Saudi Pharmaceutical Journal 29 (2021) 315–323

Contents lists available at ScienceDirect

Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Original article

Efficacy of clotrimazole for the management of oral candidiasis: A meta-analysis of randomized clinical trials

Thamer A. Almangour [a,*], Keith S. Kaye [b], Mohammed Alessa [a], Khalid Eljaaly [c,d], Fadilah Sfouq Aleanizy [e], Aynaa Alsharidi [f], Fahad M. Al Majid [f], Naif H. Alotaibi [f], Abdullah A Alzeer [a,*], Faris S. Alnezary [g,h], Abdullah A. Alhifany [i]

[a] Department of Clinical Pharmacy, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia
[b] Director of Clinical Research, Division of Infectious Diseases, University of Michigan Medical School, 5510A MSRB I, SPC 5680, 1150 W. Medical Center Drive, Ann Arbor, MI 48109-5680, United States
[c] Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia
[d] Pharmacy College, University of Arizona, Tucson, AZ, United States
[e] Department of Pharmaceutics, College of Pharmacy, King Saud University, P.O. Box 22452, Riyadh 11495, Saudi Arabia
[f] Division of Infectious Diseases, Department of Internal Medicine, College of Medicine, King Saud University, PO Box 7805, Riyadh 11472, Saudi Arabia
[g] Department of Clinical and Hospital Pharmacy, College of Pharmacy, Taibah University, Medinah, Saudi Arabia
[h] University of Houston College of Pharmacy, Pharmacy Practice and Translational Research, 4901 Calhoun Rd #3044, Houston, TX 77204, United States
[i] Department of Clinical Pharmacy, College of Pharmacy, Umm Al-Qura University P.O. Box 13578 Makkah 21955, Saudi Arabia

ARTICLE INFO

Article history:
Received 12 November 2020
Accepted 6 March 2021
Available online 24 March 2021

Keywords:
Clotrimazole
Oral candidiasis
Systematic review
Meta-analysis

ABSTRACT

Purpose: To assess the efficacy and safety of topical application of clotrimazole versus others in the treatment of oropharyngeal candidiasis (OPC).
Method: Four electronic databases, registries of ongoing trials, and manual search were used to identify randomized controlled trials (RCTs) that compared the efficacy of clotrimazole to other antifungal agents in patients who were clinically diagnosed with oral candidiasis up to November 1st, 2019. Primary outcomes were clinical response and mycological cure rates. Secondary outcomes include relapse rate, incidence of systemic infections, and compliance. Adverse effects were also evaluated.
Results: Sixteen RCTs with a total of 1685 patients were included. Half of the eligible studies were considered at high risk of performance bias and more than a third, at high risk of reporting bias. Our analysis showed no significant difference in clinical response between clotrimazole and all other antifungal agents. However, clotrimazole was less effective in terms of mycologic cure and relapse rate. Sensitivity analysis comparing clotrimazole to other topical antifungal agents only showed no differences in clinical response, microbiologic cure or relapse. Further sensitivity analysis showed significant efficacy of fluconazole over clotrimazole.
Conclusion: This meta-analysis indicated that clotrimazole is less effective than fluconazole but as effective as other topical therapies in treating OPC. Well-designed high-quality RCT is needed to validate these findings.

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OPC, oropharyngeal candidiasis; OR, odds ratio.

* Corresponding authors at: Department of Clinical Pharmacy, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia (T.A. Almangour)
E-mail addresses: talmangour@gmail.com, talmangour@ksu.edu.sa (T.A. Almangour), keithka@med.umich.edu (K.S. Kaye), faleanizy@KSU.EDU.SA (F. Sfouq Aleanizy), aalsharidi@ksu.edu.sa (A. Alsharidi), almajid@ksu.edu.sa (F.M. Al Majid), nalotaibi4@ksu.edu.sa (N.H. Alotaibi), aalzeer@ksu.edu.sa (A.A Alzeer), falnezar@central.uh.edu (F.S. Alnezary), falnezar@central.uh.edu , aahifany@uqu.edu.sa (A.A. Alhifany).

Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.jsps.2021.03.003

1. Introduction

Candida is a part of normal flora residing on the skin, in gastrointestinal, and genitourinary tracts. About 45% of healthy individuals carry candida in their oral cavities (Shin et al., 2003). In certain conditions when host immune defense is compromised, candida can multiply in the superficial epithelium of the oral mucosa and become pathogenic causing oropharyngeal candidiasis (OPC), a common fungal infection (Farah et al., 2010; Millsop & Fazel, 2016; Naglik et al., 2003). *Candida albicans* is the most etiologic species of OPC; however, *C. glabrata, C. dubliniensis, and C. krusei, C. tropicalis*, and *C. parapsilosis* have also been described (Patel et al., 2012; Sangeorzan et al., 1994). Multiple predisposing factors are associated with OPC including human immunodeficiency virus (HIV) infection, solid organ or hematologic malignancies, chemotherapy, radiotherapy, diabetes mellitus, hyposalivation, denture use, as well as exposure to broad-spectrum antibiotics, immunomodulators, and xerostomic agents (Belazi et al., 2005; Compagnoni et al., 2007; Farah et al., 2010; Figueiral et al., 2007; Palmer et al., 1996; Scully, 2003; Soysa et al., 2008; Worthington et al., 2002). Diagnosis is generally made by physical examination and medical history review and confirmed by microscopic examination with a potassium hydroxide preparation that reveals pseudohyphae or budding yeast from swaps or scrapings obtained from oral lesions as well as cultures positive for candida species (Thompson et al., 2010).

Several topical and systemic antifungal agents are currently available for the treatment of OPC. For mild disease, topical agents, including clotrimazole troches, miconazole mucoadhesive buccal, or nystatin suspension, are recommended (Pappas et al., 2016). For moderate to severe cases, oral fluconazole is recommended

Table 1
PICOS strategy for clinical evidence.

PICOS	Clinical Review
Population	Patients with oral candidiasis
Intervention	Clotrimazole used in treating oral candidiasis regardless of dosage regimen
Comparator	Placebo or other antifungal therapies
Outcome	Clinical response, mycological cure, relapse rate, and adverse outcomes
Study design	Published or unpublished randomized controlled trials of any size and duration

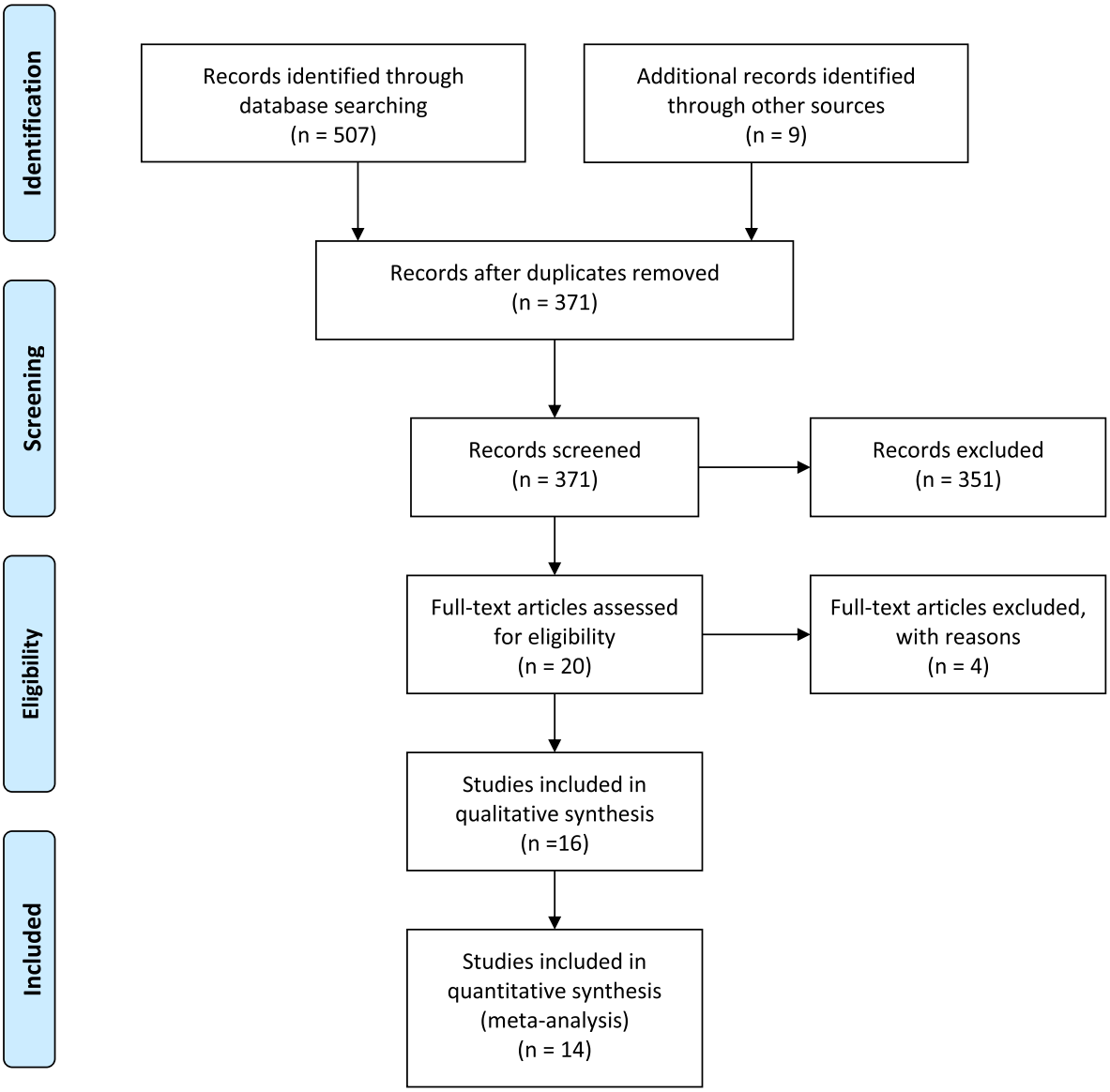

Fig. 1. Search strategy: Study selection process using preferred reporting items for systematic reviews and meta-analysis (PRISMA).

as first-line systemic antifungal agent (Pappas et al., 2016). Topical application to manage OPC minimizes drug interactions and adverse effects known to be associated with systemic antifungal agents; however, limitations exist such as local irritation, unpalatable taste, sugar content especially when used in patients with dental caries or uncontrolled diabetes, and lack of compliance due to the need for frequent administration (Sherman et al., 2002; Thompson et al., 2010).

As with all azole-type antifungal agents, clotrimazole primarily exhibits its pharmacological action through the inhibition of 14-α-lanosterol demethylation and, therefore, interferes with the biosynthesis of ergosterol, a major component of the fungal cell membrane (Hitchcock et al., 1990). For the treatment of OPC, clotrimazole is usually formulated to contain a 10 mg troche that is slowly dissolved in the mouth 5 times daily for 14 days (Crowley & Gallagher, 2014; Pappas et al., 2016). Several trials have evaluated the safety and efficacy of topical clotrimazole in the treatment of OPC but to date, no systematic review has been published to evaluate these findings. The aim of this review is to assess the safety and efficacy of topical application of clotrimazole versus others in the treatment of OPC taking into consideration all dosage regimens (dose, formulation, frequency, and duration) and all patient populations.

2. Materials and method

This review was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Shamseer et al., 2015).

2.1. Search strategies

The search was conducted by two independent authors (TA and MA) who identified eligible studies through a comprehensive search of four databases: Medline through PubMed, Embase, Web of Science, and Cochran Central Register of Controlled Trials (CENTRAL). These databases were searched up to November 2019 using Patients, Intervention, Comparator, Outcome, and Study design (PICOS) strategy (Table 1). In our search strategy, the following terms were used in combination: (“candidiasis” OR “candidiosis” OR “oral candidiasis” OR “oral candidiases” OR “oropharyngeal candidiasis” OR “thrush” OR “candida stomatitis” OR “prosthetic stomatitis” OR “candida mucositis” OR “oral moniliasis” OR “rhomboid glossitis”) AND “clotrimazole” AND (“randomized controlled trial” OR “controlled clinical trial” OR “randomized controlled study” OR “RCT”). Other sources were used to search for more studies, which include registries of ongoing trials: clinicaltrial.gov, controlled-trial.com, centerwatch.com, and world health organization portal. A hand search was conducted by checking the reference lists of articles retrieved.

2.2. Inclusion criteria

We included published and unpublished randomized controlled trials that compared the efficacy of clotrimazole to placebo or other antifungal agents in patients who were diagnosed with oral candidiasis with no restriction on age, gender, or race. Diagnosis of oral candidiasis was based on clinical signs and symptoms, which confirmed by positive potassium hydroxide smear examination and positive local fungal cultures. All formulations, dosages, and durations were considered in this review.

Table 2
Characteristics of included studies.

Study	Year	Country	Total No. eligible patients	Mean age (years)	Diagnosis of OC	Clotrimazole				Control				
						Formulation	Dose (mg)	Frequency (times/day)	Duration (days)	Medication	Formulation	Dose (mg)	Frequency (times/day)	Duration (days)
(Montes et al., 1976)	1976	USA	12	32	C + M	Troches	10	10	14	Clotrimazole	Troches	50	10	14
(Kirkpatrick & Alling, 1978)	1978	USA	20	26	C + M	Troches	10	5	14	Placebo	Troches	–	5	14
(Yap & Bodey, 1979)	1979	USA	48 (52 episodes)	44	C + M	Troches	10	5	14	Clotrimazole	Troches	50	5	14
(Lawson & Bodey, 1980)	1980	USA	84 (88 episodes)	43	C + M	Troches	50	5	14	Nystatin	Vaginal tablet	–	5	14
(Shechtman et al., 1984)	1984	USA	16	–	C + M	Troches	10	5	2–28	Placebo	Troches	–	5	2–28
(Thamlikitkul et al., 1988)	1988	Thailand	45	38	C + M	Troches	10	4	7	Ketoconazole	Tablets	200	1	7
(Koletar et al., 1990)	1990	USA	39	33	C + M	Troches	10	5	14	Fluconazole	Capsules	100	1	14
(Conrad & Lentnek, 1990)	1990	USA	86	40	C + M	Troches	10	5	14	Nystatin	Pastille	1–2 [a]	5	14
(Redding et al., 1992)	1992	USA	24	–	C + M	Troches	10	5	14	Fluconazole	Tablets	100	1	14
(Pons et al., 1993)	1993	USA	334	37	C + M	Troches	10	5	14	Fluconazole	Capsules	100	1	14
(Sangeorzan et al., 1994)	1994	USA	45 (82 episodes)	39	C + M	Troches	10	5	14	Fluconazole	Capsules	100[b]	1	14
(Murray et al., 1997)	1997	USA	162	40	C + M	Troches	10	5	14	Itraconazole	Solution	200	1	14
(Linpiyawan et al., 2000)	2000	Thailand	29	32	–	Troches	10	5	7	Itraconazole	Solution	100	2	7
(Sabitha et al., 2005)	2005	India	74	–	C	1% solution	2–4 drops	4	14	Garlic	Paste	qs [c]	4	14
(Sholapurkar et al., 2009)	2009	India	89	50	C + M	mouth paint	- [d]	3	14	Fluconazole	Mouth rinse	- [d]	3	14
(Vazquez et al., 2010)	2010	USA	578	37	C + M	Troches	10	5	14	Miconazole	Buccal tab	50	1	14

C = Clinical diagnosis; Co = control; I = intervention; M = mycological diagnosis; OC = oral candidiasis.
a. This is a 3-arm study: clotrimazole 10 mg vs 1 nystatin pastille (200,000 units) vs 2 nystatin pastilles (400,000 units).
b. After initial 200 mg dose.
c. Quantity sufficient to cover the entire lesion with one drop of 2% lignocaine jelly.
d. 1% mouth paint to be applied to affected area with index finger vs 2 mg/ml fluconazole in distilled water to rinse 5 ml for 2–3 min then swallow.

2.3. Outcome measure

Primary outcomes were clinical response rate defined as the cure or improvement of signs and symptoms attributable to the oral lesion as well as mycological cure rate defined as negative culture's result. Secondary outcomes include relapse rate, the incidence of systemic infections, and compliance. Adverse effects were also evaluated.

2.4. Study selection, data extraction, and quality assessment

Two reviewers (TA and MA) independently reviewed the titles and abstracts of all identified studies. Selected studies were reviewed as full text for further assessment of inclusion. Double data extraction was conducted independently by two reviewers (TA and MA).

For the quality assessment and risk of bias of the included studies, the Cochrane Handbook for Systematic Review of Interventions (Version 5.1.0) and the RevMan 5.3 software were used. Quality assessment was undertaken independently by two authors (TA and AA).

2.5. Statistical analysis

Quantitative analyses of efficacy, including clinical, mycological, and relapse rate for clotrimazole were conducted using Stata 15.1 (StataCorp LP, College Station, Texas, USA) software. The efficacy outcomes were measured as odds ratio (OR), reported with its 95% confidence interval (CI), and plotted on a forest plot. Heterogeneity was evaluated using I^2 index that ranged from 0% to 100%. We used the I^2 value of 50% as the cutoff for significant heterogeneity. If no significant heterogeneity was detected, a fixed-effects model was used to determine the combined effect estimate. If significant heterogeneity was detected, fixed-effects and random-effects models were both used. Due to the limited number of studies reporting these outcomes and variability in the method of reporting, systemic infections, compliance, and adverse effects were evaluated using descriptive analysis.

3. Results

3.1. Search results

The initial search through the databases yielded 507 studies (Fig. 1). Duplicate studies (n = 145) were initially excluded using bibliographic management software (EndNote X8.1). Through the initial screening of the titles and abstracts of the remaining 371 results, 351 studies were excluded, among which, 331 studies were irrelevant, 12 studies were duplicates, 4 were nonclinical, and 4 studies in registries of ongoing trials were excluded due to either no results being available or participants not yet having been recruited. Full texts of the remaining 20 study manuscripts were thoroughly assessed for eligibility. Four studies were excluded because a primary outcome of interest was not clearly reported in one study, whereas three studies evaluated different outcomes than what we measure in this analysis. No study was excluded due to the unavailability of the full text version of the article. Sixteen trials were included in the systematic review.

3.2. Characteristics of included studies

Sixteen trials were published between 1976 and 2010, and the majority were conducted in the United States. A total of 1685 patients were included with an average age ranging between 26 and 50 years. The clotrimazole troche was the formulation used in 14 studies. Clotrimazole 10 mg 5 times daily for 14 days was the most used regimen. Seven studies specifically addressed HIV patients and 3 studies restrictively included cancer patients. Comparators were placebo in 2 studies, fluconazole in 5 studies, itraconazole in 2 studies, nystatin in 2 studies, different doses of clotrimazole in 2 studies, as well as ketoconazole, miconazole and garlic, each in a single study (Table 2).

3.3. Study quality and risk of bias assessment

Half of the eligible studies were judged to have a high risk of performance bias, while 6 out of 16 studies were judged to have a high risk of reporting bias. Detailed risk of bias assessment for each included study and across all studies is summarized in Fig. 2 and Fig. 3. There was a high agreement on the risk of bias assessment between authors.

3.4. Efficacy assessment

Clinical and mycological outcomes of the individual studies are summarized in Table 3. Meta-analysis of clinical and mycological outcomes of clotrimazole is summarized in Table 4. Twelve studies compared the efficacy of clotrimazole to all other (topical and systemic) antifungal agents. Two studies were excluded from the overall quantitative analysis due to unclear reporting in one study while clinical and mycological outcomes were not assessed separately in the other study. An additional study was excluded from

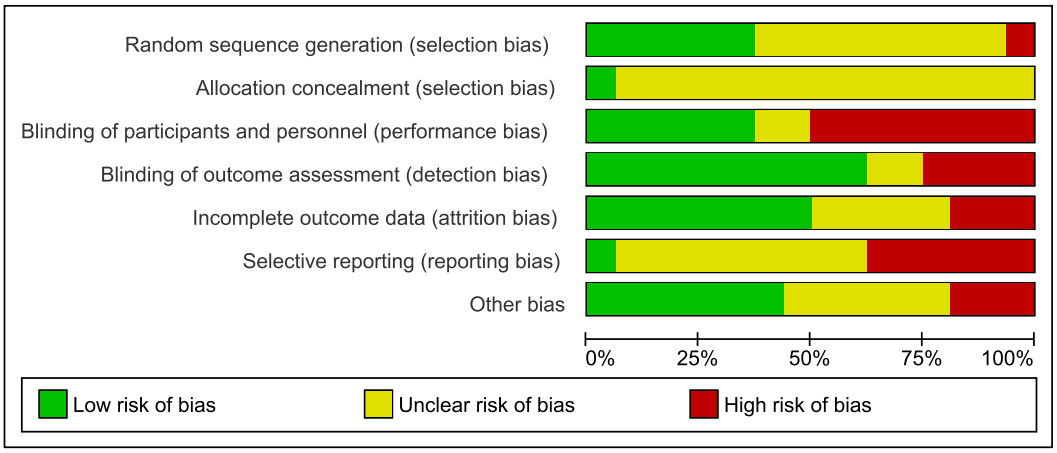

Fig. 2. Risk of bias graph: review authors' judgement about each risk of bias item presented as percentages across all included studies.

the quantitative analysis of mycological cure because a separate assessment for this outcome was not provided. Therefore, 10 studies were included in the quantitative analysis of clinical response and showed no significant difference (OR = 0.85, 95% CI = 0.65–1.11, I-squared = 45.0%) (Conrad & Lentnek, 1990; Koletar et al., 1990; Lawson & Bodey, 1980; Murray et al., 1997; Pons et al., 1993; Redding et al., 1992; Sabitha et al., 2005; Sangeorzan et al., 1994; Sholapurkar et al., 2009; Vazquez et al., 2010) while 9 studies were included in the quantitative analysis of mycological cure and showed that clotrimazole was significantly less likely to achieve mycological cure in a fixed-effects model (OR = 0.62, 95% CI = 0.49–0.79, I-squared = 58.1%) and random-effects model (OR = 0.56, 95% CI = 0.36–0.88, I-squared = 58.1%) (Koletar et al., 1990; Lawson & Bodey, 1980; Murray et al., 1997; Pons et al., 1993; Redding et al., 1992; Sabitha et al., 2005; Sangeorzan et al., 1994; Sholapurkar et al., 2009; Vazquez et al., 2010).

Sensitivity analysis was conducted to compare the efficacy of clotrimazole troches to fluconazole tablets or capsules (Fig. 4) and showed that clotrimazole is significantly less likely to achieve clinical response and mycological cure (clinical OR = 0.23, 95% CI = 0.09–0.57; mycological OR = 0.40, 95% CI = 0.26–0.61) (Koletar et al., 1990; Pons et al., 1993; Redding et al., 1992; Sangeorzan et al., 1994). Moreover, when efficacy of clotrimazole was compared to only other topical antifungal agents (Fig. 5), there was no significant difference in meta-analysis for clinical response using data from 3 studies (OR = 1.20, 95% CI = 0.87–1.67) (Conrad & Lentnek, 1990; Lawson & Bodey, 1980; Vazquez et al., 2010) and for mycological cure using data from 2 studies (OR = 0.93, 95% CI = 0.66–1.32) (Lawson & Bodey, 1980; Vazquez et al., 2010). The reason for excluding one study for mycological cure was because a separate assessment for this outcome was not provided. Further sensitivity analysis was conducted to compare clotrimazole troches to placebo and reported that clotrimazole is significantly more likely to achieve clinical response and mycological cure (clinical OR = 61.63, 95% CI = 6.95–546.12; mycological OR = 27.83, 95% CI = 3.15–246.12) (Kirkpatrick & Alling, 1978; Shechtman et al., 1984).

3.5. Safety assessment

Fifteen trials provided safety evaluations. Seven of the 15 trials reported an absence of adverse effects of clotrimazole while 8 trials reported specific adverse effects, gastrointestinal adverse effects being the most reported. An altered taste sensation, headache, dizziness, pruritus, rash, sweating, anemia, cough, dry mouth, fatigue, abnormal liver function tests, increased gamma-glutamyltransferase, and pain were also reported. The distribution of adverse effects of clotrimazole and comparators across studies is shown in Table 5.

3.6. Secondary outcomes

The relapse of OPC was reported in 11 studies. Four studies (Koletar et al., 1990; Pons et al., 1993; Redding et al., 1992; Sangeorzan et al., 1994) reported the relapse of OPC after clotrimazole troches compared to fluconazole tablets or capsules (Fig. 4). Relapse of OPC was significantly higher after treatment with clotrimazole compared to fluconazole using a fixed-effects model (OR = 2.04, 95% CI = 1.17–3.55, I-squared = 52.9%) and random-effects model (OR = 3.45, 95% CI = 1.06–11.30, I-squared = 52.9%). Ten studies reported the relapse of OPC after clotrimazole therapy compared to all other antifungal agents (topical and systemic) (Conrad & Lentnek, 1990; Koletar et al., 1990; Lawson & Bodey, 1980; Linpiyawan et al., 2000; Murray et al., 1997; Pons et al., 1993; Redding et al., 1992; Sangeorzan et al., 1994; Thamlikitkul et al., 1988; Vazquez et al., 2010). When data from these 10 studies were pooled in meta-analysis, relapse was significantly higher after clotrimazole therapy (OR = 1.46, 95% CI = 1.08–1.97). However, when relapse after clotrimazole therapy was compared to only other topical antifungal agents (Fig. 5), there was no significant difference when data from 3 studies were pooled in meta-analysis (OR = 1.11, 95% CI = 0.73–1.70) (Conrad & Lentnek, 1990; Lawson & Bodey, 1980; Vazquez et al., 2010). Meta-analysis of relapse rate of clotrimazole are summarized in Table 4.

Two studies reported the incidence of systemic infections. In one study, 3 (12%) patients in clotrimazole 10 mg group versus 1

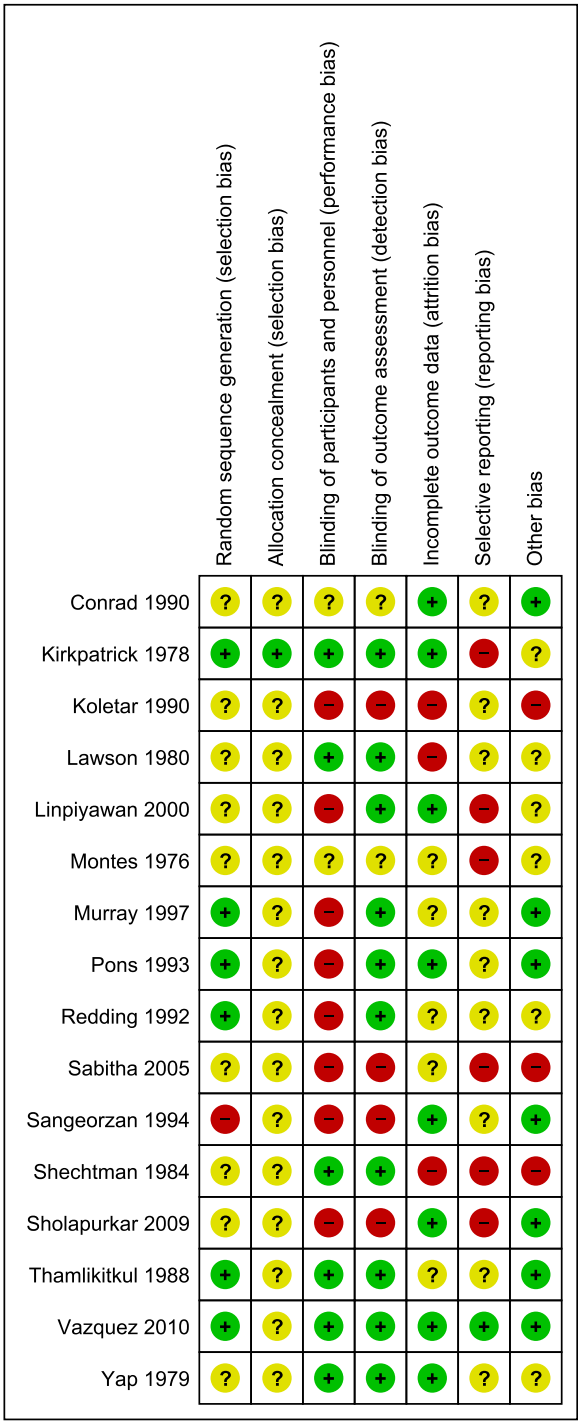

Fig. 3. Risk of bias summary: review authors' judgement about each risk of bias item for each included study.

Table 3
Clinical and mycological outcomes of clotrimazole versus control agents.

Study	Specific population studied	Control	% Clinical response [a] (No. of clinical responses/Total evaluable patients)			% Mycological cure [b] (No. of mycological cures/Total evaluable patients)		
			Clotrimazole	Control	P-value	Clotrimazole	Control	P-value
(Montes et al., 1976)	Non-specific	Clotrimazole 50 mg	100 (6/6)	100 (6/6)	NS	50 (3/6)	50 (3/6)	NS
(Kirkpatrick & Alling, 1978)	Non-specific	Placebo	100 (10/10)	10 (1/10)	P < 0.001	90 (9/10)	10 (1/10)	–
(Yap & Bodey, 1979) [c]	Cancer	Clotrimazole 50 mg	96 (25/26)	96 (25/26)	–	34 (9/26)	69 (18/26)	–
(Lawson & Bodey, 1980) [c]	Cancer	Nystatin	94 (34/36)	100 (30/30)	–	56 (20/36)	47 (14/30)	–
(Shechtman et al., 1984)	Cancer	Placebo	86 (6/7)	17 (1/6)	P = 0.025	43 (3/7)	0 (0/6)	P = 0.12
(Thamlikitkul et al., 1988)	Non-specific	Ketoconazole	100	100	–	64	64	–
(Koletar et al., 1990)	HIV	Fluconazole	65 (11/17)	100 (16/16)	P = 0.018	20 (3/15)	75 (12/16)	P = 0.004
(Conrad & Lentnek, 1990)	Non-specific	Nystatin	83 (19/23)	77 & 79 [d]	NS	52 (12/23)	29 & 47 [d]	NS
(Redding et al., 1992)	HIV	Fluconazole	73 (8/11)	100 (13/13)	NS	63 (5/8)	85 (11/13)	NS
(Pons et al., 1993)	HIV	Fluconazole	94 (128/136)	98 (149/152)	NS	48 (56/118)	65 (89/136)	P = 0.005
(Sangeorzan et al., 1994) [c]	HIV	Fluconazole	91 (31/34)	96 (45/47)	NS	27 (9/33)	49 (22/45)	NS
(Murray et al., 1997)	HIV	Itraconazole	70 (52/74)	77 (58/75)	P = 0.349	32 (24/74)	60 (45/75)	P < 0.001
(Linpiyawan et al., 2000)	HIV	Itraconazole	100 (15/15) [e]	100 (12/12)	NS	–	–	–
(Sabitha et al., 2005)	Non-specific	Garlic paste	87 (26/30)	100 (26/26)	P > 0.05	50 (15/30)	46 (12/26)	P > 0.05
(Sholapurkar et al., 2009)	Non-specific	Fluconazole	79 (22/28)	96 (26/27)	P < 0.05	86 (24/28)	89 (24/27)	NS
(Vazquez et al., 2010)	HIV	Miconazole	69 (199/287)	65 (188/290)	P = 0.1	25 (71/287)	27 (79/290)	P = 0.58

HIV = human immunodeficiency virus; NS = not statistically significant
a. Defined as cure or improvement at end of treatment.
b. Defined as negative findings on culture or absence of pseudohyphae/budding yeast on smear at end of treatment.
c. Denominators in this study represent total number of episodes instead of total number of patients.
d. Clinical cure was 77% (13/17) in 1 nystatin pastille group vs 79% (15/19) in 2 nystatin pastilles group. Clinical plus mycological cure was 29% (5/17) in 1 nystatin pastille group vs 47% (9/19) in 2 nystatin pastilles group.
e. This is a global evaluation: a summary of clinical and mycological cure or improvement.

Table 4
Meta-analysis of the efficacy of clotrimazole.

Control	Clinical response				Mycological cure				Relapse			
	No. of studies	No. of patients	OR (95% CI)	I^2 (%)	No. of studies	No. of patients	OR (95% CI)	I^2 (%)	No. of studies	No. of patients	OR (95% CI)	I^2 (%)
Placebo	2	33	61.63 (6.95–546.12)	0	2	33	27.83 (3.15–246.12)	0	–	–	–	–
Fluconazole	4	426	0.23 (0.09–0.57)	0	4	384	0.40 (0.26–0.61)	21.4	4	271	FEM: 2.04 (1.17–3.55) REM: 3.45 (1.06–11.30)	52.9
Other topical and systemic agents	10*	1388	0.85 (0.65–1.11)	45	9	1287	FEM: 0.62 (0.49–0.79) REM: 0.56 (0.36–0.88)	58.1	10*	918	1.46 (1.08–1.97)	17.6
Other topical agents	3*	702	1.20 (0.87–1.67)	0	2	643	0.93 (0.66–1.32)	0	3*	475	1.11 (0.73–1.70)	0

FEM = fixed-effects model; REM = random-effects model.
*one of the studies was divided into 2 comparisons.

(4%) patient in clotrimazole 50 mg group developed systemic candidiasis after initially achieving clinical cure of OPC (Yap & Bodey, 1979). In the second study, 5 (14%) and 4 (13%) patients developed systemic candidiasis in clotrimazole and nystatin groups, respectively, despite having initial cure or improvement of oropharyngeal infection (Lawson & Bodey, 1980).

4. Discussion

To our knowledge, this is the first systematic review and meta-analysis exclusively and comprehensively analyzing the literature on efficacy and safety of clotrimazole in the treatment of OPC in various patient population. Although other systematic reviews in the treatment of OPC have been previously published, these either addressed other antifungal agents (Lyu et al., 2016; Zhang et al., 2016) or specific patient population including patients with denture stomatitis, HIV, and cancer (Emami et al., 2014; Pienaar et al., 2010; Worthington et al., 2010).

This meta-analysis showed that clotrimazole is significantly more effective than placebo with regards to both clinical response and mycological cure of OPC. However, it showed that clotrimazole is significantly less effective than fluconazole in clinical response and mycological cure and associated with significantly more relapse. Although no significant difference was demonstrated in clinical response, clotrimazole was significantly less effective with regards to mycological cure rate and was associated with significantly more OPC relapse compared to other antifungal agents including both systemic and topical therapies when data from all studies were pooled in one analysis. However, when clotrimazole was compared to only other topical antifungal agents, no significant difference in clinical response, mycological cure, or relapse rate was demonstrated. Given the topical application of clotrimazole, adverse effects are expected to be mild. Gastrointestinal adverse reactions were the most frequently reported adverse effects and no serious reactions were reported. Our descriptive analysis of 2 studies demonstrated that systemic candidiasis may occur after topical antifungal therapy despite initial cure or improvement of OPC, although this occurred infrequently. The incidence rate of OPC did not significantly differ when clotrimazole 10 mg was compared to higher doses or to nystatin.

Topical antifungal agents, including clotrimazole, are often indicated for the management of OPC, because of their limited systemic exposure, adverse effects, and drug interactions usually associated with systemic antifungal therapies (Albengres et al., 1998). Furthermore, the growing trends of non-albicans species along with fluconazole-resistant *C. albicans* after repeated exposure may further intensify the importance of initiating topical antifungal agents particularly in mild cases (Patel et al., 2012).

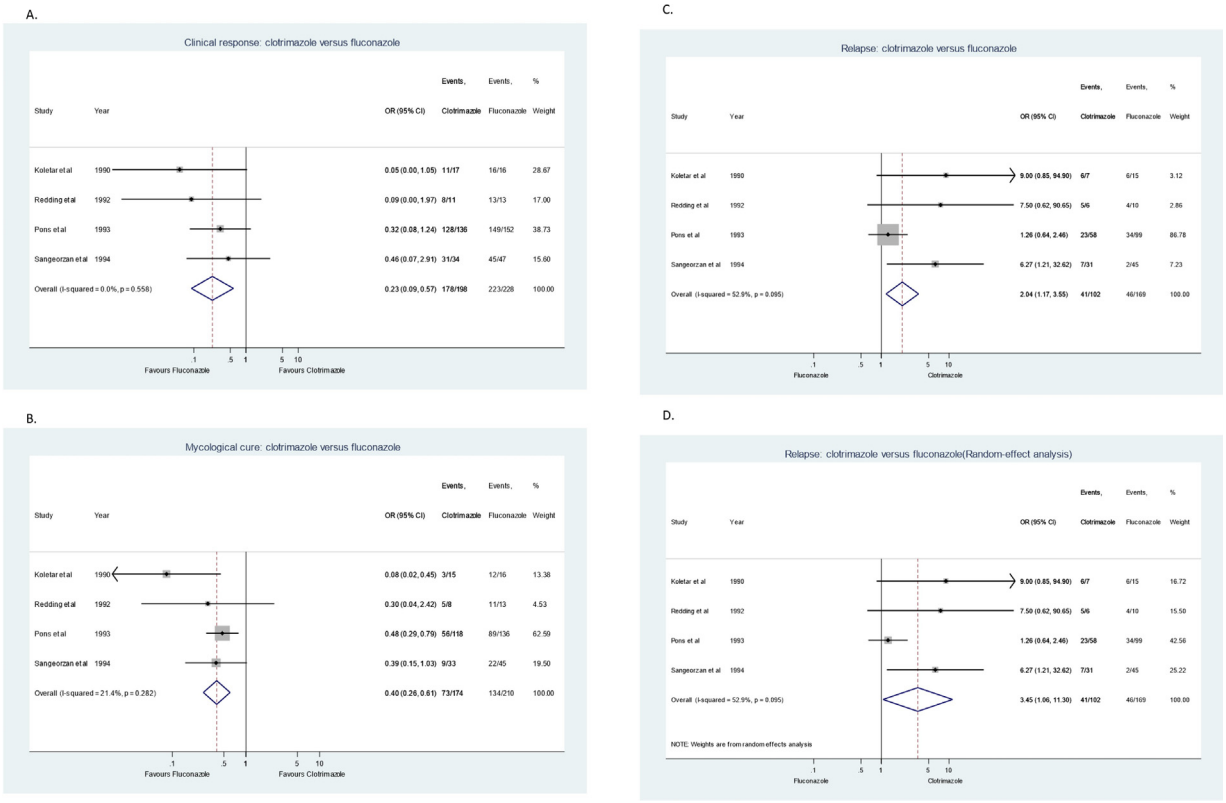

Fig. 4. Forest plots for the evaluation of clotrimazole versus fluconazole in the treatment of oropharyngeal candidiasis. (A) Clinical response, (B) Mycological Cure, (C) Relapse rate (Fixed-effect analysis), and (D) Relapse rate (Random-effect analysis).

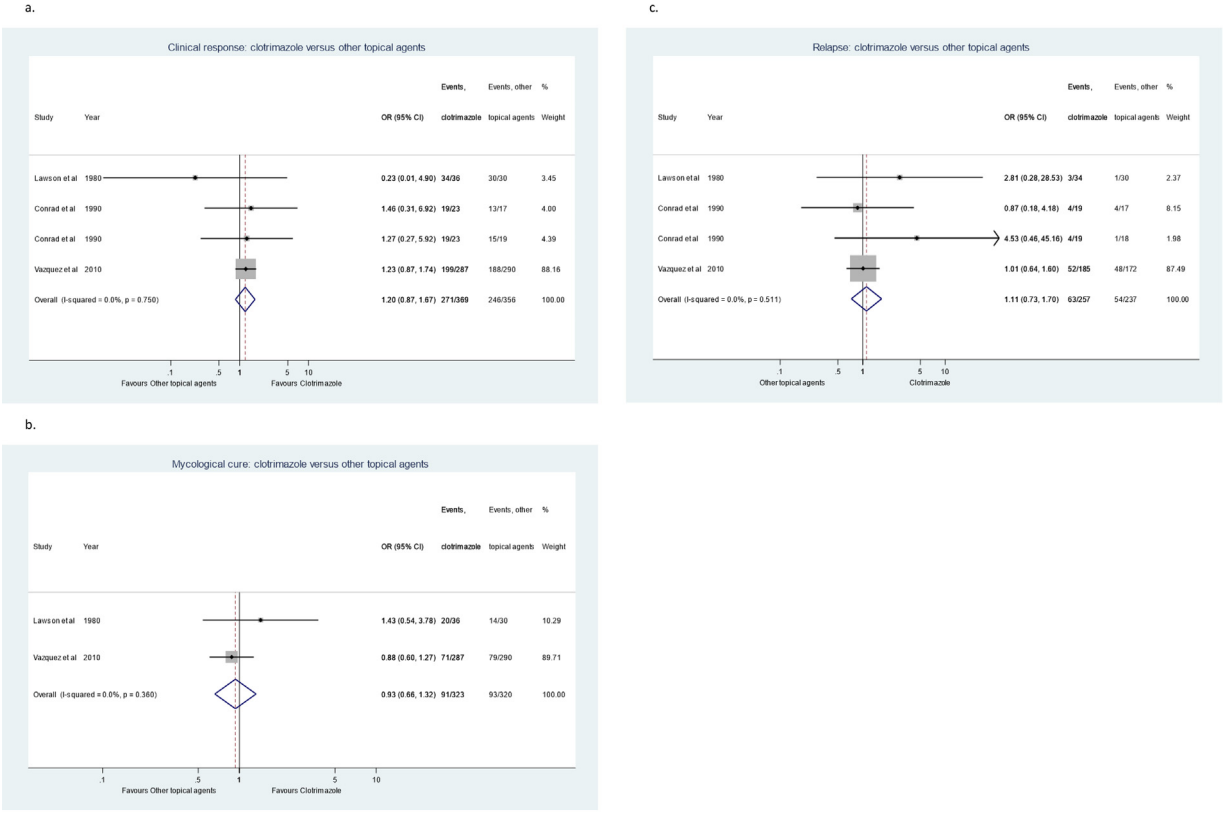

Fig. 5. Forest plots for the evaluation of clotrimazole versus other topical antifungal agents in the treatment of oropharyngeal candidiasis. (A) Clinical response, (B) Mycological Cure, (C) Relapse rate.

Table 5
Adverse effects of clotrimazole and controls.

Study	No. of evaluable patients		Control	Adverse effects of clotrimazole	Adverse effects of control
	Clotrimazole	Control			
(Montes et al., 1976)	6	6	Clotrimazole 50 mg	Pruritus in 1 patient	None
(Kirkpatrick & Alling, 1978)	10	10	Placebo	None	None
(Yap & Bodey, 1979)	24	24	Clotrimazole 50 mg	Nausea and abdominal pain in 1 patient (group not specified)	Nausea and abdominal pain in 1 patient (group not specified)
(Lawson & Bodey, 1980)	36 episodes	30 episodes	Nystatin	Nausea in 20 patients	Nausea in 3 patients
(Shechtman et al., 1984)	7	6	Placebo	–	–
(Thamlikitkul et al., 1988)	23	22	Ketoconazole	None	None
(Koletar et al., 1990)	17	16	Fluconazole	Nausea in 3 patients (2/3 discontinued therapy due to nausea and altered taste sensation)	Nausea in 3 patients
(Conrad & Lentnek, 1990)	26	19 & 23 *	Nystatin	None	None
(Redding et al., 1992)	11	13	Fluconazole	Nausea in 2 patients	Flatulence in 1 patient
(Pons et al., 1993)	158	176	Fluconazole	Gastrointestinal in 22 patients;Headache, dizziness, pruritus, rash, sweating, or dry mouth in 13 patients	Gastrointestinal in 26 patients;Headache, dizziness, pruritus, rash, sweating, or dry mouth in 16 patients
(Sangeorzan et al., 1994)	22	23	Fluconazole	None	Rash in 1 patient
(Murray et al., 1997)	81	81	Itraconazole	Gastrointestinal in 20 patients, rash in 5 patients, headache in 5 patients, and abnormal liver function tests in 5 patients	Gastrointestinal in 21 patients, rash in 5 patients, and abnormal liver function tests in 7 patients
(Linpiyawan et al., 2000)	15	14	Itraconazole	None	Transient elevation in liver enzymes in 2 patients
(Sabitha et al., 2005)	30	26	Garlic paste	None	Bad odour in 5 patients
(Sholapurkar et al., 2009)	28	27	Fluconazole	None	Gastrointestinal in 1 patient
(Vazquez et al., 2010)	287	290	Miconazole	152 patients reported $\geq$ 1 of the following: gastrointestinal, headache, anemia, cough, dry mouth, fatigue, increased GGT, and pain	161 patients reported $\geq$ 1 of the following: gastrointestinal, headache, anemia, cough, dry mouth, fatigue, increased GGT, and pain

GGT = gamma-glutamyltransferase; OC = oral candidiasis.
* 1 nystatin pastille group (n = 19); 2 nystatin pastille group (n = 23).

In the 2016 update by the Infectious Diseases Society of America (IDSA) clinical practice guideline for the management of candidiasis, clotrimazole troches, 10 mg 5 times daily was recommended as first line for the treatment of mild OPC (Pappas et al., 2016). However, the World Health Organization recommended clotrimazole only as an alternative agent when fluconazole is not available or contraindicated in HIV infected adults and children ("WHO Guidelines Approved by the Guidelines Review Committee," 2014). Both guidelines supported their recommendations with a number of individual randomized controlled trials. Our review, however, focused solely on clotrimazole and included 16 randomized controlled trials that were analyzed quantitatively and qualitatively for multiple efficacy outcomes using both fixed and random-effects models to provide more supportive evidence that may be considered in the future iterations of these guidelines.

A few limitations of this review should be highlighted. First, risk of bias cannot be excluded as several studies in this review were considered at high risk of performance bias and reporting bias. Moreover, all except one did not provide sufficient information about allocation concealment. In addition, although dosing regimens for clotrimazole and comparators such as fluconazole were similar across several studies, not all studies consistently evaluated the same formulation, dose, frequency, and duration of study medications. Few studies were excluded from the quantitative analysis due to unclear reporting of certain outcomes. Finally, approximately one-half the studies reported an absence of adverse effects related to clotrimazole therapy which might indicate inaccurate reporting leading to overestimation of its favorable safety profile. Therefore, the results of this meta-analysis should be interpreted with caution.

In summary, clotrimazole is an effective agent for the treatment of OPC. Our analysis showed no significant difference in clinical response between clotrimazole and all other antifungal agents when data from all studies (including both topical and systemic agents) were pooled together in a single analysis. However, clotrimazole was less effective in terms of mycologic cure and relapse rate. Of note, when clotrimazole was compared exclusively to other topical antifungal agents, there were no differences in clinical response, microbiologic cure or relapse. Clotrimazole is significantly more effective than placebo but less effective than fluconazole. That makes clotrimazole a considerable alternative option to treat OPC when fluconazole is unavailable or contraindicated. Compliance with clotrimazole remains a major concern due to the need for multiple daily administration. High quality randomized controlled trials are needed to validate these findings.

CRediT authorship contribution statement

Thamer A. Almangour: Conceptualization, Investigation, Methodology, Supervision. **Keith S. Kaye:** Conceptualization, Investigation, Methodology. **Mohammed Alessa:** Literature review and double data extraction. **Khalid Eljaaly:** Methodology. **Fadilah Sfouq Aleanizy:** . **Aynaa Alsharidi:** Review and Validation. **Fahad M. Al Majid:** . **Naif H. Alotaibi:** . **Abdullah A Alzeer:** Investigation, Methodology. **Faris S. Alnezary:** Investigation, Methodology. **Abdullah A. Alhifany:** Statistical analysis.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The authors extend their appreciation to the Deanship of Scientific Research at King Saud University for funding this work through research group No (RG- 1441-437). We would also like to thank the Deanship of Scientific Research at Umm Al-Qura University for supporting this work by Grant Code:19-MED-1-02-0003.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

References

Albengres, E., Le Louet, H., Tillement, J.P., 1998. Systemic antifungal agents. Drug interactions of clinical significance. Drug Saf. 18 (2), 83–97. https://doi.org/10.2165/00002018-199818020-00001.

Belazi, M., Velegraki, A., Fleva, A., Gidarakou, I., Papanaum, L., Baka, D., Karamitsos, D., 2005. Candidal overgrowth in diabetic patients: potential predisposing factors. Mycoses 48 (3), 192–196. https://doi.org/10.1111/j.1439-0507.2005.01124.x.

Compagnoni, M.A., Souza, R.F., Marra, J., Pero, A.C., Barbosa, D.B., 2007. Relationship between Candida and nocturnal denture wear: quantitative study. J. Oral Rehabil. 34 (8), 600–605. https://doi.org/10.1111/j.1365-2842.2007.01754.x.

Conrad, D.A., Lentnek, A.L., 1990. Comparitive evaluation on nystatin pastille and clotrimazole troche for the treatment of candidal stomatitis in immunocompromised patients. Curr. Therap. Res. – Clin. Exp. 47 (4), 627–636.

Crowley, P.D., Gallagher, H.C., 2014. Clotrimazole as a pharmaceutical: past, present and future. J. Appl. Microbiol. 117 (3), 611–617. https://doi.org/10.1111/jam.12554.

Emami, E., Kabawat, M., Rompre, P.H., Feine, J.S., 2014. Linking evidence to treatment for denture stomatitis: a meta-analysis of randomized controlled trials. J. Dent. 42 (2), 99–106. https://doi.org/10.1016/j.jdent.2013.11.021.

Farah, C.S., Lynch, N., McCullough, M.J., 2010. Oral fungal infections: an update for the general practitioner. Aust. Dent. J. 55 (Suppl 1), 48–54. https://doi.org/10.1111/j.1834-7819.2010.01198.x.

Figueiral, M.H., Azul, A., Pinto, E., Fonseca, P.A., Branco, F.M., Scully, C., 2007. Denture-related stomatitis: identification of aetiological and predisposing factors – a large cohort. J. Oral Rehabil. 34 (6), 448–455. https://doi.org/10.1111/j.1365-2842.2007.01709.x.

Hitchcock, C.A., Dickinson, K., Brown, S.B., Evans, E.G., Adams, D.J., 1990. Interaction of azole antifungal antibiotics with cytochrome P-450-dependent 14 alpha-sterol demethylase purified from Candida albicans. Biochem. J. 266 (2), 475–480.

Kirkpatrick, C.H., Alling, D.W., 1978. Treatment of chronic oral candidiasis with clotrimazole troches. A controlled clinical trial. N. Engl. J. Med. 299 (22), 1201–1203. https://doi.org/10.1056/nejm197811302992201.

Koletar, S.L., Russell, J.A., Fass, R.J., Plouffe, J.F., 1990. Comparison of oral fluconazole and clotrimazole troches as treatment for oral candidiasis in patients infected with human immunodeficiency virus. Antimicrob. Agents Chemother. 34 (11), 2267–2268.

Lawson, R.D., Bodey, G.P., 1980. Comparison of clotrimazole troche and nystatin vaginal tablet in the treatment of oropharyngeal candidiasis. Curr. Therap. Res. – Clin. Exp. 27 (6 I), 774–779.

Linpiyawan, R., Jittreprasert, K., Sivayathorn, A., 2000. Clinical trial: clotrimazole troche vs. itraconazole oral solution in the treatment of oral candidosis in AIDS patients. Int. J. Dermatol. 39 (11), 859–861.

Lyu, X., Zhao, C., Yan, Z.M., Hua, H., 2016. Efficacy of nystatin for the treatment of oral candidiasis: a systematic review and meta-analysis. Drug Des Devel Ther 10, 1161–1171. https://doi.org/10.2147/dddt.s100795.

Millsop, J.W., Fazel, N., 2016. Oral candidiasis. Clin. Dermatol. 34 (4), 487–494. https://doi.org/10.1016/j.clindermatol.2016.02.022.

Montes, L.F., Soto, T.G., Parker, J.M., Ramer, G.N., 1976. Clotrimazole troches: a new therapeutic approach to oral candidiasis. Cutis 17 (2), 277–280.

Murray, P.A., Koletar, S.L., Mallegol, I., Wu, J., Moskovitz, B.L., 1997. Itraconazole oral solution versus clotrimazole troches for the treatment of oropharyngeal candidiasis in immunocompromised patients. Clin. Ther. 19 (3), 471–480.

Naglik, J.R., Challacombe, S.J., Hube, B., 2003. Candida albicans secreted aspartyl proteinases in virulence and pathogenesis. Microbiol. Mol. Biol. Rev. 67 (3), 400–428.

Palmer, G.D., Robinson, P.G., Challacombe, S.J., Birnbaum, W., Croser, D., Erridge, P.L., Zakrzewska, J.M., 1996. Aetiological factors for oral manifestations of HIV. Oral Dis. 2 (3), 193–197.

Pappas, P.G., Kauffman, C.A., Andes, D.R., Clancy, C.J., Marr, K.A., Ostrosky-Zeichner, L., Sobel, J.D., 2016. Clinical practice guideline for the management of candidiasis: 2016 update by the infectious diseases society of America. Clin. Infect. Dis. 62 (4), e1–e50. https://doi.org/10.1093/cid/civ933.

Patel, P.K., Erlandsen, J.E., Kirkpatrick, W.R., Berg, D.K., Westbrook, S.D., Louden, C., Patterson, T.F., 2012. The changing epidemiology of oropharyngeal candidiasis in patients with HIV/AIDS in the era of antiretroviral therapy. AIDS Res. Treat. 2012, 262471. https://doi.org/10.1155/2012/262471.

Pienaar, E.D., Young, T., Holmes, H., 2010. Interventions for the prevention and management of oropharyngeal candidiasis associated with HIV infection in adults and children. Cochrane Database Syst. Rev. (11), Cd003940 https://doi.org/10.1002/14651858.CD003940.pub3.

Pons, V., Greenspan, D., Debruin, M., 1993. Therapy for oropharyngeal candidiasis in HIV-infected patients: a randomized, prospective multicenter study of oral fluconazole versus clotrimazole troches. The Multicenter Study Group. J. Acquir. Immune Defic. Syndr. 6 (12), 1311–1316.

Redding, S.W., Farinacci, G.C., Smith, J.A., Fothergill, A.W., Rinaldi, M.G., 1992. A comparison between fluconazole tablets and clotrimazole troches for the treatment of thrush in HIV infection. Spec. Care Dentist. 12 (1), 24–27.

Sabitha, P., Adhikari, P.M., Shenoy, S.M., Kamath, A., John, R., Prabhu, M.V., Padmaja, U., 2005. Efficacy of garlic paste in oral candidiasis. Trop. Doct. 35 (2), 99–100. https://doi.org/10.1258/0049475054037084.

Sangeorzan, J.A., Bradley, S.F., He, X., Zarins, L.T., Ridenour, G.L., Tiballi, R.N., Kauffman, C.A., 1994. Epidemiology of oral candidiasis in HIV-infected patients: colonization, infection, treatment, and emergence of fluconazole resistance. Am. J. Med. 97 (4), 339–346.

Scully, C., 2003. Drug effects on salivary glands: dry mouth. Oral Dis. 9 (4), 165–176.

Shamseer, L., Moher, D., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Stewart, L. A., 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 350, g7647. https://doi.org/10.1136/bmj.g7647.

Shechtman, L.B., Funaro, L., Robin, T., Bottone, E.J., Cuttner, J., 1984. Clotrimazole treatment of oral candidiasis in patients with neoplastic disease. Am. J. Med. 76 (1), 91–94.

Sherman, R.G., Prusinski, L., Ravenel, M.C., Joralmon, R.A., 2002. Oral candidosis. Quintessence Int. 33 (7), 521–532.

Shin, E.S., Chung, S.C., Kim, Y.K., Lee, S.W., Kho, H.S., 2003. The relationship between oral Candida carriage and the secretor status of blood group antigens in saliva. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 96 (1), 48–53. https://doi.org/10.1067/moe.2003.S1079210403001604.

Sholapurkar, A.A., Pai, K.M., Rao, S., 2009. Comparison of efficacy of fluconazole mouthrinse and clotrimazole mouthpaint in the treatment of oral candidiasis. Aust. Dent. J. 54 (4), 341–346. https://doi.org/10.1111/j.1834-7819.2009.01160.x.

Soysa, N.S., Samaranayake, L.P., Ellepola, A.N., 2008. Antimicrobials as a contributory factor in oral candidosis–a brief overview. Oral Dis. 14 (2), 138–143. https://doi.org/10.1111/j.1601-0825.2006.01357.x.

Thamlikitkul, V., Danpakdi, K., Visuthisakchai, S., Kulpreedarat, T., 1988. Randomized controlled trial of clotrimazole troche and ketoconazole for oropharyngeal candidiasis. J. Med. Assoc. Thai. 71 (12), 654–658.

Thompson 3rd, G.R., Patel, P.K., Kirkpatrick, W.R., Westbrook, S.D., Berg, D., Erlandsen, J., Patterson, T.F., 2010. Oropharyngeal candidiasis in the era of antiretroviral therapy. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 109 (4), 488–495. https://doi.org/10.1016/j.tripleo.2009.11.026.

Vazquez, J., Patton, L., Epstein, J., Ramlachan, P., Mitha, I., Noveljic, Z., Attali, P., 2010. Randomized, comparative, double-blind, double-dummy, multicenter trial of miconazole buccal tablet and clotrimazole troches for the treatment of oropharyngeal candidiasis: study of miconazole lauriad® efficacy and safety (SMiLES). HIV Clin Trials 11 (4), 186–196. https://doi.org/10.1310/hct1104-186.

. WHO Guidelines Approved by the Guidelines Review Committee, 2014. In: Guidelines on the Treatment of Skin and Oral HIV-Associated Conditions in Children and Adults. Geneva: World Health Organization Copyright (c) World Health Organization.

Worthington, H.V., Clarkson, J.E., Eden, O.B., 2002. Interventions for preventing oral candidiasis for patients with cancer receiving treatment. Cochrane Database Syst. Rev. (3), Cd003807 https://doi.org/10.1002/14651858.cd003807.

Worthington, H.V., Clarkson, J.E., Khalid, T., Meyer, S., McCabe, M., 2010. Interventions for treating oral candidiasis for patients with cancer receiving treatment. Cochrane Database Syst. Rev. (7), Cd001972 https://doi.org/10.1002/14651858.CD001972.pub4.

Yap, B.S., Bodey, G.P., 1979. Oropharyngeal candidiasis treated with a troche form of clotrimazole. Arch. Intern. Med. 139 (6), 656–657.

Zhang, L.W., Fu, J.Y., Hua, H., Yan, Z.M., 2016. Efficacy and safety of miconazole for oral candidiasis: a systematic review and meta-analysis. Oral Dis. 22 (3), 185–195. https://doi.org/10.1111/odi.12380.