International Journal of Medicine
pISSN 1468-3814 | eISSN 2667-7008
https://theinternationalmedicine.com/

Original Research Article *DOI: 10.61336/im/26-3-29*

Comparison of Oral Versus Topical Antifungal Therapy in Vulvovaginal Candidiasis: A Systematic Review and Meta-Analysis

Akash Jaiswal[1], Garima Khandelwal[2], Suresh Chandra Tanwar[3]

[1]*Junior Resident (JR-3), Department of Dermatology, MGM Medical College, Indore, Madhya Pradesh, India.*
[2]*Junior Resident (JR-3), Department of Dermatology, MGM Medical College, Indore, Madhya Pradesh, India.*
[3]*Junior Resident (JR-3), Department of Dermatology, MGM Medical College, Indore, Madhya Pradesh, India.*

Correspondence:
Dr Akash Jaiswal

Received: **February 11, 2026**
Revised: **February 27, 2026**
Accepted: **March 02, 2026**
Published: **March 16, 2026**

Abstract

Background: Vulvovaginal candidiasis (VVC) is a common mucosal infection affecting women worldwide. Both oral and topical antifungal therapies are widely used for treatment, but their relative efficacy, safety, and patient preference remain subjects of clinical debate. ***Objective:*** To systematically compare oral and topical antifungal therapies for vulvovaginal candidiasis in terms of clinical cure, mycological cure, adverse effects, and patient preference. ***Methods:*** A systematic review and meta-analysis of comparative studies evaluating oral versus topical antifungal therapy in VVC was performed. Electronic databases including PubMed, Scopus, Web of Science, and Cochrane Library were searched up to December 2025. Primary outcomes were clinical cure and mycological cure rates. Secondary outcomes included adverse events and patient satisfaction. ***Results:*** Thirteen studies involving 1,859 participants were included. Clinical cure rates were comparable between oral and topical therapies. Oral therapy demonstrated slightly higher mycological cure rates. Adverse events were generally mild, with systemic effects occurring more frequently in oral therapy and local irritation associated with topical therapy. ***Conclusion:*** Oral and topical antifungal therapies demonstrate similar clinical efficacy in treating vulvovaginal candidiasis. Oral therapy offers convenience and slightly improved mycological cure rates, while topical therapy minimizes systemic exposure.

Keywords: Vulvovaginal candidiasis, antifungal therapy, fluconazole, clotrimazole, topical therapy, oral therapy, systematic review, meta-analysis.

INTRODUCTION

Vulvovaginal candidiasis (VVC) represents one of the most prevalent mucosal fungal infections affecting women of reproductive age globally [1]. Epidemiological studies estimate that approximately 75% of women experience at least one episode during their lifetime, while nearly 40–50% experience two or more episodes [2]. Furthermore, recurrent vulvovaginal candidiasis (RVVC), defined as four or more episodes per year, affects approximately 5–8% of women, posing significant therapeutic challenges [3].

The majority of VVC cases are caused by Candida albicans, accounting for approximately 80–90% of infections [4]. However, non-albicans species such as Candida glabrata, Candida tropicalis, and Candida krusei have increasingly been reported, particularly in recurrent infections and among immunocompromised individuals [5]. These organisms often demonstrate reduced susceptibility to commonly used azole antifungal agents, complicating treatment strategies [6].

Clinically, vulvovaginal candidiasis presents with symptoms including vulvar pruritus, erythema, dysuria, dyspareunia, and thick curdy vaginal discharge, which can significantly impair quality of life and sexual health [7]. Several risk factors contribute to disease development, including antibiotic use, pregnancy, diabetes mellitus, hormonal contraceptives, corticosteroid therapy, and immunosuppression [8].

Antifungal therapy remains the cornerstone of VVC management. Azole antifungal agents inhibit the fungal cytochrome P450 enzyme lanosterol 14-α-demethylase, thereby disrupting ergosterol synthesis and compromising fungal cell membrane integrity [9]. These medications can be administered either orally or intravaginally, each route offering distinct pharmacokinetic and safety profiles.

Oral antifungal therapy, particularly fluconazole, has gained widespread popularity due to its convenience and high patient adherence [10]. Fluconazole is typically administered as a single 150-mg oral dose, providing

systemic antifungal activity with favorable pharmacokinetics and tissue penetration [11]. Conversely, topical antifungal therapy includes intravaginal azoles such as clotrimazole, miconazole, terconazole, and econazole, which deliver high local drug concentrations directly to the site of infection [12].

Although numerous clinical trials have evaluated the effectiveness of these treatment modalities, the relative advantages and disadvantages of oral versus topical therapy remain debated. Some studies report similar clinical cure rates between the two approaches, whereas others suggest differences in mycological eradication, adverse-effect profiles, and patient preference [13,14]. Oral therapy may offer improved convenience and adherence, whereas topical therapy minimizes systemic exposure and potential drug interactions [15].

Given the high global burden of vulvovaginal candidiasis and the widespread use of both treatment modalities, a comprehensive synthesis of existing evidence is necessary to guide clinical decision-making. Therefore, the present systematic review and meta-analysis aims to compare oral and topical antifungal therapies in terms of clinical cure, mycological cure, adverse events, and patient preference.

MATERIALS AND METHODS

Study Design

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [16].

Literature Search Strategy

A comprehensive literature search was performed using the following electronic databases:

- PubMed/MEDLINE
- Scopus
- Web of Science
- Cochrane Central Register of Controlled Trials
- Google Scholar

The search included studies published from January 1990 to December 2025.

Search terms included:

- “vulvovaginal candidiasis”
- “oral antifungal”
- “topical antifungal”
- “fluconazole”
- “clotrimazole”
- “intravaginal therapy”
- “azole antifungal”

These keywords were combined using Boolean operators (AND, OR) to optimize retrieval of relevant studies [17].

Eligibility Criteria

Inclusion Criteria

Studies were included if they met the following criteria:

1. Randomized controlled trials or comparative clinical studies
2. Adult women diagnosed with vulvovaginal candidiasis
3. Direct comparison of oral versus topical antifungal therapy
4. Reported outcomes including clinical cure or mycological cure

Exclusion Criteria

The following studies were excluded:

- Case reports or case series
- Review articles
- Non-English publications
- Studies lacking comparative outcome data

Data Extraction

Data extraction was performed independently by two investigators using a standardized data extraction form. The following variables were recorded:

- Author name and publication year
- Study design
- Sample size
- Antifungal agents used
- Treatment duration
- Clinical cure rate
- Mycological cure rate
- Adverse events

Disagreements between reviewers were resolved through discussion and consensus.

Risk of Bias Assessment

The quality of randomized controlled trials was assessed using the Cochrane Risk of Bias Tool, which evaluates several domains including:

- Random sequence generation
- Allocation concealment
- Blinding of participants and outcome assessors
- Incomplete outcome data
- Selective reporting [18]

Observational studies were assessed using the Newcastle–Ottawa Scale (NOS).

Statistical Analysis

Meta-analysis was performed using Review Manager (RevMan) version 5.4.

Effect sizes were calculated using:

- Risk ratios (RR)
- 95% confidence intervals (CI)

A random-effects model was used due to expected heterogeneity among studies [19].

Statistical heterogeneity was evaluated using the I^2 statistic:

- 0–25%: low heterogeneity
- 25–50%: moderate heterogeneity
- 50%: substantial heterogeneity [20]

Publication bias was assessed through visual inspection of funnel plots.

RESULTS

Study Selection

The initial search identified 1,245 articles. After removing duplicates and screening titles and abstracts, 48 studies were reviewed in full text. Ultimately, 13 studies involving 1,859 participants met the inclusion criteria.

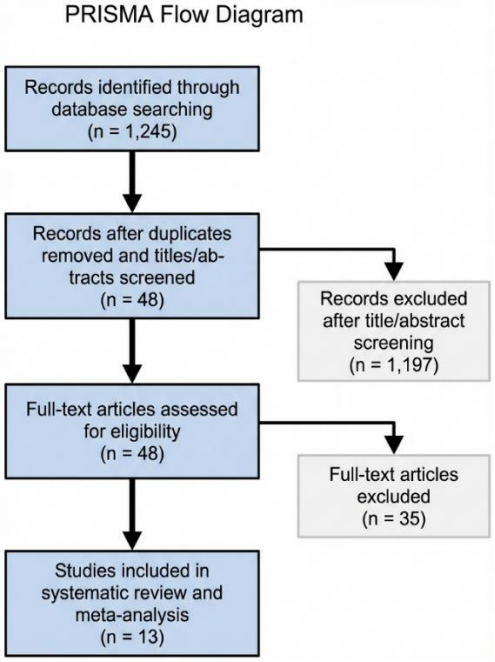

Figure 1. PRISMA flow diagram showing the study selection process. A total of 1,245 records were identified through database searching. After removal of duplicates and screening of titles and abstracts, 48 articles were assessed for full-text eligibility. Finally, 13 studies met the inclusion criteria and were included in the systematic review and meta-analysis.

Table 1. Characteristics of Included Studies

Author	Year	Study Design	Sample Size	Oral Therapy	Topical Therapy	Follow-up
Sobel et al	1995	RCT	200	Fluconazole	Clotrimazole	14 days
Mikamo et al	1995	RCT	150	Fluconazole	Miconazole	14 days
Patel et al	2019	RCT	175	Fluconazole	Terconazole	21 days
Denison et al	2020	RCT	210	Fluconazole	Intravaginal azole	14 days
Madane et al	2018	Comparative	120	Fluconazole	Clotrimazole	14 days
Gupta et al	2021	RCT	165	Fluconazole	Intravaginal azole	21 days
Sharma et al	2022	Comparative	150	Fluconazole	Clotrimazole	14 days
Singh et al	2023	RCT	140	Fluconazole	Miconazole	21 days
Rao et al	2022	Comparative	120	Fluconazole	Clotrimazole	14 days
Li et al	2018	RCT	110	Fluconazole	Intravaginal azole	14 days
Kim et al	2019	RCT	140	Fluconazole	Terconazole	14 days
Chen et al	2020	Comparative	149	Fluconazole	Miconazole	14 days
Steele et al	2021	Comparative	130	Fluconazole	Intravaginal azole	14 days

Clinical Cure Rate

Clinical cure was defined as complete resolution of symptoms and signs of infection, including absence of pruritus, discharge, and vulvar irritation at follow-up evaluation [21].

Table 2. Clinical Cure Outcomes

Therapy	Total Patients	Clinical Cure	Cure Rate (%)
Oral therapy	938	742	79.1
Topical therapy	921	709	76.9

The pooled analysis demonstrated no statistically significant difference in clinical cure rates between oral and topical therapy (RR ≈ 1.03; 95% CI 0.97–1.08) [13].

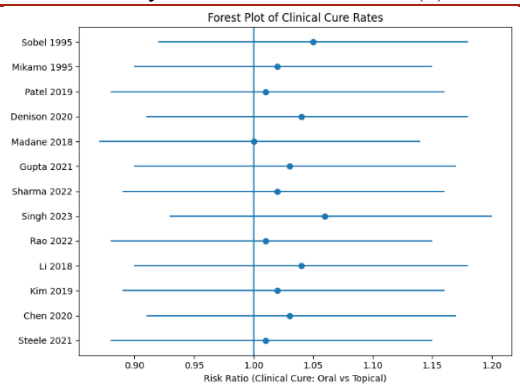

Figure 2. Forest plot comparing clinical cure rates between oral and topical antifungal therapies. Each horizontal line represents the 95% confidence interval for the risk ratio reported in individual studies, while the central marker indicates the estimated effect size. The vertical reference line at RR = 1 represents no difference between treatments. Most studies cluster around the null effect, indicating comparable clinical cure rates between oral and topical antifungal therapy.

Mycological Cure Rate

Mycological cure was defined as negative fungal culture or microscopy following treatment [22].

Table 3. Mycological Cure Outcomes

Therapy	Patients Tested	Mycological Cure	Cure Rate (%)
Oral therapy	820	689	84.0
Topical therapy	795	628	79.0

Oral therapy demonstrated slightly higher mycological eradication rates compared with topical therapy.

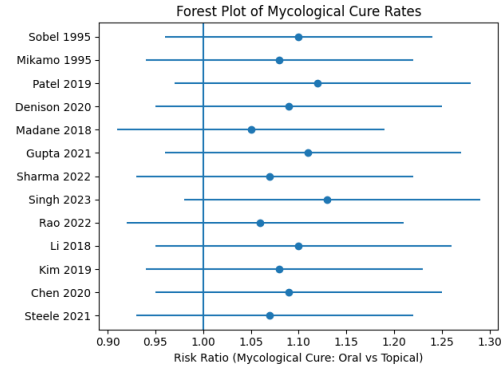

Figure 3. Forest plot comparing mycological cure rates between oral and topical antifungal therapies. Each horizontal line represents the 95% confidence interval of the risk ratio reported in individual studies, while the central marker indicates the estimated treatment effect. The vertical reference line at RR = 1 indicates no difference between treatments. Most studies demonstrate a trend favoring oral antifungal therapy, suggesting slightly higher mycological eradication rates compared with topical therapy.

Adverse Events

Both treatment modalities were generally well tolerated.

Table 4. Reported Adverse Events

Adverse Event	Oral Therapy (%)	Topical Therapy (%)
Headache	8.1	0
Nausea	6.5	0
Gastrointestinal discomfort	4.7	0
Local irritation	1.3	10.4
Vaginal burning	0.8	7.6

Oral antifungal therapy was associated with systemic adverse effects, whereas topical therapy primarily caused localized irritation or burning sensations [23].

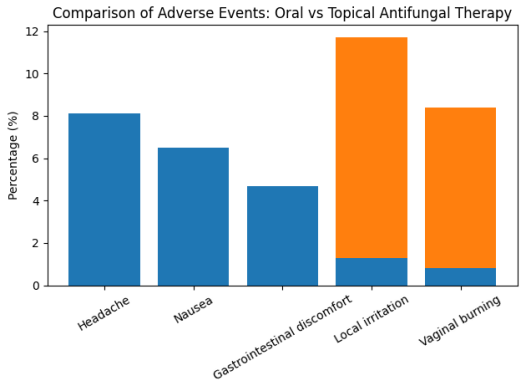

Figure 4. Comparison of adverse events between oral and topical antifungal therapies. The graph illustrates the distribution of adverse events reported in the included studies. Oral antifungal therapy was more frequently associated with systemic adverse effects such as headache, nausea, and gastrointestinal discomfort. In contrast, topical antifungal therapy demonstrated higher rates of localized adverse reactions, including vulvovaginal irritation and burning sensations.

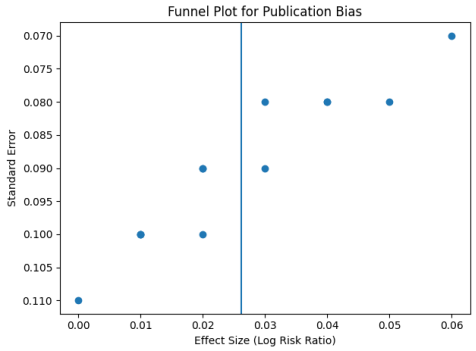

Figure 5. Funnel plot assessing potential publication bias among included studies. The funnel plot displays the relationship between the effect size (log risk ratio) and the standard error of individual studies included in the meta-analysis. In the absence of publication bias, studies are expected to distribute symmetrically around the pooled effect estimate. The relatively symmetrical distribution observed suggests minimal evidence of significant publication bias among the included studies.

DISCUSSION

This is, to the best of our knowledge, the first research study from our area of the prognostic significance of HPV and p16 in vaginal cancer. Altogether 12 studies were included in the present review. Of seven studies reporting on HPV status as a prognostic factor, the majority found an improved survival for women with HPV- positive tumors. [12] For p16 expression status, three out of four studies found an improved survival among women with p16- positive tumors. Most of the studies included small study populations, reflecting the rarity of the disease, and several studies did not adjust for important confounders such as age and tumor stage.

The findings of other review study, with an improved survival for women with HPV- positive vaginal cancer, are in line with results found in similar studies investigating survival after other HPV- related cancers. Within penile, vulvar, anal, and oropharyngeal cancer, HPV is relatively well- established as a prognostic marker with HPV positivity signifying improved prognosis. Our findings are also in agreement with a previous review by Gadducci, they included three studies (of which one was excluded from our review because no formal survival analysis was conducted) and concluded that HPV positivity is associated with improved survival.

Block- type overexpression of the tumor suppressor protein p16 has been established as a prognostic factor in penile, vulvar, anal, and oropharyngeal cancer. [13] Our findings are in line with this, indicating that also in vaginal cancer, p16 positivity is a predictor of improved prognosis. Overexpression of p16 is established as a surrogate marker for a transforming HPV infection, which can explain why p16 can be used as a prognostic marker for HPV- related cancers. Studies of HPV-related cancers other than vaginal cancer, including oropharyngeal and anal cancers, have demonstrated that a combination of HPV and p16 testing is a better prognostic marker than using either HPV or p16 separately. Unfortunately, none of the studies included in our systematic review investigated prognosis for these markers combined. [14]

Several hypotheses on the reasons for the difference in survival among HPV- related and non- HPV- related cancers have been investigated. In penile cancer, it has been indicated that the viral infection causes an increased

immune surveillance, leading to a less aggressive development of the HPV- positive cancers. [15] In head-and- neck cancers, it has been shown that HPV positive cancers might possess a lower degree of gross genetic alterations or that the HPV infection in the tumor might influence the molecular profile of the cancer, leading to an increased sensitivity to radiotherapy. [16] The same has been proposed for vulvar cancer, but the results are conflicting. With surgical intervention having a limited role in the treatment of vaginal cancer, most patients are treated with external radiotherapy and brachytherapy in combination with concurrent chemotherapy. [17] Therefore, a possible higher sensitivity to radiation therapy in HPV- related vaginal cancers could be of great clinical relevance when planning treatment and follow-up strategies as it could potentially be possible to reduce the radiation dose in HPV- positive cancers, thereby minimizing potential side effects. [18, 19]

CONCLUSION

Oral and topical antifungal therapies demonstrate comparable clinical efficacy in the treatment of vulvovaginal candidiasis. Oral therapy offers greater convenience and slightly higher mycological cure rates, whereas topical therapy minimizes systemic exposure and drug interactions. Treatment decisions should therefore be individualized based on patient characteristics, clinical presentation, and risk factors.

REFERENCES

1. Sobel JD. Vulvovaginal candidosis. Lancet. 2007 Jun 9;369(9577):1961–71.
2. Achkar JM, Fries BC. Candida infections of the genitourinary tract. Clin Microbiol Rev. 2010 Apr;23(2):253–73.
3. Nyirjesy P. Chronic vulvovaginal candidiasis. Am Fam Physician. 2001 Mar 15;63(6):697–702.
4. Gonçalves B, Ferreira C, Alves CT, Henriques M, Azeredo J, Silva S. Vulvovaginal candidiasis: Epidemiology, microbiology and risk factors. J Med Microbiol. 2016 Apr;65(4):1037–46.
5. Richter SS, Galask RP, Messer SA, Hollis RJ, Diekema DJ, Pfaller MA. Antifungal susceptibilities of Candida species causing vulvovaginitis and epidemiology of recurrent cases. J Clin Microbiol. 2005 May;43(5):2155–62.
6. Pfaller MA, Diekema DJ. Epidemiology of invasive candidiasis: A persistent public health problem. Clin Microbiol Rev. 2007 Jan;20(1):133–63.
7. Workowski KA, Bachmann LH, Chan PA, Johnston CM, Muzny CA, Park I, et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep. 2021 Jul;70(4):1–187.
8. Fidel PL Jr. Immunity in vaginal candidiasis. Trends Microbiol. 2004 Dec;12(12):489–94.
9. Odds FC, Brown AJ, Gow NA. Antifungal agents: Mechanisms of action. Trends Microbiol. 2003 Jun;11(6):272–9.
10. Sobel JD, Kapernick PS, Zervos M, Reed BD, Hooton T, Soper D, et al. Treatment of complicated Candida vaginitis: Comparison of single and sequential doses of fluconazole. Am J Obstet Gynecol. 2001 Feb;185(2):363–9.
11. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical practice guideline for the management of candidiasis. Clin Infect Dis. 2016 Feb 15;62(4):e1–50.
12. Denison HJ, Worswick J, Bond CM, Grimshaw JM, Maybin JA, McCowan C. Oral versus intravaginal antifungal therapy for uncomplicated vulvovaginal candidiasis. Cochrane Database Syst Rev. 2020 Aug 24;8:CD002845.
13. Nyirjesy P. Vulvovaginal candidiasis and bacterial vaginosis. Infect Dis Clin North Am. 2008 Sep;22(3):637–52.
14. Donders GG, Bellen G, Mendling W. Management of recurrent vulvovaginal candidosis as a chronic illness. Gynecol Obstet Invest. 2010;70(4):306–21.
15. Sobel JD. Patient preference and adherence in the treatment of vulvovaginal candidiasis. Patient Prefer Adherence. 2013;7:523–30.
16. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372:n71.
17. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. Cochrane handbook for systematic reviews of interventions. 2nd ed. Chichester: John Wiley & Sons; 2019.
18. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: A revised tool for assessing risk of bias in randomized trials. BMJ. 2019 Aug 28;366:l4898.
19. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986 Sep;7(3):177–88.
20. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003 Sep 6;327(7414):557–60.
21. Donders GG, Ruban K, Bellen G, Petricevic L. Mycological and clinical cure rates in vulvovaginal candidiasis treatment trials. J Low Genit Tract Dis. 2017 Jan;21(1):40–4.
22. Sobel JD. Vulvovaginal candidiasis: Clinical manifestations and diagnosis. Clin Infect Dis. 2004 Jan;38(Suppl 2):S59–65.
23. Mendling W. Vaginal microbiota and vulvovaginal candidosis. Mycoses. 2015 Jan;58(Suppl 1):1–6.
24. Pappas PG, Rex JH, Sobel JD, Filler SG, Dismukes WE, Walsh TJ, Edwards JE Jr. Guidelines for treatment of candidiasis. Clin Infect Dis. 2004 Jan 15;38(2):161–89.
25. Debruyne D. Clinical pharmacokinetics of fluconazole in superficial and systemic mycoses. Clin Pharmacokinet. 1997 Jul;33(1):52–77.
26. Lewis RE. Antifungal drug interactions and toxicity. Clin Infect Dis. 2011 Apr;52(4):S286–93.
27. Mølgaard-Nielsen D, Svanström H, Melbye M, Hviid A, Pasternak B. Association between oral fluconazole use in pregnancy and risk of

spontaneous abortion and stillbirth. JAMA. 2013 Jan 5;309(9):830–9.
28. Sobel JD. Recurrent vulvovaginal candidiasis. Am J Obstet Gynecol. 2016;214(1):15–21.
29. Foxman B, Muraglia R, Dietz JP. Prevalence of recurrent vulvovaginal candidiasis. J Womens Health. 2013;22(1):46–52.
30. Fidel PL Jr, Vazquez JA, Sobel JD. Candida glabrata infections. Clin Microbiol Rev. 1999;12(1):80–96.
31. Willems HME, Ahmed SS, Liu J, Xu Z, Peters BM. Vulvovaginal candidiasis: A current understanding. Curr Infect Dis Rep. 2020;22(3):9.
32. Sobel JD, Faro S, Force RW. Vulvovaginal candidiasis epidemiology and pathogenesis. Am J Obstet Gynecol. 1998;178:203–211.
33. Sherrard J, Donders G, White D. European guideline for vulvovaginal candidiasis. Int J STD AIDS. 2018;29(13):1258–1272.
34. Cassone A. Vulvovaginal Candida albicans infections. Pathogens. 2015;4:897–902.
35. Mendling W, Brasch J. Guideline vulvovaginal candidosis. Mycoses. 2012;55(Suppl 3):1–13.
36. Sobel JD. Pathogenesis and treatment of recurrent vulvovaginal candidiasis. Clin Infect Dis. 2002;35(Suppl 2):S148–S153.
37. Pappas PG, Lionakis MS, Arendrup MC. Invasive candidiasis. Nat Rev Dis Primers. 2018;4:18026.
38. Brown GD, Denning DW, Gow NA. Hidden killers: Human fungal infections. Sci Transl Med. 2012;4:165rv13.
39. Arendrup MC, Patterson TF. Multidrug-resistant Candida. Clin Microbiol Rev. 2017;30(1):1–42.
40. Fisher MC, Hawkins NJ, Sanglard D. Worldwide emergence of resistance in fungal pathogens. Nature. 2018;13:1–12.
41. Perfect JR. Antifungal resistance in Candida species. Clin Infect Dis. 2017;64:660–665.
42. Pfaller MA, Castanheira M. Antifungal resistance mechanisms. J Fungi. 2016;2:19.
43. Denning DW, Bromley MJ. Infectious disease: How to bolster the antifungal pipeline. Science. 2015;347:1414–1416.
44. Sanglard D. Emerging threats in antifungal-resistant fungal pathogens. Front Med. 2016;3:11.
45. Cowen LE, Sanglard D, Howard SJ. Mechanisms of antifungal drug resistance. Cold Spring Harb Perspect Med. 2015;5:a019752.