Efficacy of antifungal drugs in the treatment of vulvovaginal candidiasis: a Bayesian network meta-analysis

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Purpose: Antifungal drugs are used frequently in the treatment of vulvovaginal candidiasis (VVC), but have shown controversial results. In this study, we aimed to evaluate the effectiveness of different antifungal drugs in the treatment of VVC and to provide an evidence-based reference for clinical use.

Methods: The published studies on the effectiveness of antifungal drugs in the treatment of VVC (up to April 2018) were retrieved from PubMed, Embase, the Cochrane Library, and ClinicalTrials.gov. We sifted through the literature according to Patients, Interventions, Comparisons and Outcomes principle, extracted data on the basic characteristics of the study, and evaluated the quality of included studies. We used R software for statistical analysis.

Results: In total, 41 randomized controlled trials were included in this meta-analysis. The relative risk of VVC associated with ten drugs, including placebo, fluconazole, clotrimazole, miconazole, itraconazole, ketoconazole, econazole, butoconazole, terbinafine, and terconazole, was analyzed. The following drugs appeared to show more efficacy than placebo in the treated patients: fluconazole (OR = 6.45, 95% CrI 4.42–9.41), clotrimazole (OR = 2.99, 95% CrI 1.61–5.55), miconazole (OR = 5.96, 95% CrI 3.17–11.2), itraconazole (OR = 2.29, 95% CrI 1.21–4.33), ketoconazole (OR = 1.18, 95% CrI 1.06–1.31), and terconazole (OR = 1.83, 95% CrI 1.28–2.55). The value of surface under the cumulative ranking curve of each drug was as follows: placebo (0.5%), fluconazole (91.5%), clotrimazole (2.99, 95% CrI 1.61–5.55), miconazole (5.96, 95% CrI 3.17–11.2), itraconazole (2.29, 95% CrI 1.21–4.33), ketoconazole (1.18, 95% CrI 1.06–1.31), and terconazole (1.83, 95% CrI 1.28–2.55).

Conclusion: Antifungal drugs are effective in the treatment of VVC. Fluconazole appeared to be the best drug for the treatment of VVC according to our analysis.

Keywords: vulvovaginal candidiasis, antifungal drugs, randomized controlled trials, network meta-analysis

Introduction

Vulvovaginal candidiasis (VVC) is an infectious disease affecting the female genital tract and is caused by Candida spp. Of all the VCC cases, 80%–90% are caused by Candida albicans, and a minority are caused by Candida glabrata, Candida parapsilosis, and Candida tropicalis.1 As one of the most common infectious diseases of the female genital tract, VVC is found worldwide affecting the health of women at all levels of the society.2 With the widespread use of corticosteroids, broad-spectrum antibiotics, and immunosuppressants, as well as the emergence of AIDS, VVC is more commonly encountered in clinical practice,3,4 and the treatment of VVC has become a hot issue.
Antifungal drugs exert their effect by changing the permeability of fungal cell membrane. At present, two groups of antifungal drugs are mainly used to treat VVC: polyene antifungal drugs and pyrrole ring antifungal drugs. The former group is represented by amphotericin B. Amphotericin B has a strong antifungal activity and a wide antibacterial spectrum, but it is quite toxic. The latter group includes azoles, such as ketoconazole, fluconazole, and itraconazole. These are also most widely used and have a wide antibacterial spectrum.5,6

To evaluate the clinical efficacy of different antifungal drugs in the treatment of VVC and to provide an evidence-based reference for clinical use, we conducted a network meta-analysis based on randomized controlled trials on the efficacy of antifungal drugs in the treatment of VVC.

Methods

Search strategy

The published studies on the effectiveness of antifungal drugs in the treatment of oral candidiasis (up to April 2018) were retrieved from PubMed, Embase, the Cochrane Library, and ClinicalTrials.gov, with keywords including “Vulvovaginal Candidiases” [MeSH] OR “Vulvovaginal Candidiases” [MeSH] OR “Vulvovaginal Moniliasis” [MeSH] OR “Vaginal Yeast Infections” [MeSH] OR “Genital Vulvovaginal Candidiases” [MeSH] OR “Genital Vulvovaginal Candidiases” [MeSH] OR “Monilial Vaginitides” [MeSH] OR “Monilial Vaginitis” [MeSH] AND “Antifungal Agents” [MeSH] OR “Itraconazole” [MeSH] OR “Miconazole” [MeSH] OR “Clotrimazole” [MeSH] OR “Fluconazole” [MeSH] OR “Ketoconazole” [MeSH] OR “Econazole” [MeSH] OR “Butoconazole” [MeSH] OR “Terbinafine” [MeSH] OR “Terconazole” [MeSH] AND “Randomized Controlled Trials” [MeSH] OR “RCT” [MeSH].

Inclusion and exclusion criteria

We included randomized controlled trials written in English, regardless of whether or not specific random allocation methods and blind data hiding scheme are mentioned and the timing of publication. Study subjects were females with typical clinical symptoms and signs of VVC confirmed by mycological examination.

We imported the literature retrieved from the database into EndNote and eliminated duplicates. We screened the titles and abstracts according to the Patients, Interventions, Comparisons and Outcomes principle, and then read the full text of the eligible articles. The data were extracted and evaluated by two reviewers. Any differences in opinion were discussed and resolved by the reviewers. The following data were extracted: first author of the study, publication time, sample size, age, and intervention measures. Quality evaluation was performed using Cochrane risk-of-bias assessment tool.

Statistical analysis

We conducted a network meta-analysis (Bayesian approach) which included both direct and indirect evidence in the network. Direct comparison was performed using Stata14.0 software for statistical analysis. The risk of vulvovaginal candidiasis in each group was compared using the OR. Before the combined data were analyzed by meta-analysis, the heterogeneity of each group was tested. If there was no heterogeneity ($\chi^2>50\%$, $I^2<50\%$), the combined statistics were calculated by fixed-effect model analysis. If there was significant heterogeneity among the groups ($\chi^2<50\%$, $I^2>50\%$), the source of heterogeneity was analyzed, and a subgroup analysis of the factors leading to heterogeneity was carried out. Indirect comparison was made using R software to draw a mesh diagram.

Drugs were ranked based on the surface under the cumulative ranking curve (SUCRA) values. A drug was considered more preferable than another if it had a larger SUCRA value.

Results

Literature search results

A total of 566 studies from Medline, 596 studies from Embase, one study from Cochrane Library, and eight studies from ClinicalTrials.gov were selected. After removing duplicates, 581 studies remained. After reviewing their titles and abstracts, 521 citations were excluded. The remaining 60 citations were assessed in more detail for eligibility by reading the full text. Among them, two were excluded due to lack of relevant outcome measure, 14 were excluded due to insufficient network connections, and three were excluded due to lack of detailed information. Finally, 41 studies were used for the final data synthesis.5,7-46 The flowchart of literature search is presented in Figure 1. The risk of bias of the 41 studies included in this meta-analysis is summarized in Figure 2. The characteristics of the included studies are shown in Table 1. The pattern of evidence within the network is displayed in Figure 3.

Results of pairwise meta-analysis

Table 2 displays the results produced by pairwise meta-analysis. The following drugs appeared to show more efficacy than placebo in the treated patients: fluconazole (OR $=6.45$, 95% CI $=4.42$–9.41), clotrimazole (OR $=2.99$, 95% CI $=1.94$–$$\leq$$
Crl 1.61–5.55), miconazole (OR = 5.96, 95% CrI 3.17–11.2), itraconazole (OR = 2.29, 95% CrI 1.21–4.33), ketoconazole (OR = 2.40, 95% CrI 1.55–3.71), butoconazole (OR = 1.18, 95% CrI 1.06–1.31), and terconazole (OR = 5.60, 95% CrI 2.78–11.3). Moreover, there was no significant heterogeneity among the studies for the above results (P-heterogeneity > 0.05 and I² < 50%).

Network meta-analysis
Table 3 displays the results produced by network meta-analysis. The following nine drugs appeared to show more efficacy than placebo in the treated patients: fluconazole (OR = 26.0, 95% CrI 14.0–50.0), clotrimazole (OR = 17.0, 95% CrI 8.70–34.0), miconazole (OR = 12.0, 95% CrI 6.30–22.0), itraconazole (OR = 14.0, 95% CrI 6.40–32.0), ketoconazole (OR = 13.0, 95% CrI 6.10–27.0), econazole (OR = 14.0, 95% CrI 5.10–38.0), butoconazole (OR = 25.0, 95% CrI 12.0–56.0), terbinafine (OR = 5.20, 95% CrI 1.70–35.0), and terconazole (OR = 18.0, 95% CrI 7.80–43.0).

The corresponding SUCRA values of the drugs were as follows: placebo (0.5%), fluconazole (91.5%), clotrimazole (61.8%), miconazole (33.8%), itraconazole (50.5%), ketoconazole (42.8%), econazole (46.8%), butoconazole (82.2%), terbinafine (20.9%), and terconazole (65.0%) (Figure 4). Incorporating adjuvants particularly fluconazole appeared to be the best strategy for the treatment of oral candidiasis.

Publication bias
The results of the comparison-adjusted funnel plots did not reveal any evidence of apparent asymmetry (Figure 5). No significant publication bias was observed.
| Study                  | Year | Study location | Treatments | Treatment 1 Age (years) | Cases/n | Treatment 2 Age (years) | Cases/n | Treatment 3 Age (years) | Cases/n |
|------------------------|------|----------------|------------|-------------------------|---------|-------------------------|---------|-------------------------|---------|
| Andersen et al         | 1989 | France         | Fluconazole| 32.1                    | 143/169 | Clotrimazole            | 30.6    | 131/161                 |         |
| Cori et al             | 2006 | Croatia        | Fluconazole| NA                      | 41/56   | Clotrimazole            | NA      | 9/13                    |         |
| Costa et al            | 2004 | Brazil         | Fluconazole| NA                      | 30/38   | Itraconazole            | NA      | 27/42                   |         |
| de Puzio et al         | 2003 | Italy          | Fluconazole| >18.0                   | 29/38   | Itraconazole            | >18.0   | 21/32                   |         |
| Fan et al              | 2015 | China          | Fluconazole| 19.0–45.0               | 24/287  | Miconazole              | 19.0–45.0| 220/290                 |         |
| Feralbas et al         | 2006 | Turkey         | Fluconazole| 17.0–54.0               | 10/15   | Itraconazole            | 17.0–54.0| 6/10                    |         |
| Li et al               | 2015 | China          | Fluconazole| 29.6                    | 46/58   | Terconazole             | 31.0    | 47/66                   |         |
| McClelland et al       | 2015 | USA            | Fluconazole| 24.0–34.0               | 75/118  | Placebo                 | 23.0–35.0| 30/116                  |         |
| Mendling et al         | 2004 | Germany        | Fluconazole| NA                      | 129/161 | Clotrimazole            | NA      | 117/154                 |         |
| Mikamo et al           | 1995 | Japan          | Fluconazole| 18.0–54.0               | 38/50   | Clotrimazole            | 18.0–54.0| 30/50                   |         |
| Mikamo et al           | 1998 | Japan          | Fluconazole| 18.0–55.0               | 40/50   | Itraconazole            | 17.0–55.0| 42/50                   |         |
| O-Prasertswat and Bourlert | 1995 | China         | Fluconazole| 33.9±8.1                | 42/53   | Clotrimazole            | 35.3±8.4| 40/50                   |         |
| Osser et al            | 1991 | Sweden         | Fluconazole| 16.0–52.0               | 100/121 | Econazole               | 18.0–60.0| 84/114                  |         |
| Seidman and Skokos     | 2005 | USA            | Fluconazole| 37.0±2.2                | 76/93   | Butoconazole            | 38.8±13.8| 56/88                   |         |
| Sekhavat et al         | 2011 | Iran           | Fluconazole| 39.4±3.1                | 60/72   | Clotrimazole            | 42.2±15.9| 49/70                   |         |
| Sobel et al            | 1995 | USA            | Fluconazole| 18.0–63.0               | 133/182 | Clotrimazole            | 17.0–64.0| 118/176                 |         |
| Sobel et al            | 2004 | USA            | Fluconazole| NA                      | 160/166 | Placebo                 | NA      | 23/154                  |         |
| Stein et al            | 1991 | USA            | Fluconazole| 18.0–51.0               | 80/90   | Clotrimazole            | 18.0–60.0| 88/95                   |         |
| Stein and Mummaw       | 1993 | USA            | Itraconazole| 18.0–43.0               | 35/48   | Clotrimazole            | 18.0–33.0| 19/20                   |         |
| Timonen                | 1992 | Finland        | Fluconazole| >18.0                   | 50/54   | Miconazole              | >18.0   | 33/47                   |         |
| Tobin et al            | 1992 | UK             | Itraconazole| >18.0                   | 60/92   | Clotrimazole            | >18.0   | 49/88                   |         |
| van Heusden et al      | 1990 | Netherlands    | Fluconazole| NA                      | 47/49   | Miconazole              | NA      | 48/50                   |         |
| Zhou et al             | 2016 | China          | Fluconazole| 29.9±6.5                | 61/110  | Clotrimazole            | 29.4±6.2| 62/115                  |         |
| Sobel et al            | 1994 | USA            | Ketoconazole| >18.0                   | 86/101  | Clotrimazole            | >18.0   | 41/51                   |         |
| Fong                   | 1992 | Canada         | Itraconazole| 18.0–65.0               | 17/22   | Clotrimazole            | 18.0–65.0| 21/22                   |         |
| Gerhard et al          | 1989 | USA            | Ketoconazole| >18.0                   | 27/45   | Placebo                 | >18.0   | 21/47                   |         |
| Kutzer et al           | 1988 | UK             | Fluconazole| 17.0–65.0               | 63/80   | Ketoconazole            | 17.0–72.0| 55/72                   |         |
| Sobel                  | 1994 | USA            | Clotrimazole| 31.9                    | 15/21   | Placebo                 | 31.9    | 6/21                    |         |
| van der Meijden et al  | 1986 | Netherlands    | Ketoconazole| 29.0±6.9                | 20/23   | Miconazole              | 28.0±7.4| 18/19                   |         |
| Kjaeldgaard            | 1986 | USA            | Terconazole| >18.0                   | 18/20   | Clotrimazole            | >18.0   | 17/20                   |         |
| Puolakka and Tuimala   | 1983 | Finland        | Terconazole| 16.0–46.0               | 40/49   | Miconazole              | 18.0–47.0| 34/49                   |         |
| Corson et al           | 1991 | USA            | Terconazole| 18.0–54.0               | 250/299 | Miconazole              | 18.0–54.0| 239/294                 |         |
| Thomason et al         | 1990 | USA            | Terconazole| NA                      | 40/50   | Miconazole              | NA      | 34/50                   |         |
| Brown et al            | 1999 | USA            | Butoconazole| 18.0–65.0               | 93/101  | Miconazole              | 18.0–65.0| 90/104                  |         |
| Ruf and Vitse          | 1990 | France         | Butoconazole| 18.0–56.0               | 26/29   | Econazole               | 16.0–49.0| 24/32                   |         |
| Kaufman et al          | 1989 | USA            | Butoconazole| >18.0                   | 101/115 | Miconazole              | >18.0   | 93/114                  |         |
| Hajman                 | 1988 | Sweden         | Butoconazole| 20.0–63.0               | 28/32   | Clotrimazole            | 19.0–32.0| 24/31                   |         |
| Brown et al            | 1986 | USA            | Butoconazole| >18.0                   | 26/32   | Miconazole              | >18.0   | 21/30                   |         |
| Adamson et al          | 1986 | USA            | Butoconazole| NA                      | 92/97   | Clotrimazole            | NA      | 74/88                   |         |
| Stettendorf et al      | 1982 | USA            | Clotrimazole| 16.0–62.0               | 45/54   | Econazole               | 16.0–66.0| 41/57                   |         |
| Perera and Seneviratne  | 1994 | Sri Lanka      | Econazole   | NA                      | 49/51   | Clotrimazole            | NA      | 45/50                   |         |
Discussion

VVC has a high incidence and recurrence rate, but its pathogenesis is not yet clear. At present, it is believed that the pathogenesis and recurrence of VVC are related to many factors, such as the increasing resistance of Candida, the local immune response of host against Candida, and the change of virulence factor of Candida. Available data show that 75% of women have VVC at least once in their lifetime, and 50% of women with VVC have recurrent infections, with the highest incidence found among women of reproductive age. VVC is the most common cause of vaginal infections, second only to bacterial vaginitis. Candida has a high rate of intravaginal colonization; it can be isolated from the vagina of about 20% of healthy asymptomatic women and 30% of pregnant women.

Candida, as a part of normal flora, can be found on the surface of the skin, digestive tract, and genitourinary tract; however, the mechanism of colonization and pathogenicity of Candida are unclear. The pathogens of VVC include C. albicans, C. tropicalis, C. parapsilosis, Candida krusei, and C. glabrata. C. albicans is the main pathogen of VVC, and accounts for 73.8%–95.0% of all Candida spp. isolated from the vagina. The most common non-albicans species is C. glabrata, which accounts for 10%–20% of all VVC pathogens. VVC causes increased leucorrhea, vulva itching, burning pain, urinal pain, and intercourse pain, and seriously affects the physical and mental health of the majority of women. Therefore, there is an urgent need for most suitable drugs for the treatment of VVC.

Table 2 Summary ORs of antifungal drugs and heterogeneity of each direct comparison

| Comparison                      | OR (95% CI) | P-heterogeneity | P   | Tau² |
|---------------------------------|-------------|-----------------|-----|------|
| Fluconazole vs placebo          | 6.45 (4.42, 9.41) | –               | –   | <0.001 |
| Clotrimazole vs placebo         | 2.99 (1.61, 5.55) | –               | –   | 0.001 |
| Miconazole vs placebo           | 5.96 (3.17, 11.2) | 0.32            | 0.0%| <0.001 |
| Itraconazole vs placebo         | 2.29 (1.21, 4.33) | –               | –   | 0.011 |
| Ketoconazole vs placebo         | 2.40 (1.55, 3.71) | 0.894           | 0.0%| <0.001 |
| Butoconazole vs placebo         | 1.18 (1.06, 1.31) | –               | –   | <0.001 |
| Terconazole vs placebo          | 5.60 (2.78, 11.3) | –               | –   | <0.001 |
| Clotrimazole vs fluconazole     | 0.94 (0.89, 0.99) | 0.387           | 5.7%| 0.016 |
| Miconazole vs fluconazole       | 0.90 (0.84, 0.96) | 0.108           | 46.7%| 0.001 |
| Itraconazole vs fluconazole     | 0.92 (0.80, 1.06) | 0.408           | 0.0%| 0.245 |
| Ketoconazole vs fluconazole     | 0.97 (0.82, 1.15) | –               | –   | 0.728 |
| Econazole vs fluconazole        | 0.89 (0.77, 1.02) | –               | –   | 0.100 |
| Butoconazole vs fluconazole     | 0.78 (0.65, 0.94) | –               | –   | 0.008 |
| Terbinafine vs fluconazole      | 0.50 (0.21, 1.20) | –               | –   | 0.121 |
| Terconazole vs fluconazole      | 0.89 (0.73, 1.10) | –               | –   | 0.296 |
| Itraconazole vs clotrimazole    | 0.96 (0.75, 1.23) | 0.002           | 47.1%| 0.738 |
| Ketoconazole vs clotrimazole    | 1.05 (0.90, 1.24) | –               | –   | 0.476 |
| Econazole vs clotrimazole       | 0.97 (0.76, 1.24) | 0.032           | 38.4%| 0.821 |
| Butoconazole vs clotrimazole    | 1.13 (1.03, 1.24) | 0.987           | 0.0%| 0.013 |
| Terconazole vs clotrimazole     | 1.06 (0.83, 1.34) | –               | –   | 0.634 |
| Ketoconazole vs miconazole      | 1.08 (0.92, 1.27) | 0.066           | 44.7%| 0.349 |
| Butoconazole vs miconazole      | 1.08 (1.01, 1.16) | 0.844           | 0.0%| 0.037 |
| Terconazole vs miconazole       | 1.04 (0.98, 1.12) | 0.281           | 13.9%| 0.210 |
| Terbinafine vs itraconazole     | 0.56 (0.22, 1.43) | –               | –   | 0.224 |
| Butoconazole vs econazole       | 1.19 (0.95, 1.51) | –               | –   | 0.137 |
At present, pyrrole ring drugs are mainly used to treat VVC in clinical practice. Pyrrole ring drugs such as imidazoles and triazoles are related to the inhibition of ergosterol synthesis in fungi and thus destroy the integrity of fungal cell membrane and achieve the antifungal effect.\textsuperscript{54} The most common drugs represented by imidazoles are clotrimazole, ketoconazole, and miconazole. Triazoles are represented by fluconazole and itraconazole. Triazole antifungal drugs have a high bioavailability and strong antifungal effect, and the associated liver toxicity is relatively small.\textsuperscript{55}

This network meta-analysis attempted to analyze the effectiveness of different antifungal drugs in the treatment of VVC and to provide an evidence-based reference for clinical use. Our analysis suggested that antifungal drugs are effective in the treatment of VVC, and fluconazole appeared to be the best drug for the treatment of VVC. The American and European guidelines for the treatment of VVC, based on a large number of evidence-based clinical practice, recommended the use of fluconazole (150 mg) for the treatment of moderate-to-severe VVC, which is consistent with our results.

Fluconazole is a triazole antifungal drug that can inhibit or kill fungi by competitively inhibiting the synthesis of ergosterol. It has shown a significant effect in the treatment of deep fungal infections, especially those caused by \textit{C. albicans} and \textit{Cryptococcus neoformans}.\textsuperscript{56} Since it was launched in 1988, fluconazole has been widely used in clinical practice because of its excellent pharmacokinetic properties, such as broad antifungal spectrum, low hepatotoxicity, good oral absorption, high bioavailability, and wide tissue distribution.\textsuperscript{57} Designated by the WHO as the first choice for the treatment of systemic fungal infections, fluconazole is effective
for various human and animal fungal infections, such as Candida infection (including systemic candidiasis in normal or immune-impaired people and animals), new cryptococcus infection (including intracranial infection), Malassezia, Microsporum, and Trichophyton infections, psoriasis, dermatitis, and rougherosporum (including intracranial infection). The antibacterial activity of fluconazole in vitro was found to be significantly lower than that of ketoconazole, but the antifungal activity of this drug was significantly higher than ketoconazole in vitro.57

This meta-analysis also has some limitations. The results of statistical heterogeneity analysis of the antifungal drugs are limited in randomized controlled trials. In addition, the limited evidence of a dose-dependent association between antifungal drugs and VVC treatment provides limited confidence in the study findings. Second, there is no record for a standardized treatment of VVC, which leads to difference in results between the trials; therefore, these results should be carefully interpreted with caution. Third, the study durations were short in these randomized controlled trials and patients included in these trials might be different from patients in the real life. Fourth, these findings may not be generalizable to a specific group of patients because randomized controlled trials tended to exclude participants. Fifth, most of the including studies have not enough detail in their reports, such as the absence of a random allocation method, the implementation of the allocation concealment, or the implementation of the blind law, which leads to existence of varying degrees of bias and risk.

Our findings underscore the notion that antifungal drugs are effective in the treatment of VVC, and fluconazole appeared to be the best drug for the treatment of VC according to our analysis. However, due to the low quality of the included studies, this conclusion needs to be further confirmed by high-quality research with a large sample.

Author contributions
Fei Cheng was responsible for the concept and design of the review, the acquisition of data, the analysis and interpretation of data, and for the preparation of the manuscript. Fen Qin was responsible for the acquisition of data and for the preparation of the manuscript. Quan Wang was responsible for the analysis and interpretation of data and for the preparation of the manuscript. Chunlian Zhang and Caiyun Fang was responsible for the acquisition of data. Liping Zhang and Hailin Chen was responsible for the analysis.
and interpretation of data and for the preparation of the manuscript. Mi Zhang was responsible for the preparation of the manuscript. All authors read and approved the final version of the manuscript. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure
The authors report no conflicts of interest in this work.

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