Antimicrobial Resistance in Vulvovaginitis

Jack D. Sobel, MD

Address
Division of Infectious Diseases, Harper Hospital,
3990 John R, Detroit, MI 48201, USA.
E-mail: jsobel@intmed.wayne.edu

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Although antimicrobial resistance has had an enormous impact on selection and utilization of antibiotics in virtually all aspects of clinical medicine, both inpatient and community based, little attention has been directed at antimicrobial resistance occurring in vaginal infections. Little evidence exists that frequent relapses of bacterial vaginosis or vulvovaginal candidiasis are due to antimicrobial resistance. Similarly, metronidazole-resistant trichomoniasis remains rare. Nevertheless, abuse of over-the-counter antimycotics, as well as widespread prescription of systemic oral azoles, could result in spread of azole-resistant *Candida albicans*, and even more likely could lead to an increase in non-*albicans Candida* species with intrinsic azole resistance. Problematic species include *Candida glabrata* and rarely *Candida krusei*.

Introduction

During the past five decades, one has seen the pendulum of antimicrobial resistance and antibiotic discovery swing to and fro. With few exceptions, virtually all the major microbial bacterial, fungal, parasitic, and viral pathogens have been associated with acquisition of resistance. Most clinical resistance develops in profoundly immunocompromised or debilitated hosts. Unfortunately, resistance has also developed in occasional pathogens in otherwise healthy hosts. Vulvovaginal infections are extremely common in healthy women and are responsible for enormous morbidity. Not infrequently, however, women suffer from refractory clinical disease or present with frequent recurrences of vulvovaginal infections. It should be emphasized that in the overwhelming majority of patients, recalcitrant disease or frequently relapsing symptoms are rarely the result of resistance. The most common cause of difficult-to-treat vulvovaginitis is an incorrect diagnosis. Unfortunately, there has been little progress in the development of diagnostic aids to facilitate making an accurate diagnosis. Accordingly, before antimicrobial resistance is considered, every effort should be made to confirm the diagnosis of the specific form of vaginitis. Nevertheless, evidence has recently surfaced of emerging resistance in some vulvovaginal infections.

Bacterial Vaginosis

Although the majority of patients with bacterial vaginosis respond well when treated with conventional oral and topical antibacterial agents, frequent recurrences are by no means uncommon [1,2•] In fact, almost a third of the compliant patients completing antibacterial therapy develop a recurrence of identical symptoms within 3 months [1]. Recurrent bacterial vaginosis has been the focus of many investigations, and as yet no adequate explanation exists for this common recurrence. Theories of recurrent bacterial vaginosis include reinfection from an infected sexual partner, persistence of pathogenic bacteria within the vagina, the presence of as yet unidentified pathogens, as well as the failure to re-establish a protective H_2O_2-positive *Lactobacillus*-dominant vaginal flora. Finally, the possibility of metronidazole and clindamycin resistance among the bacterial species responsible for bacterial vaginosis has also been considered. Little attention has been directed at the latter possibility. In our own laboratory, monitoring for metronidazole resistance has been negative. In general clinical practice, metronidazole resistance is also extremely rare among anaerobic gram-negative species. There are only sporadic reports of resistant vaginal anaerobes present in women with recurrent bacterial vaginosis [3,4]. Nevertheless, the subject has not been adequately studied. Clindamycin resistance among *Bacteroides* and *Prevotella* species is not uncommon. Patients with recurrent bacterial vaginosis, relapsing after clindamycin therapy, are invariably treated with metronidazole, without a dramatic impact on reduction of clinical recurrence rates.

The Role of Antifungal Resistance in *Candida* Vaginitis

Prior to the availability of oral azoles (fluconazole, ketoconazole, and itraconazole) for treatment of vaginal candidiasis in the late 1980s, *Candida* vaginitis was effectively treated with topical imidazoles. During this period, no evidence of azole resistance was forthcoming. Antifungal susceptibility

tests were not available and cultures identifying *Candida* species were not frequently performed. The introduction of oral fluconazole for the treatment of vaginal candidiasis was accompanied by considerable concern by many experts, who felt that the use of an oral systemic agent, especially when prescribed as a single-dose regimen, would inevitably result in the development of resistance among *Candida* species responsible for both *Candida* vaginitis and life-threatening candidemia. It would now appear that there was some basis for these very early concerns.

Before turning to *Candida* vaginitis, it should be emphasized that antifungal resistance has become a major concern in oropharyngeal, esophageal, and systemic *Candida* infections [5–7]. Regardless of the anatomical site, refractory clinical disease in no way proves that antimicrobial resistance exists. There are numerous causes as to why patients fail to respond, including noncompliance, lack of absorption, incorrect dosing, as well as drug interactions. Accordingly, before resistance is considered, every effort should be made to exclude other factors responsible for clinical failure. After isolation of the offending pathogen, in vitro resistance should then be confirmed. Concerns about antifungal resistance have largely emerged as a result of refractory oropharyngeal candidiasis in HIV-infected individuals. What began as an anecdotal problem in the early 1990s increased to involve 7% to 10% of HIV-infected patients, predominantly those with an advanced immunodeficiency [7]. Prior to the introduction of highly active antiretroviral therapy, the development of refractory oropharyngeal and esophageal candidiasis represented a major clinical challenge. These patients presented with azole refractory disease in which high-level fluconazole resistance was present, but in addition, cross-resistance to all other available systemic azoles was evident [8,9]. Moreover, not infrequently these patients also responded poorly to systemic amphotericin therapy. Fortunately, with the introduction of highly active antiretroviral therapy, there has been a dramatic decline in the frequency of azole-refractory mucosal candidiasis. This, however, continues to be a significant problem. Faced with the development of fluconazole resistance, a variety of newer azoles have been introduced that are active in vitro and clinically against resistant strains of *Candida albicans* responsible for oropharyngeal and esophageal disease [10]. Only infrequently is clinically refractory mucosal candidiasis involving the oropharynx and esophagus the result of infection caused by non-*albicans Candida* species.

At the time that refractory oropharyngeal candidiasis was seen in HIV-infected patients, similarly resistant *Candida* vaginitis was not observed. This discrepancy has not been adequately explained. Several years after the availability of fluconazole, the first report of azole-resistant *Candida* vaginitis was reported in an HIV-negative woman who had been exposed to a variety of topical azoles in addition to high doses of oral fluconazole [11]. Refractory *Candida* vaginitis was due to a *C. albicans* strain with high levels of fluconazole resistance (> 64 μg/mL). The patient was effectively cured by prolonged intravaginal therapy with boric acid. Over the next few years and until the present date, *C. albicans* resistant to fluconazole and other systemic azoles has rarely been responsible for *Candida* vaginitis. However, in a recent study that dealt with complicated *Candida* vaginitis in a highly selected group of women seen at university centers, the baseline study enrollment prevalence of fluconazole-resistant *C. albicans* was found to be 3.6% [12••]. This observation was a surprise finding and is of considerable concern since it reflects the potential for an increased occurrence of fluconazole resistance in yeast vaginitis.

Of greater significance than acquired fluconazole resistance in *C. albicans* strains is the potential for an increase in vaginitis due to non-*albicans Candida* species with intrinsic fluconazole resistance. The majority of the non-*albicans Candida* species still remains susceptible to fluconazole at concentrations achieved in the vaginal secretions and tissues. Two species, however, represent a significant challenge to the efficacy of fluconazole. *Candida glabrata* is the second most common species of *Candida* responsible for fungal vaginitis [13]. The epidemiology of *C. glabrata* vaginitis remains obscure, and estimates of the frequency of vaginitis due to *C. glabrata* vary by geographic site in the United States. Most studies indicate that *C. glabrata* remains an infrequent cause of vaginitis, estimated between 5% and 10% only [12••]. Evidence of a significant increase in the frequency of *C. glabrata* vaginitis is scanty. The minimum inhibitory concentrations of *C. glabrata* to virtually all azoles are approximately 10- to 100-fold higher than those seen with *C. albicans* [13]. Accordingly, clinical response rates with conventional dosing of fluconazole result in only a 50% cure [13]. In general, the problem of *C. glabrata* vaginitis is significantly greater than the current threat of azole resistance in vaginal *C. albicans*.

Although rare, vaginitis caused by *Candida krusei* represents yet one more example of intrinsic fluconazole resistance causing refractory disease. *C. krusei*, in contrast to *C. glabrata*, is predictably resistant to fluconazole, but is also resistant to flucytosine that is now the drug of choice for the treatment of *C. glabrata* infections. Moreover, *C. glabrata* is frequently resistant to miconazole, the most widely used topical imidazole agent. Clinical experience with this rare cause of vaginitis indicates that the disease is extremely refractory, requiring prolonged therapy with either vaginal clotrimazole or boric acid or, alternatively, with oral ketoconazole and itraconazole.

Since refractory oropharyngeal candidiasis first emerged in HIV-infected individuals, it is conceivable that studies of the microbiology of *Candida* vaginitis in HIV-infected women might provide insight into the future likelihood of antifungal resistance appearing in *Candida* vaginitis in HIV-negative women. Longitudinal studies that have followed HIV-infected women for several years indicate that with exposure to fluconazole, there is a tendency for a switch in vaginal flora to occur, with progressive colonization of the

vagina with *C. glabrata* [9,14••]. Moreover, this increased colonization rate is accompanied by a gradual step-wise increase in minimum inhibitory concentration values to fluconazole and other azoles [9,14••] The appearance of fluconazole resistance with rising minimum inhibitory concentrations in *C. glabrata* may be a forerunner of fluconazole resistance in vaginal isolates of *C. albicans*.

It should be emphasized that most women—whether HIV positive or negative—who present with recurrent *Candida* vaginitis have *C. albicans* infection, and, more importantly, harbor *C. albicans* strains highly susceptible to azoles [15,16]. In a patient with recurrent *Candida* vaginitis, it is prudent to obtain a culture. Determining the species of the *Candida* isolate is more important than performing antifungal susceptibility tests. Nevertheless, the overwhelming majority of recurrent episodes are due to relapses caused by highly susceptible strains [15,16]. The cause of the relapses remains incompletely explained, but in no small way is it the result of treatment with fungistatic, rather than fungicidal agents. This allows vaginal persistence of the original pathogens that continue to colonize the vagina in small numbers only to cause recurrent disease when microenvironmental changes in the vagina permit disease to occur. Fortunately, *C. glabrata* with reduced susceptibility to azoles is associated with a significantly lower attack rate of symptomatic vaginitis [9] Any future progress in management of recurrent *Candida* vaginitis will require the development of fungicidal agents.

Trichomoniasis

Trichomonal resistance to metronidazole was reported within 2 years of its introduction and is now reported in many areas of the world. For the most part, resistance is low level, with only mildly elevated minimum inhibitory concentrations (≤50 μg/mL), and estimated to be approximately 5% [17]. Low-level resistance invariably responds to a dose higher than conventional metronidazole therapy and, therefore, clinicians can adequately deal with low-level metronidazole resistance simply by increasing the daily dose of metronidazole to 2 g per day and by prolonging the duration of therapy from 7 to 14 days [18]. High-level metronidazole resistance is fortunately rare. It is estimated that high-level resistance occurs in approximately one in 2000 to one in 3000 cases. The resistance may be aerobically mediated by a decreased transcription of the ferredoxin gene, or anaerobically produced by decreased nonexistent activities of pyruvate-ferredoxin oxireductase hydrogenase [19]. Knowledge of metronidazole-resistant trichomoniasis has been facilitated by the now widely available culture techniques that allow the diagnosis to be confirmed as well as the organisms to be retained for in vitro laboratory studies. Although not fully standardized, in vitro laboratory tests of metronidazole resistance are now available, and the Centers for Disease Control and Prevention will accept samples appropriately transported for susceptibility testing.

The clinical expression of infection with strains demonstrating metronidazole resistance is indistinguishable from that of metronidazole-susceptible strains, resulting in mild to severe vulvovaginitis with an offensive, purulent vaginal discharge. Resistant cases are invariably associated with prolonged suffering with recalcitrant disease persisting for several years. Therapeutic options for treating women with metronidazole-resistant trichomoniasis are extremely limited and, therefore, the diagnosis should always be confirmed. Recurrent trichomoniasis is usually caused by susceptible strains in patients who have been noncompliant, or who are reinfected by a male partner who has not been simultaneously treated with metronidazole.

Once the diagnosis of metronidazole resistance has been made clinically and the diagnosis confirmed by culture technique, appropriate therapy can be given in the absence of susceptibility testing. Since most patients have low-level resistance, as mentioned above, increasing the dose and duration of therapy with metronidazole to total doses ranging between 20 and 40 grams of metronidazole will usually result in eradication of infection [17]. Determining the optimal dose of metronidazole for treating male partners of women with resistant *Trichomonas* has not been determined.

When patients present with high-level metronidazole-resistant trichomoniasis, few therapeutic options exist. Nyirjesy *et al*. [20] reported considerable success with topical paromomycin cream. Unfortunately, paromomycin is not widely available and its use has been associated with a high frequency of local vulvovaginal irritation and toxicity. Another option is to use another nitroimidazole agent, tinidazole. This relative of metronidazole has also been available for many years, but not marketed in the United States. In vitro, tinidazole has only modest advantages over metronidazole in susceptible cases. The safety profile is moderately improved with enhanced tolerance. Historically, the advantages of tinidazole in the treatment of drug-susceptible trichomoniasis did not appear to justify its introduction to the United States. For reasons that are unclear, tinidazole is often highly active against metronidazole-resistant strains of *Trichomonas vaginalis* [21]. In limited studies, prolonged high-dose therapy with both oral and vaginal tinidazole appears to be active and achieve a 90% success rate with resistant trichomoniasis [22,23••]. The optimal daily dose and duration of tinidazole therapy is unknown. Sobel *et al*. [23••] reported considerable success using a dose of 2 g per day of tinidazole give in two to four divided doses and given for a minimum of 14 days together with intravaginal therapy with tinidazole oral tablets at a dose of 500 mg twice a day. It is unknown whether a shorter duration of therapy with tinidazole would be equally effective.

Conclusions

Antimicrobial resistance is frequently considered by clinicians when patients present with refractory unresponsive vaginitis or with frequent relapses of disease. By far, the most common explanation for these events is not in vitro or in vivo antimicrobial resistance, but incorrect diagnosis. Lack of specificity of signs and symptoms of vaginitis, together with lack of laboratory diagnostic aids, all too often result in presumptive diagnosis and empiric therapy. Fortunately, true antimicrobial resistance is rare and should only be considered when refractory or chronic vaginitis is confirmed by available laboratory diagnostic tests. Nevertheless, constant surveillance is required to monitor the development of resistance in patients with vaginitis, especially since a plethora of alternative antifungal and antiprotozoan drugs are not available.

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