Fluconazole-Resistant *Candida* VVC Emerging

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EXPERT ANALYSIS FROM THE ANNUAL MEETING OF THE INFECTIOUS DISEASES SOCIETY FOR OBSTETRICS AND GYNECOLOGY

CHICAGO – Even though the numbers remain small, fluconazole-resistant *Candida albicans* vulvovaginitis appears to be emerging as a thorny clinical problem, one expert suggests.

Since its introduction in 1990 as a prophylactic antifungal agent after bone marrow transplantation, fluconazole (Diflucan) has become established as the dominant therapy for vulvovaginal candidiasis (VVC) worldwide. In North America alone, roughly 8 million cases of recurrent vulvovaginitis are reported annually, with more than 90% due to *C. albicans*.

"So the possibility of resistance is a tremendous problem and concern," asserted Dr. Jack D. Sobel, chief of the division of infectious diseases and professor of obstetrics and gynecology at Wayne State University in Detroit.

Women with recurrent vulvovaginitis are treated with induction and prolonged, low-dose maintenance fluconazole regimens to achieve an asymptomatic state. Successful control, not cure, is achieved in more than 90%. Susceptibility testing for *C. albicans* is not standard of care, so there is very little published data on prolonged fluconazole use, Dr. Sobel said at the meeting.

He and his colleagues published the only study to address the issue of resistance, and it failed to identify any evidence of fluconazole resistance in isolates of *C. albicans* after just 1 year of follow-up (N. Engl. J. Med. 2004;351:876-83).

Nystatin: Old is New Again

Although it was patented back in 1957 as the world's first antifungal, antibiotic nystatin upstaged newer antifungal agents when used to treat vulvovaginal candidiasis caused by *Candida glabrata* in sequential, prospective clinical trials.

On day 7 to day 14 of follow-up, mycological cure of *C. glabrata* vulvovaginitis was achieved by 15 of 16 women (94%) treated with a nystatin vaginal suppository, compared with 8 of 19 (42%) given a miconazole nitrate vaginal suppository, 5 of 9 (56%) given oral fluconazole (Diflucan) and 7 of 15 (47%) given oral itraconazole (Sporanox). At day 30 to day 35 of follow-up, mycological cure rates, based on a positive or negative *Candida* culture, were 94%, 33%, 56%, and 40%, respectively.

"Nystatin vaginal suppository could be a therapy choice for vulvovaginal candidiasis caused by *Candida glabrata*," Dr. Shangrong Fan said at the meeting.

While *C. albicans* is the most commonly isolated species, various studies have reported a shift towards infections caused by non-*albicans Candida* species such as *C. glabrata*.

The women were enrolled prospectively in separate, sequential, nonrandomized clinical trials and treated with nystatin vaginal suppository at 20 MU per day for 7 days or two 1,200-mg doses of miconazole vaginal suppositories 72 hours apart or oral fluconazole two 150-mg doses 72 hours apart or oral itraconazole 200 mg two times for 1 day.

Dr. Fan, an obstetrician/gynecologist and his colleagues at Peking University Shenzhen Hospital in Shenzhen, China, also conducted an in vitro susceptibility study. The in vitro susceptible rate of *C. glabrata* on nystatin was 100% (57/57), compared with 90% (51/57) for miconazole, 58% (40/69) for fluconazole, and 87% (58/67) for itraconazole. Resistance to nystatin or miconazole was not observed, and occurred in 3% of strains exposed to fluconazole and 1.5% exposed to itraconazole.

Dr. Fan and his associates reported no relevant financial disclosures.

Clinicians at Wayne State's Vaginitis Clinic, however, have observed an uptick in the frequency of refractory *Candida* vulvovaginitis cases in the last 10 years among the more than 500 women with recurrent vulvovaginitis that they follow. The women present either on a maintenance fluconazole regimen with a breakthrough of symptoms accompanied by positive cultures or fail to resolve acute symptomatic vulvovaginitis with multidose fluconazole and have increased minimum inhibitory concentration (MIC) in vitro, Dr. Sobel explained.

A retrospective review of patients referred to the Vaginitis Clinic between 2000 and 2010 revealed 25 patients with clinically refractory fluconazole-resistant vulvovaginitis with confirmed in vitro resistance, with an MIC at least 2 mcg/mL (median 8 mcg/mL).

"Two-thirds of these patients were seen in the last 5 years, so the incidence is increasing," he said.

Eight patients had an MIC of 2 mcg/mL and 17 had MICs ranging from 4 to 128 mcg/mL.

Cross resistance to itraconazole (Sporanox) was present in five women and to ketoconazole (Nizoral) in four.

The cohort consists of married, insured Caucasian women with an average or above average socioeconomic status. Their mean age was 43 years (range 32-56 years). All patients had significant consumption of and recent exposure to fluconazole, with 64% on low-dose, weekly maintenance fluconazole.

Significant risk factors for refractory *Candida* VVC included more than 10 lifetime sexual partners, recent use of antibiotics, and for mycological failure included increased fluconazole exposure and older age of VVC onset.

Management

Management of refractory VVC is possible, but can be extremely difficult, Dr. Sobel acknowledged.

"When you can't use fluconazole, the closet is pretty empty," he said.

Dr. Sobel recommends initially using boric acid 600 mg per day for 14 days until an MIC is available. For those with low-level resistance, defined by an MIC of 2-4 mcg/mL, clinicians should increase the fluconazole dose to 150-200 mg twice weekly. Eleven of the 25 patients in the study cohort were controlled on this regimen, with five eventually discontinuing fluconazole.

"In patients with high level resistance, treatment depends on the presence of azole cross-resistance," he said.

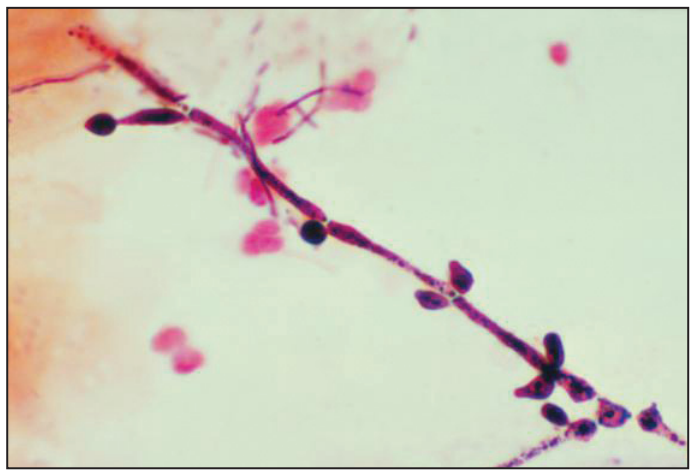
Among eight such patients, three were successfully controlled on 200 mg per day of itraconazole, and four of five were controlled on ketoconazole 100 mg per day, both typically for several months.

One patient required daily gentian violet for 14 days, with cure, and three patients were controlled on boric acid three times per week.

The novel, oral broad-spectrum antifungal, voriconazole (Vfend) is a possibility, but is rarely used because it is so poorly tolerated, Dr. Sobel said. Audience members questioned whether flucytosine (Ancobon), a synthetic antimycotic, can be employed. Specialty pharmacies can formulate it, but at $1,500 to $2,000 per tube is out of reach for most women. The ancient antifungal antibiotic nystatin is a far cheaper alternative, but should be given at 100,000 units daily per vagina only, Dr. Sobel said.

"We urgently need new classes of antifungal agents for *Candida* vaginitis," he said.

Dr. Sobel and his colleagues reported no relevant financial disclosures. ■



COURTESY CDC/DR. STUART BROWN

This is a photomicrograph of a vaginal smear identifying *Candida albicans* using a Gram-stain technique.