CANDIDA CONUNDRUMS: USE OF NYSTATIN IN AZOLE RESISTANT CANDIDA ISOLATES

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Background:

Vulvovaginal candidiasis is a common cause of vaginal discharge and genital itching affecting the majority of women at least once before the age of 55. *Candida albicans* is responsible for approximately 90% of infections¹ and *Candida glabrata* the most common non-albicans type isolated². The incidence of *C. glabrata* and azole resistant *C. albicans* is increasing^{3, 4}.

5% of those affected with *Candida* species suffer with recurrent episodes (more than 4 episodes per year) ^{5, 6}. Following suppressive treatment there can continue to be return of symptoms which may be due to relapse from persistent vaginal reservoir of *Candida* rather than infection with a new strain ⁷.

Methods:

We evaluated the cases of 13 women with complicated, recurrent *Candida* who attended a specialised female problem clinic in a London Genito-urinary medicine clinic. Clinical data was extracted from electronic patient record systems. This included clinical and treatment history, mycological investigations and resultant optimised treatment regime.

	Years since symptom onset	Previous regimens	Species	S	I	R	Optimised treatment following sensitivities	Outcome: symptoms and culture
1	3	7	<i>C. albicans</i>	F		F	N/FX induction and 3/week maintenance 6/12	Symptoms controlled. Culture and slide positive with incorrect use.
2	11	4	<i>C. glabrata</i>	M N	I C	F	P od 2/12 & N induction → N 3/week maintenance 6/12	Symptoms controlled, slide and culture negative
3	2+	1	<i>C. glabrata</i>	I M N		F	N/FX 2x induction → symptoms returned C weekly pessary 6/12	Culture negative but symptoms returned and improved with azole.
4	3	2	<i>C. glabrata</i>	F I			I od 14d → N/FX induction	Symptoms controlled, culture negative
5	7	3	<i>C. albicans</i>	F N C	I M	F	N/FX induction & I od 7d 3/12 later: C pessary every 72h → 3/week	Symptom free for 3 months and then culture positive.
6	1	3	1) <i>C. glabrata</i>	M N	C	I F	N/FX induction → symptoms returned. F 150mg fortnightly	Culture negative but symptoms returned and improved with azole.
			2) <i>C. albicans</i>	F I M				
7	3	2	<i>C. albicans</i>	C I	M	F	I od stopped as deranged LFT. N induction & weekly maintenance 6/12	Symptoms controlled, culture negative
8	3	2	<i>C. albicans</i>	I		F	N induction	Symptoms improved, no culture follow up yet as on going.
9	17	3	1) <i>S. cerevisiae</i>	N M	C F I		N induction slow relief. C weekly pessary 6/12	Symptoms improved with azole, no culture follow up yet as on going.
			2) <i>C. albicans</i>	F I M N C				
10	1	2	<i>C. albicans</i>	I N C	F M		N induction	Symptoms improved, no culture follow up yet.
11	<1	3	<i>C. albicans</i> <i>C. glabrata</i>	F I			N induction and 2/week maintenance partial relief. I bd 14d → od 2/12	Symptoms improved with azole, no culture follow up yet as on going.
12	2	2	<i>C. nivariensis</i>	F I			N induction no relief → C pessary 7d	Symptoms improved with azole, no culture follow up as on going.
13	2+	4	<i>C. krusei</i>	N C	I M		N/FX induction → 2/week maintenance 2/12	Culture negative, symptoms persist, referred immunology
Table 1: F = fluconazole, I = itraconazole, M= miconazole, N = nystatin, C = clotrimazole, FX = flucytosine, P = posaconazole Nystatin/flucytosine induction regimen: N 100 000 units PV, FX 1g PV od 14 days Nystatin maintenance: N 100 000 units PV 2 - 3/ week							Key:	Response to nystatin regimen
								Response and relapse
								Poor response to nystatin

Conclusion:

Women with repeated episodes of vulvovaginal candidiasis where standard treatment is ineffective should have samples sent for mycological analysis at an early stage to prevent prolonged ineffective treatment and reduce the risk of further resistance to azoles. Minimum inhibitory concentrations (MIC) with sensitivity testing can guide effective treatments, however higher pH environments within the vagina may cause reduction in efficacy of treatments in-vivo, especially if isolates are at a threshold of resistance⁸. Based on serum drug level testing, the dose of azole was adjusted in case 2 to increase efficacy of treatment in view of MIC from sensitivity testing.

Patient preference and presence of symptoms is also important when considering an effective regimen as intra-vaginal therapy is not tolerated by all women. Follow up of patients with culture should be utilised to identify treatment efficacy or failure.

For women with *Candida* species exhibiting azole resistance, topical nystatin therapy as an induction and maintenance treatment can be an effective regime which should be considered alongside optimisation of other contributory factors such as diabetes, hyperoestrogenic states, immunosuppression⁹. Combination regimens with nystatin and appropriate azoles utilising sensitivity results is also effective.

Resources:

1. Odds F.C. et al. Candida and Candidosis: A Review and Bibliography, 2nd edn, Odds F.C. (ed), Baillière Tindall, London 1988, p. 124. 2. Sobel J.D. Vulvovaginal candidosis. *Lancet*. 1997;369(9577):2061. 3. Horowitz AB, Gaxiola D, et al. Solving pathogens in vulvovaginal candidiasis: Implications for patient care. *J Clin Pharmacol*. 1992;32(3):248. 4. Vermitsky JP et al. Survey of vaginal-flora *Candida* species isolates from women of different age groups by use of species-specific PCR detection. *J Clin Microbiol*. 2008 Apr;46(4):1501-3. Epub 2008 Feb 7. 5. Geijer AM, Fantom B, Ilse BW. The epidemiology of vulvovaginal candidiasis among university students. *Am J Public Health*. 1995;85(8 Pt 1):1146. 6. Foxman B, et al. Prevalence of recurrent vulvovaginal candidiasis in 5 European countries and the United States: results from an internet panel survey. *J Low Genit Tract Dis*. 2013;17(3):340. 7. Vazquez JA et al. Karyotyping of *Candida albicans* isolates obtained longitudinally in women with recurrent vulvovaginal candidiasis. *J Infect Dis*. 1994;170(6):1566. 8. Marchaim D, et al. Fluconazole-resistant *Candida albicans* vulvovaginitis. *Obstet Gynecol*. 2012;120(6):1407. 9. Sobel J.D. *Candida* vaginitis. *Infect Dis Clin Pract*. 1994;3:334.