

# In the search for appropriateness in the cure of vaginitis: a model of anti-fungal stewardship?

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**Abstract.** – Antimicrobial resistance remains a worldwide issue with a major clinical and economic impact, leading to exceeding mortality, increased frequency of hospitalization and a great burden on the healthcare systems. Vulvovaginitis, especially when due to mixed infections, has emerged as a condition for which appropriate selection of antimicrobial therapy and proper antimicrobial stewardship programs (ASPs) may contribute to minimizing the resistance development. This review discusses the appropriateness of selecting treatment for vulvovaginitis in order to reduce the development of resistance in gynecological practice.

Narrative review based on a selection of literature performed according to the Authors' experience and a MEDLINE search using the following keywords: "vaginitis" OR "Candida" OR "fungal infection" AND "antifungal therapy". No limits were applied, but papers were selected for inclusion in this narrative review according to their relevance to the topic, as judged by the Authors.

Worldwide, antimicrobial treatment in gynecology and ASPs focuses on prescribing systemic and expensive antifungal drugs, while treatment selection should consider several factors. Recently, topical azoles have been recommended as suitable alternatives to oral systemic azoles, given their similar efficacy in limiting clinical recurrence. In particular, fenticonazole has already been proposed as an alternative to systemic antifungal drugs to limit the onset of resistance.

Optimizing the selection of antimicrobial treatment can help reduce the development of resistance in gynecological practice. Given its wide action spectrum and ability to exert antimicrobial activity against fungi, bacteria and mixed infections, fenticonazole may be considered a suitable first-line, empiric therapy for vaginal and mixed infections, avoiding alteration of intestinal microflora and minimizing the risk of selection of drug-resistant microbial strains.

#### Key Words:

Antimicrobial resistance, Vulvovaginitis, Anti-fungal stewardship, Antimicrobial therapy, Anti-fungal

drugs, Candidiasis, Systemic treatment, Oral azoles, Fluconazole, Topical azoles, Fenticonazole.

## Introduction

Even in the COVID-19 era, antimicrobial resistance remains a worldwide issue with a significant clinical and economic impact<sup>1</sup>. Indeed, antimicrobial resistance results in prolonged infections in susceptible individuals, leading to increased mortality, more frequent hospitalization, and a great burden on healthcare systems. Furthermore, antimicrobial resistance particularly affects people from developing countries, who often have only scant access to expensive antibiotics for second-line treatment.

Antimicrobial resistance is a widespread phenomenon in all fields of medicine, and gynecology makes no exception<sup>2-4</sup>. In particular, vulvovaginitis, especially due to mixed infections, has emerged as a condition for which appropriate selection of antimicrobial therapy and the establishment of adequate antimicrobial stewardship programs (ASPs) may contribute to minimizing the development of resistance<sup>2</sup>. Worldwide, there is an increasing tendency to prescribe oral medications as first-line therapy for vulvovaginitis, while treatment selection should consider several factors<sup>5,6</sup>. Remarkably, inappropriate treatment of uncomplicated infections can affect the ecological characteristics of pathogenic fungi and worsen the outcome of infections.

This narrative review will discuss the appropriateness of selecting treatment for vulvovaginitis.

This is a narrative review based on a selection of literature performed according to the Authors' experience and knowledge of the topic

supplemented by a MEDLINE search using the following keywords: “(vaginitis OR Candida OR fungal infection” AND “antifungal therapy)”. No limits were applied, but papers were selected for inclusion in this narrative review according to their relevance to the topic, as judged by the Authors. The list of references of the retrieved papers was also checked for other potential sources of evidence.

### Vulvovaginitis and Resistance

Although resistant vulvovaginitis was considered rare until the last decades, mounting evidence shows this is an increasingly reported condition. In 2012, Marchaim et al<sup>7</sup> reported 25 cases of candidemia over an 11-year period. All patients had received fluconazole treatment 6 months before the development of candidemia, and treatment of resistant infection was complicated and prolonged.

Since then, the emergence of resistant Candidiasis has been well documented in the last decade<sup>8,9</sup>. A recent Cochrane meta-analysis summarized the existing evidence by evaluating 23 studies on 2,212 women (17-67 years old), most of whom were infected by *Candida albicans*<sup>10</sup>. In most cases, anti-fungal treatment was compared with placebo (six studies), while four studies compared oral vs. topical therapy. A high or unclear risk of bias was disclosed, mainly due to insufficient blinding and poor reporting. Meta-analyses of the six studies comparing antifungal drug treatment (oral or topical) with placebo showed that there may be a clinically relevant reduction in clinical recurrence at 6 months ( $n=697$ ; relative risk [RR]: 0.36; 95% CI: 0.21-0.63; number needed to treat for an additional beneficial outcome [NNTB]=2;  $I^2 = 82\%$ ; low-certainty evidence) and 12 months ( $n=585$ ; RR: 0.80, 95% CI: 0.72–0.89; NNTB=6;  $I^2 = 21\%$ ; low-certainty evidence). Remarkably, the risk of onset of resistance emerged when comparing oral drug treatment and topical treatment at both 6 months ( $n=206$ ; RR: 1.66, 95% CI: 0.83-3.31;  $I^2 = 0\%$ ; very low-certainty evidence) and 12 months ( $n=206$ ; RR: 0.95, 95% CI: 0.71-1.27;  $I^2 = 10\%$ ; very low-certainty evidence). Overall, the rate of adverse events was below 5% in all the treatment arms. On these bases, it is possible to conclude that active treatment with oral or topical anti-fungals may reduce clinical recurrences compared to no therapy, with a limited burden of adverse events. However, oral and topical treatments were similar in their efficacy

in limiting recurrences. Therefore, new guidance on the optimal treatment strategy, medication, dose, and frequency is needed according to emerging evidence<sup>10</sup>.

### Guidelines for Treatment and Relevance for Clinical Practice

Several guidelines on the treatment of resistant Candidiasis have been issued over the past years. The European Society of Clinical Microbiology and Infectious Diseases guidelines, published in 2012, pointed out that pathogen identification and susceptibility testing should be assessed before the institution of therapy in recurrent/complicated vaginitis and patients with prior azole exposure<sup>11</sup>. However, this recommendation is often disregarded in clinical practice<sup>12,13</sup>. In the guidelines issued by the Infectious Diseases Society of America in 2016, echinocandins (caspofungin loading dose 70 mg, then 50 mg daily micafungin 100 mg daily anidulafungin loading dose 200 mg, then 100 mg daily) are recommended as initial therapy. Fluconazole intravenous or oral (800 mg 12 mg/kg loading dose, then 400 mg 6 mg/kg daily) is proposed as an acceptable alternative to echinocandins in the first-line setting for selected patients, including those who are not critically ill and who are unlikely to have a fluconazole-resistant *Candida* species<sup>14</sup>. However, the dosage selection in those guidelines is based on studies published years ago<sup>15,16</sup>, which may not immediately represent current *Candida* epidemiology. More recently, the NICE clinical knowledge summary, published in 2021, suggests oral azoles or intra-vaginal imidazoles as first-line therapies. However, for the first time to our knowledge, topical azoles (fenticonazole, clotrimazole, econazole, miconazole) are recommended as suitable alternatives to the previously mentioned agents if these are contraindicated or not tolerated. This is a major turning point in clinical practice as the therapeutic armamentarium becomes broader, facilitating the appropriate treatment selection.

Among different topical azoles, fenticonazole has already been proposed as an alternative to fluconazole to limit the onset of resistance<sup>2,5</sup>.

### Impact of Drug Regimens

Several factors seem to influence the development of antimicrobial resistance, including host-, pathogen-, environment- and drug-related factors. In particular, one variable under the

control of the prescriber is the drug regimen, which has a potential impact on the risk of resistance<sup>10,17</sup>.

Prior treatment with fluconazole does represent a modifiable risk factor for the isolation of fluconazole-nonsusceptible *Candida* species. In 2012, Shah et al<sup>18</sup> evaluated the effects of prior fluconazole therapy, including dose and duration, on fluconazole susceptibility among *Candida* species of 133 hospitalized patients with candidemia. In total, 9/107 (8%) patients with fluconazole-susceptible *Candida* and 9/26 (35%) of those patients with fluconazole-nonsusceptible *Candida* had previous fluconazole exposure (RR: 3.03; 95% CI: 1.57-5.86;  $p=0.0022$ ), thus suggesting a higher risk of developing resistant Candidiasis in association with previous fluconazole therapy.

Concerning the comparison of oral fluconazole to topical fenticonazole, in a randomized study, Murina et al<sup>19</sup> evaluated the efficacy of fluconazole 150 mg ( $n=40$ ) and intra-vaginal fenticonazole 600 mg ( $n=40$ ) in the short-course treatment of acute vulvovaginal Candidiasis. Two sequential doses of the study drugs were given 3 days apart in both arms. At 7 days after completion of the treatment course, 77.5% of patients were clinically cured (Sobel score  $<4$ ) in the fluconazole group, compared with 80% of those receiving fenticonazole ( $p=0.876$ ); an advantage for fenticonazole was also observed in terms of time to resolution of pruritus (4.5 days with fluconazole vs. 2.3 with fenticonazole;  $p=0.047$ ). At 30 days after completion of treatment, three patients in the fluconazole group and two patients in the fenticonazole group were still showing clinical signs of vulvovaginal Candidiasis. These findings support the similar efficacy of oral fluconazole and high-dose topical fenticonazole in VCC treatment. A more recent study by Cacaci et al<sup>20</sup> has further corroborated these findings. In this *in vitro* study, the activity of fenticonazole against *C. albicans* and *C. glabrata* isolates from mucosa was consistently higher than that of fluconazole.

Interestingly, for *C. albicans* isolates, fenticonazole's minimum inhibitory concentration ranged from 0.2 to 2.0 mg/L among fluconazole-nonresistant isolates and from 1.0 to 8.0 mg/L in fluconazole-resistant isolates. Corresponding figures for *C. glabrata* isolates were 0.5-2.0 mg/L and 0.5-4.0 mg/L, respectively. These data lend support to the higher activity of fenticonazole in fluconazole-resistant isolates.

## Running the Appropriateness in Superficial Infections

The current debate about antimicrobial treatment in gynecology and ASPs for anti-fungal therapies focuses on optimizing the prescription of systemic and expensive anti-fungal drugs<sup>2</sup>. Indeed, the very high number of prescriptions for some systemic oral azoles, such as fluconazole and itraconazole, remains a neglected issue in community and hospital practice<sup>2</sup>. Itraconazole, in particular, follows non-linear pharmacokinetics leading to a rapid accumulation of the drug in tissues; moreover, at a high oral dose of itraconazole, absolute oral bioavailability increases, and there is an increase in  $AUC_{0-48h}$ <sup>21</sup>. At present, ASPs are implemented, in most cases, in acute-care hospitals. However, the largest part of antibiotic prescriptions in gynecology are given in the outpatient setting<sup>22</sup>, which is more difficult to control.

Furthermore, ASP strategies applied in acute-care hospitals cannot be automatically extrapolated to general community medicine, given the differences in patients and available resources. Indeed, high-cost drugs (new azoles, echinocandins, and lipid formulations of polyenes) are generally only used in hospitals. In addition, it is essential to remember that oral azoles are not devoid of the risk of systemic adverse effects<sup>23-25</sup> and can influence intestinal microbiota<sup>5</sup>.

On the other hand, effective topical treatment could save prescriptions for systemic drugs, with a consequent reduction of perturbation on intestinal microbiota and, potentially, the risk of developing resistance<sup>5</sup>. In the case of superficial fungal infections, it should be taken into account that inexpensive drugs are available and represent suitable and effective options also in the community gynecological setting. Topical azoles were neglected until a few years ago, but the recent NICE guidelines have stressed their importance as alternatives to systemic treatment<sup>26</sup>. Their use is also supported by the recent Cochrane analysis by Cooke et al<sup>10</sup>, which proved the similar efficacy of oral and topical treatment on the onset of recurrence.

Despite the lack of relevant and significant studies demonstrating local topical therapy's superiority or greater advantage over systemic therapy, evaluating a first therapeutic approach based on topical treatment is convincing. This is possible because of the noticeable reduction of adverse effects observed, mainly due to interactions with many drugs (especially those with a significant metabolic impact on cytochromes) or systemic

azoles therapies, often not yet optimized in their posology. It is very undesirable to use fluconazole at 150 or 200 mg daily since suboptimal plasma levels are obtained in adult women, favoring the selection of resistant strains or those with reduced clinical response<sup>18</sup>. Moreover, it is well established that over the past 20 years, *non-C. albicans* strains have been increasingly responsible for cases of vulvovaginitis, leading to the need for alternative therapies to fluconazole. Thus, the preferable choice in the first episodes should be a local topical therapy with a broad-spectrum drug with evidence of efficacy even on bacterial isolates, since most of the time, the treatment occurs without a well-defined diagnostic workup.

Fenticonazole is a topical anti-fungal drug endowed with a broad spectrum of action and high efficacy for treating Candidiasis and mixed infections. Indeed, a broad spectrum of action is of utmost importance in daily gynecological practice. Although current guidelines recommend testing to identify the specific pathogen, this recommendation is often disregarded in clinical practice due to a lack of time and resources<sup>12,13</sup>. Therefore, the use of fenticonazole as a first-line treatment can be suggested, reserving a more targeted selection of therapy according to the results of pathogen testing in the case of recurrence, in line with current recommendations for uncomplicated cystitis<sup>27-30</sup>. Additionally, given the availability of different formulations, fenticonazole can be considered a first-line choice in treating non-severe fungal infections while minimizing the risk of selecting drug-resistant strains. The efficacy of fenticonazole in treating bacterial and fungal infections has been shown in multiple clinical studies (Tumietto et al<sup>2</sup> for a review). In particular,

the use of higher-dose fenticonazole, although not approved worldwide, appears promising according to existing preliminary evidence showing that its efficacy is at least similar to oral fluconazole<sup>31</sup>. However, further studies on larger populations from clinical practice are necessary to explore this finding further.

Furthermore, recent data from a study by Sanguinetti et al<sup>32</sup> highlighted the potential microbicidal activity of fenticonazole at supra-minimum inhibitory concentrations, such as those achieved in topically treated skin or mucosa during vaginitis episodes. The same study also suggested that increasing fenticonazole concentration may help overcome interference between *C. albicans* and bacterial species in mixed infections, thereby diminishing the risk of resistance.

## Conclusions

Optimizing antimicrobial treatment selection can help reducing the development of resistance in gynecological practice (Table I). Given its broad spectrum of action and ability to exert antimicrobial activity against fungi, bacteria, and mixed infections, fenticonazole may be considered a suitable first-line, empiric therapy for vaginal and mixed infections with different etiology, avoiding alteration of intestinal microflora and minimizing the risk of selection of drug-resistant microbial strains.

## Conflict of Interest

The Authors declare that they have no conflict of interests.

**Table I.** Suggestions for improved antimicrobial stewardship.

Antimicrobial treatment for vulvovaginitis is usually focused on the prescription of systemic and expensive drugs (e.g., fluconazole and itraconazole); however, oral azoles are not devoid of the risk of systemic adverse effects and can affect intestinal microbiota, mainly by their interactions with many drugs or their not yet optimized posology
Usage of topical azoles was neglected until a few years ago, but the recent NICE guidelines pointed out their importance as alternatives to systemic treatment, given their similar efficacy on the onset of recurrence
Fenticonazole is a topical anti-fungal drug with a broad action spectrum and high efficacy in treating Candidiasis and mixed infections; it could be used as a first-line treatment reserving a more targeted therapy in the case of recurrence
Fenticonazole has a potential microbicidal activity at supra-minimum inhibitory concentrations; higher doses could help prevent the interference between <i>Candida albicans</i> and bacterial species in mixed infections, thus diminishing the risk of resistance
Overall, fenticonazole may be considered a suitable first-line therapy for vaginal and mixed infections with different etiology, avoiding alteration of intestinal microflora and minimizing the risk of drug-resistance development

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### Authors' Contribution

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### Ethics Approval

Not required.

### Consent to Participate

Not required.

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