57, 95% CI 0.36–0.91, without heterogeneity; rash: five trials, RR 0.63, 95% CI 0.40–0.99, without heterogeneity).

Only three trials reported on susceptibility of *C. albicans* baseline isolates. In one of these studies, 10% of isolates exhibited fluconazole resistance [minimum inhibitory concentration (MIC) ≥8 μg/mL]. However, outcomes were not reported specifically in this sub [28]. Another study reported three cases of fluconazole resistance (MIC ≥8 μg/mL) among 227 cases of *C. albicans*, all of which had persistent mucosal lesions [27]. An additional trial comparing fluconazole with voriconazole reported three cases of fluconazole-resistant (MIC >50 μg/mL) *C. albicans*; all three comprised one-third of the nine ??% cases that concluded in fluconazole treatment failure [25].

3.2. Other comparisons

Two trials evaluated the use of AmpB deoxycholate vs. caspofungin. No difference was observed for the outcomes of clinical response or combined clinical and endoscopic response. However, both trials reported that endoscopic response was significantly more likely with caspofungin (RR 0.77, 95% CI 0.64–0.93, without heterogeneity), and AEs were significantly more common with AmpB (including any AEs, severe AEs, diarrhoea and fever). One of these trials found no difference in early relapse rate between groups [31].

An additional trial compared micafungin with anidulafungin for any type of fungal infection. Oesophageal candidiasis was reported

in 16 patients overall; this small sample did not yield statistical power for statistical inference [32]. Similarly, the only trial that compared AmpB and fluconazole only included 31 individuals. Clinical response with fluconazole was 11/13 (85%), compared with 6/12 (50%) with AmpB (P=0.096) [33].

4. Discussion

This systematic review and meta-analysis of RCTs included 12 trials comparing various systemic drugs for the treatment of candida oesophagitis. The most common intervention was oral fluconazole, compared with other azoles or echinocandins. The vast majority of included individuals were HIV-seropositive. The predefined primary outcome was clinical response, a typical patient-related outcome. Overall, this study found no advantage of echinocandins or azoles other than fluconazole over fluconazole in terms of efficacy for the treatment of candida oesophagitis. For the primary outcome of clinical response, no significant difference was demonstrated between fluconazole and other azoles or fluconazole and echinocandins (RR 1.02, 95% CI 0.97–1.07). Dosing and duration differences did not influence the results. Additionally, no significant difference between fluconazole and comparators was demonstrated for other efficacy outcomes, including combined endoscopic and clinical response, endoscopic response, and mortality. Nevertheless, compared with echinocandins, the use of fluconazole had a trend for higher rates of endoscopic response, as well as significantly higher rates of mycological response and lower early relapse rates. No significant difference was demonstrated between fluconazole and comparators for overall AEs, severe AEs or AEs requiring drug discontinuation. However, fever and rash were significantly more common with fluconazole.

The significant heterogeneity observed for the outcomes of clinical response and endoscopic response stemmed from one large trial [22]. This was the only open label study included in this analysis, demonstrating outcomes favouring fluconazole, the investigated drug. Accordingly, the absence of blinding could have biased the results.

Data regarding other comparisons were scarce. Two trials compared caspofungin with AmpB and found significantly better endoscopic response rates with the former (RR 0.77, 95 % CI 0.64–0.93), along with lower AE rates.

In the network meta-analysis by Zeng *et al.*, no significant difference was demonstrated between fluconazole and itraconazole, micafungin or posaconazole for the treatment of either candida oesophagitis or oropharyngeal candidiasis [15]. Only four trials were included in this meta-analysis comparing fluconazole with systemic drugs other than ketoconazole for oesophagitis. The authors concluded that no antifungal intervention was superior to fluconazole for oesophageal candidiasis, which was consistent with the present results. Only one trial comparing echinocandins with fluconazole for candida oesophagitis was included in the meta-analysis. Hence, the findings of higher relapse rate and mycological failure with echinocandins were not captured by this study [15].

Guidelines for treating HIV-positive individuals with candida oesophagitis recommend a 14–21-day course of fluconazole, administered either orally or intravenously, at a daily dose of 100–400 mg or oral itraconazole solution. Alternatives that have evidence of lower strength include isavuconazole, voriconazole, echinocandins and AmpB [34]. Similarly, the guidelines of the Infectious Diseases Society of America on management of candidiasis also recommend fluconazole, 200–400 mg daily, for 14–21 days as first-line therapy for candida oesophagitis [35]. These recommendations are in line with the present findings of similar clinical and endoscopic response with fluconazole and other drugs, and a higher relapse rate and mycological failure with echinocandins. This higher relapse rate is mentioned in both guidelines, based on individual trials, although no formal meta-analysis has been conducted previously. Data regarding the penetration of echinocandins to oesophageal tissue are scarce, and it is unclear whether relapse may be related to low residual tissue concentrations of echinocandins compared with other antifungals [36]. Preclinical studies on echinocandins in experimental oesophageal candidiasis suggested dose-dependent clearance of *C. albicans* [37,38]. Although the recommended dose of fluconazole is 200–400 mg/day, none of the trials used a dose >200 mg/day; this aspect should be evaluated further in clinical studies.

Limitations of this meta-analysis include the limitations that originated from the methodological quality of the individual trials. All trials included in the primary outcome analysis had unclear risk of bias for allocation concealment, and the largest included trial was open label. The external validity is somewhat diminished as the vast majority of included individuals were HIV-positive. As such, the results cannot be generalized for populations with other types of immunosuppression. Eleven of the 12 included studies were published before 2005, when the prevalence of non-*albicans* isolates was low. It should also be mentioned that four of the included trials compared fluconazole with itraconazole, administered in capsules in three trials. The effectiveness of the latter drug is possibly limited by poor absorption, with probable underexposure in some individuals.

In summary, this study found that fluconazole was at least as effective and safe as other azoles and echinocandins for the treatment of candida oesophagitis, mainly in HIV-positive individuals. Use of echinocandins resulted in lower mycological cure rates and higher relapse rates. Additional RCTs including a broader immunocompromised population and a wider spectrum of *Candida* spp., including fluconazole-resistant isolates, should be conducted to guide optimal treatment in the current clinical setting.

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Competing interests

None declared.

Ethical approval

Not required.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2022.106590.

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