MEDICAL REVIEW

Antifungal Resistance in Yeast Vaginitis

Erica Dun

School of Epidemiology and Public Health, Yale University, New Haven, Connecticut

The increased number of vaginal yeast infections in the past few years has been a disturbing trend, and the scientific community has been searching for its etiology. Several theories have been put forth to explain the apparent increase. First, the recent widespread availability of low-dosage, azole-based, over-the-counter antifungal medications for vaginal yeast infections encourages women to self-diagnose and treat, and women may be misdiagnosing themselves. Their vaginitis may be caused by bacteria, parasites or may be a symptom of another underlying health condition. As a result, they may be unnecessarily and chronically expose themselves to antifungal medications and encourage fungal resistance. Second, medical technology has increased the life span of seriously immune compromised individuals, yet these individuals are frequently plagued by opportunistic fungal infections. Long-term and intense azole-based antifungal treatment has been linked to an increase in resistant Candida and non-Candida species. Thus, the future of limiting antifungal resistance lies in identifying the factors promoting resistance and implementing policies to prevent it.

DEFINITION OF THE PROBLEM

Vaginal yeast infections are an unfortunate but common problem among women. It is estimated that 13 million cases are reported annually in the United States [1]. Three out of four women will experience at least one yeast infection during their reproductive years, and about half will have recurrent infections [2]. In recent years, the number of vaginal yeast infections has been dramatically increasing. In fact, not only has there been an increase in the number of vaginal yeast infections, but the number of fungal infections, in general, is on the rise. Coinciding with the increase in fungal infections is the increased use of new and old antifungal therapies. Antifungal medications have appeared on drugstore shelves, available without a prescription. Among the most visible and highly advertised antifungal medications are cures for vaginal yeast infections. It is believed that the widespread availability of these antifungals, which formerly required a prescription, has contributed to an environment conducive to breeding antifungal resistance.

Women are now more likely to self-medicate when symptoms of itching, burning, irritation, and vaginal discharge arise. Single-celled eukaryotic yeast of the genus Candida are the primary perpetrators of

---

a To whom all correspondence should be addressed: Erica Dun, James H. Quillen College of Medicine, East Tennessee State University, P.O. Box 70577, Johnson City, TN 37614. Tel.: 423-439-8847; Fax: 423-439-8773.

b Abbreviations: OTC, over-the-counter; P45014adm, 14-a-demethylase; amp B, amphotericin B.

Submitted: December 1999; Accepted: February 2000.
yeast infections or vulvovaginal candidiasis. Macroscopically, Candida develop into smooth, soft, white/cream-colored colonies with an unmistakable beer-like odor [3]. Overgrowth of Candida in the vagina produces localized symptoms of itching, burning, and irritation. Abnormal discharge characterized by a cottage-cheese-like consistency may occur. However, discharge, irritation, and painful urination are also the symptoms of several other types of vaginitis. Bacteria are the most common cause of vaginitis. Trichomoniasis or “trich,” a sexually transmitted disease, is another leading cause. It is produced by a single-celled proto parasite called Trichomonas vaginalis. Diagnosing the true cause of vaginitis from the clinical presentation is difficult because there are several organisms that produce similar symptoms.

Vulvovaginal candidiasis can be clinically differentiated vaginal secretions for evidence of yeast forms. Visualization of yeast can be performed by clinicians through three quick diagnostic methods: 10 percent KOH, saline wet mount, or Gram stain [4]. Without clinical confirmation of the etiology, women may automatically dismiss vaginitis as a fungal infection and begin an antifungal regimen. Of course, antifungals are ineffective in combating vaginitis caused by bacteria or parasites. And women may unnecessarily expose themselves to multiple over-the-counter (OTC) medications before seeking professional help.

Some women first attempt to cure yeast infections with do-it-yourself treatments and natural remedies before turning to OTC antifungal preparations. Yogurt is the most popular choice and commonly recommended by medical professionals. Adding yogurt to the vagina is believed to increase the number of Lactobacillus acidophilus bacterium. These bacteria are part of the natural flora of the vagina and produce hydrogen peroxide, which kills yeast, keeping its growth in check. Applying garlic, tea tree oil, and boric acid to the affected areas are other common home remedies. Many women report success with these treatments. In fact, the efficacy of some of these natural remedies has been scientifically tested. The successful use of boric acid vaginal capsules to treat persistent vaginitis caused by C. glabrata was reported in women who had previously failed several courses of azole treatments [5]. Nevertheless, the overwhelmingly preferred treatment for yeast infections are the OTC,azole-based antifungal medications. The azoles, which include imidazoles and triazoles, function by inhibiting ergosterol biosynthesis through the selective inhibition of fungal cytochrome P450 14-α-demethylase (P45014αdm). Without methylation of the sterol molecule during its synthesis, the sterol molecule cannot orient correctly within the phospholipid bilayer. As a result, fungal membrane fluidity and stability is disrupted, and the cell dies [6]. Azoles are fungistatic drugs. In other words, they inhibit further proliferation of yeast but do not destroy yeast cells per se. They are the preferred course of treatment for localized Candida infections, and they usually effectively cure vulvovaginal candidiasis.

For the most advanced cases of Candidiasis, the antifungal treatment regime includes amphotericin B (amp B) and/or flucytosine (5-fluorocytosine). Amp B is a broadspectrum, antifungal drug that is extremely effective in controlling systemic fungal infections. Amp B and nystatin, both polyene compounds, are fungicidal drugs that bind to fungal sterols, causing perturbations in the cell membrane. Weakening the membrane makes the fungal cells leaky and results in electrolyte imbalance and cell death. Amp B effectively eliminates fungal infections, and the prevalence of amp B-resistant strains is very low. However, polyene drugs, especially amp B, have several significant limitations, such as the necessity for intravenous use, a broad range of toxicities, including fever, chills, nausea, vomiting, anemia, thrombophlebitis, and
Table 1. Classes of antifungal drugs.

| Class    | Compounds             | Mechanism                                      | Uses               |
|----------|-----------------------|------------------------------------------------|--------------------|
| Polyene  | Amphotericin B        | Binds to sterols causing perturbations in cell | Systemic disease   |
|          | Nystatin              | membrane (fungitoxic)                          | Topical disease    |
| Azole    | Clotrimazole          | Inhibits ergosterol biosynthesis (fungistatic) | Topical disease    |
|          | Miconazole            |                                                | Systemic disease   |
|          | Ketoconazole          |                                                |                    |
|          | Fluconazole           |                                                |                    |
|          | Itraconazole          |                                                |                    |
| Pyrimidine| Fluorocytosine (5-FC)| Inhibits DNA and RNA synthesis                 | Systemic disease   |

Until recently, the issue of antifungal resistance has received little attention. More efforts have been placed on the phenomenon of antibiotic resistance. The mechanisms by which bacteria and yeast develop resistance are different. Fungi do not have the ability to transfer resistance genes between separate yeast cells. Nevertheless, mycotic resistance has become as widespread a problem as antibiotic resistance. The increased number of drug-resistant fungal infections has prompted questions about its etiology. One causal factor that warrants study is the role extensive use of OTC antifungals plays in promoting drug resistance.

**SIGNIFICANCE OF ANTIFUNGAL RESISTANCE TO PUBLIC HEALTH**

Candida is a normal part of the mucocutaneous and alimentary tract flora and lives in dynamic equilibrium with bacteria and other microorganisms. Normally, it is localized to the mouth, throat, skin, scalp, vagina, fingers, nails, bronchi, lungs, and gastrointestinal tract. Aside from vulvovaginal candidiasis, oral candidiasis or oral thrush is a common disease affecting infants. Because infants have underdeveloped immune systems, they are especially vulnerable to fungal infections such as oral thrush or diaper rash. Other superficial
funeral infections include athlete’s foot, jock itch, or dermal mycosis. *Candida* is an opportunistic fungi and rarely disseminates into serious systemic infections such as septicemia, endocarditis, and meningitis unless there is some underlying immunological dysfunction.

Within the human body, there are several nonspecific mechanisms by which fungal proliferation is controlled. Transferrins, the human iron binding proteins in the blood, deprive microbes of the iron they need for making respiratory enzymes. β-globulins also found in the serum cause a nonimmunological clumping of *Candida* and facilitate their elimination by inflammatory cells. Phagocytosis by neutrophils is the primary mechanism that prevents the establishment of fungal infections. Fungi that are too large to be ingested by phages may be killed through immunological mechanisms. Both cellular and humoral responses are evoked. Antibodies attach to the fungi, and phagocytic cells secrete lethal lysosomal enzymes into the fungi. Prolonged resistance to fungal disease is mainly mediated by T-lymphocytes. Clinical observations indicate that people with depressed immune systems are especially prone to invasive and systemic fungal infections [10].

In the late 1980s, several key studies indicated that 40 percent of patients dying from nosocomial infections were dying as a result of invasive fungal infections. Though there have been advances in drug therapy, opportunistic fungal infections are preying upon the growing number of people who are immune-compromised — people with AIDS, cancer patients, organ transplant patients, severe burn victims, as well as infants and the elderly [11]. The group at highest risk for acquiring fungal infections are AIDS patients. In 1988, approximately 58 percent of AIDS cases were associated with a mycotic infection [12]. Among the different infections, oropharyngeal candidiasis is the most common. A study conducted in 1997 showed that 90 percent of AIDS patients suffered from oropharyngeal or esophageal candidosis at some time during their illness [13]. An estimated 5 to 10 percent of patients in the advanced stages of AIDS have recurrent infections that are difficult to treat. It is believed that prolonged use of antifungal azole agents may result in the selection of azole-resistant organisms. Already, antifungal resistance to fluconazole is apparent in this population. However, there are few alternatives for preventing invasive fungal infections other than antifungal prophylaxis with fluconazole.

At the same time, the use of weaker azoles like miconazole and clotrimazole, found in OTC antifungal preparations used to treat vaginal yeast infections are also believed to contribute to the emergence of resistant *Candida* species. Since OTC azoles are used by a larger population, higher rates of azole resistance is a serious concern. An additional complication is that *Candida* may not only be resistant to OTC azoles but also cross-resistance to the stronger azoles like fluconazole and its second generation derivative, voriconazole. Spread of these cross-resistant strains would render ineffective these last-resort drugs that are needed to deal with more serious invasive infections.

**EXISTING LITERATURE ON ANTIFUNGAL RESISTANCE**

Much of the research performed on antifungal resistance has focused on the molecular mechanisms of fungal cell resistance. Studying the mechanisms by which fungi express resistance is essential in the development of new drugs that target these pathways. Three main ways fungal cells elude the toxic effects of antifungals are presently known: manipulation of key fungal sterol enzymes, over-expression of key fungal sterol enzymes, and drug-resistant pumps. The primary mechanism of drug resistance is the presence of drug-resistant efflux pumps that may expel a single drug or multiple types of drugs (multi-drug resistant pumps). Multi-drug resistant
pumps may explain the phenomenon of cross-resistance observed among the family of azole compounds.

Several studies have assessed the changing epidemiology of candidemia. The subject populations have generally included groups with underlying immunological deficits such as AIDS, cancer, or diabetes. These groups are especially prone to fungal infections, and the morbidity and mortality by fungal infections is significantly higher than in the general population. In a multi-center, randomized, double-blind, placebo-controlled trial, the efficacy of fluconazole prophylaxis on the vaginal flora of HIV-positive women was examined. The study found that women who had taken fluconazole prophylaxis had a reduction in *C. albicans* colonization but an increase in the odds of being colonized with a non-albicans species, primarily *C. glabrata*. It illustrated the shift to non-albicans species that tend to show resistance to azole-based drugs [14]. A study on bone marrow transplant patients who received fluconazole prophylaxis indicated a correlation between antifungal therapy and an increased incidence of *C. krusei*. Patients who received antifungals had a seven-fold greater frequency of *C. krusei* infection, and the *C. krusei* were determined to be resistant to fluconazole *in vitro* [15].

Patterns of resistance in immune-compromised groups have been extensively examined in the fungal literature. However, few studies have examined the prevalence of azole resistance in the general public or among a healthy population. Future studies might address the development of resistance in well populations as more people are employing antifungal prophylaxis without confirmed diagnosis of fungal infection.

REFERENCES

1. Weisberg, M. Considerations in therapy for vulvovaginal candidiasis: when and whom to treat. In: Sobel, J.D., ed. Clinical Perspectives: Terconazole, an Advance in Vulvovaginal Candidiasis Therapy. New York: McGraw-Hill; 1998, pp. 1-8.
2. Hurley, R. Recurrent *Candida* infection. Clin. Obstet. Gynaecol. 8:209-14, 1981.
3. Frey, D., Oldfield, R. J., and Briger, R. C. Color Atlas of Pathogenic Fungi. Chicago: Year Book Medical Publishers, Inc.; 1979.
4. McGregor, J.A. Contraceptive Technology: Issues and Options in Reproductive Health Care (Symposium). Washington, D.C., March 25-27, 1999.
5. Sobel, J.D. and Chaim, W. Treatment of *Torulopsis glabrata* vaginitis: retrospective review of boric acid therapy. Clin. Infect. Dis. 24:649-652, 1997.
6. Joseph-Home, T. and Hollomon, D.W. Molecular mechanisms of azole resistance in fungi. FEMS Microbiol. Lett. 149:141-149, 1997.
7. Holmberg, K. and Meyer, R.D. Diagnosis and Therapy of Systemic Fungal Infections. New York, New York: Raven Press; 1989.
8. Nguyen, M.H., Peacock, J.E., Tanner, D.C., Morris, A.J., Nguyen, M.L., Snydman, D.R., Wagener, M.M., and Yu, V.L. Therapeutic approaches in patients with Candidemia: evaluation in a multicenter, prospective, observational study. Arch. Int. Med. 155:2429-2435, 1995.
9. DeMuri, G.P. and Hostetter, M.K. Resistance to antifungal agents. Pediatr. Clin. North Am. 42:665-685, 1995.
10. Schaechter, M., Engleberg, N.C., Eisenstein, B.I., and Medoff, G. *Mechanisms of Microbial Disease*, 3rd ed. Baltimore, Maryland: Williams & Wilkins, 1998.
11. Zoffness, R. Cast of characters: a brief guide to agents of infection. Nat. Hist. 108:44-45, 1988.
12. St. Georgiev, V. Fungal infections and the search for novel antifungal agents. Ann. N.Y. Acad. Sci. 544:1-3, 1999.
13. Alexander, B.D. and Perfect, J.R. Antifungal resistance trends towards the year 2000. Drugs 54:657-678, 1997.
14. Vasquez, J.A., Sobel, J.D., Peng, G., Steele-Moore, L., Schuman, P., Holloway, W., and Neaton, J.D. Evolution of vaginal *Candida* species recovered from human immunodeficiency virus-infected women receiving fluconazole prophylaxis: the emergence of *Candida glabrata*? Clin. Infect. Dis. 28:1025-31, 1999.
15. Wingard, J.R., Merz, W.G., Rinaldi, M.G., Johnson, T.R., Karp, J.E., and Saral, R. Increase in *Candida Krusei* infection among patients with bone marrow transplantation and neutropenia treated prophylactically with fluconazole. New Engl. J. Med. 325:1274-1277, 1991.