

Case
report

Combined topical flucytosine and amphotericin B for refractory vaginal *Candida glabrata* infections

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Patients with vaginitis due to highly azole resistant *Candida glabrata* can be particularly difficult to treat. We describe three cases of longstanding vaginal candidiasis due to *C glabrata*. These had failed to respond to local and systemic antifungals. Flucytosine (1 g) and amphotericin B (100 mg) formulated in lubricating jelly base in a total 8 g delivered dose, was used per vagina once daily for 14 days with significant improvement, both clinically and microbiologically.

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Introduction

Candida glabrata is the second most common yeast recovered from the genital tract of women with vaginitis and accounts for about 5% of vaginal infections.¹ A substantial minority of *C glabrata* isolates are azole resistant^{2,3} and further resistance may be selected out by non-curative treatment. Although infections with this organism are not always associated with symptoms and clinical signs⁴ some affected women have discharge and/or vulvitis and a poor response to antifungal therapy.^{5,6}

We describe three cases of persistent vaginal candidiasis due to *C glabrata*, unresponsive to conventional antifungal therapy including boric acid. Flucytosine tablets 500 mg (Center Specialites Pharmaceutiques Cournon Cedex, France) and amphotericin B BP1998 1 mg = 859IU (Bufa BV Uitgeest Holland) were combined in lubricating jelly, Aquagel (Adams Healthcare, UK). This was used per vagina with clinical and microbiological cure. Treatment was delivered by a unit dose vaginal applicator containing amphotericin 100 mg + flucytosine 1 g based in Aquagel in a total 8 g delivered dose. This preparation has an unknown shelf life and is obtainable from the pharmacy manufacturing unit, North Staffordshire Hospital, Stoke on Trent ST4 6QG (tel 01782 552 289; fax 01782 552 916). The preparation was compounded no more than 48 hours before treatment began.

Case 1

A 42 year old woman presented with “recurrent vaginal thrush” since the age of 19. At referral she had had several recent swabs showing heavy growths of candida species in Gram stain microscopy despite 3 months’ treatment with itraconazole 100 mg twice daily for 2 days every week, two Depo-provera (Pharmacia & Upjohn) injections, and a number of other unspecified antifungal treatments including courses of nystatin pessaries. None of these produced any symptomatic response.

Vaginal swabs were positive by Gram stain and culture for *C glabrata* which persisted despite itraconazole 200 mg once daily for 14

days combined with clotrimazole 500 mg vaginal pessaries for 7 nights, intravaginal painting with gentian violet 0.5% aqueous solution for 3 days, and boric acid 600 mg in gelatine capsules once daily for 14 nights.

Intravaginal amphotericin B and flucytosine in lubricating jelly was given at night for 14 days. Her symptoms improved and Gram stain and cultures were negative 2 and 5 weeks following treatment.

Case 2

A 63 year old woman presented with a 6 year history of intermittent vulvo-vaginitis and persistent isolation of *C glabrata* on Gram stain and culture. This had failed to respond to a variety of differing types and lengths of azole therapy. She had had a hysterectomy 5 years before presentation following which she commenced subcutaneous oestrogen hormone replacement implants. One year after the hysterectomy her symptoms of vaginal discharge and vulval soreness became continuous. She had had some minor symptomatic improvement to hydrogesterone and intravaginal boric acid.

She was treated with itraconazole 100 mg daily combined with nystatin pessaries for 4 weeks followed by intravaginal boric acid for 2 weeks. Despite this, Gram stain and cultures remained positive for *C glabrata*. This was fully sensitive to antifungals in vitro (table 1).

Amphotericin B and flucytosine in lubricating jelly was given once daily for 14 days. She improved symptomatically and follow up swabs were negative by Gram stain microscopy and culture 3, 4, and 8 weeks afterwards. Seven

Table 1 Antifungal sensitivities (NCCLS method Bristol PHLS mycology reference laboratory) before treatment with intravaginal flucytosine/amphotericin B in lubricating gel

	Case 1	Case 2	Case 3
Amphotericin B	S	S	—
Flucytosine	S	S	—
Fluconazole	R	S	R
Itraconazole	R	S	R
Miconazole	—	S	—
Nystatin	—	S	—

S = sensitive, R = resistant.

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months later she presented with a 4 week history of discharge. Microscopy of a Gram stained slide was positive for spores and a non-*albicans* yeast (not further speciated) was isolated in culture. She responded symptomatically and microbiologically to nystatin pessaries at night for 14 nights.

Case 3

A 42 year old woman presented with intractable symptoms of "vaginal thrush" which had started since a hysterectomy 1 year earlier, following which she had started unopposed oestrogen hormone replacement therapy.

Microscopy of a Gram stained vaginal slide showed spores and *C glabrata* was isolated which persisted despite dydrogesterone 10 mg daily for 28 days combined with nystatin pessaries at night for 14 days, combined nystatin pessaries and itraconazole 400 mg daily for 7 days, and vaginal boric acid 600 mg daily for 14 days.

Intravaginal amphotericin B and flucytosine in lubricating jelly was given at night for 14 days. Her symptoms improved and microscopy and cultures were negative 2 and 5 weeks following treatment.

Discussion

By comparison with *C albicans*, *C glabrata* is intrinsically less sensitive to azole antifungals and, because this organism is haploid (unlike *C albicans* which is diploid) selection of drug resistant strains may occur.⁷ Persistent vaginal *C glabrata* is more likely to be found in patients who are clinically not or partially responsive to azole antifungals, older patients, diabetics, and women who have had hysterectomies.⁴ Symptoms are, however, not a reliable guide to the causative organism. It is therefore important to speciate isolates from patients presenting with problem vaginal candidosis.⁴ Because of the relatively small numbers of patients presenting with this condition, treatment of persistent *C glabrata* vaginitis is not evidence based but remains largely anecdotal. Most clinicians would start treatment with intravaginal nystatin (the only licensed alternative to azoles in the United Kingdom) and then proceed to either high dose oral itraconazole together with high dose intravaginal azole pessaries or nystatin. Following this with intravaginal boric acid 600 mg at night for 14 days.⁸ If this fails however

there has previously been no further treatment available. Intravaginal amphotericin/flucytosine offers a possible treatment for such patients.

Topical flucytosine has been used for vaginal infections caused by both *C albicans*⁹ and anti-fungal resistant non-*albicans* candidiasis^{10 11} but a suitable formulation has not been available in the United Kingdom. Although it is the only available fungicidal agent,¹ there are reservations about its topical use because of the potential development of flucytosine resistance, which occurs by mutation of a single gene. The risk of such resistance developing is thought to be reduced by combination with polyene antifungals such as amphotericin B with which flucytosine is synergistic in vitro.^{1 9}

Our three cases demonstrate that flucytosine and amphotericin in lubricating jelly may be effective in chronic vaginal *C glabrata* infection where all other available agents have failed. This treatment was well tolerated in all patients with no or minimal side effects.

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- Odds FC. *Candida and candidosis*. 2nd ed. London: Bailliere Tindall, 1988.
- Lynch ME, Sobel JD. Comparative in vitro activity of antimycotic agents against pathogenic vaginal yeast isolates. *J Med Vet Mycol* 1994;**32**:267-74.
- Otero L, Fleites A, Mendez FJ, et al. Susceptibility of *Candida* species isolated from female prostitutes with par vulvovaginitis to antifungal agents and boric acid. *Eur J Clin Microbiol Infect Dis* 1999;**18**:59-61.
- Geiger AM, Foxman B, Sobel JD. Chronic vulvovaginal candidiasis: characteristics of women with *Candida albicans*, *C glabrata* and no candida. *Genitourin Med* 1995;**71**:304-7.
- Redondo-Lopez V, Lynch M, Schmitt C, et al. *Torulopsis glabrata* vaginitis: clinical aspects and susceptibility to antifungal agents. *Obstet Gynecol* 1990;**76**:651-5.
- White DJ, Johnson EM, Warnock DW. Management of persistent vulvo-vaginal candidosis due to azole-resistant *Candida glabrata*. *Genitourin Med* 1993;**69**:112-14.
- Kerridge D, Nicholas RO. Drug resistance in the opportunistic pathogens *Candida albicans* and *Candida glabrata*. *J Antimicrob Chemother* 1986;**18**:39-49.
- Bingham JS. What to do with the patient with recurrent vulvovaginal candidiasis. *Sex Transm Inf* 1999;**75**:225-7.
- Larsson-Cohen U. Treatment of vaginal candidosis with a single dose of a new antimycotic drug, 5-fluorocytosine + Candicidin. *Castellania* 1977;**5**:81-2.
- Horowitz BJ. Topical flucytosine therapy for chronic recurrent *Candida tropicalis* infections. *J Reprod Med* 1986;**31**:821-4.
- Fidel PLJ, Vazquez JA, Sobel JD. *Candida glabrata*: review of epidemiology, pathogenesis, and clinical disease with comparison to *C. albicans*. [Review] [185 refs]. *Clin Microbiol Rev* 1999;**12**:80-96.