

Prevalence and Management of Non-albicans Vaginal Candidiasis

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9	Prevalence and Management of
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1 Abstract

2

3 **Objectives**

4 It is thought that widespread use of "over-the-counter" azoles may increase the

5 incidence of resistant Candida species such as C glabrata. Infections with species

6 other than *C. albicans* frequently do not respond to standard azole treatments.

7 Intravaginal nystatin is an option but is no longer available in the UK. In this paper,

8 we review the prevalence of non-albicans candida over the past five years, and

9 assess the efficacy of amphotericin and flucytosine vaginal cream in the treatment

- 10 of non-albicans VVC.
- 11

12 Methods

Retrospective review of all vaginal yeast isolates collected from women attending a city centre sexual health clinic between 2004 and 2008. The women prescribed amphotericin and flucytosine vaginal cream were identified through pharmacy

16 records and their clinical notes reviewed for treatment outcome.

17

18 Results

19 Between 2004-2008, the number of isolates of all *Candida* species increased with

the increase in workload of the clinic but the prevalence of non-albicans yeasts

21 remained stable at between 0.87-1.06%. Eighteen patients were prescribed

22 amphotericin and flucytosine vaginal cream. At follow up all 18 were clear of their 23 initial yeast isolate on culture but two had persistent symptoms and had positive

initial yeast isolate on culture but two had persistent symptomcultures for *C. albicans*.

cultures for *C. albica* cultures

26 **Conclusions**

27 There is no evidence of an increase in prevalence of non-albicans *Candida* species

such as *C glabrata*. We have treated 18 women who had non-albicans VVC with

amphotericin and flucytosine vaginal cream and achieved clearance of the non-

- 30 albicans species in all of them.
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1 Introduction

2 The majority of cases of vulvovaginal candidiasis (VVC) are due to *Candida albicans* 3 with other yeasts accounting for about 10%.[1] *C glabrata* causes most non-

4 albicans infections.[1] As *C. glabrata* is inherently less susceptible to fluconazole

5 than *C. albicans*, there have been concerns that the widespread use of "over-the-

6 counter" azoles, particularly fluconazole, might lead to an increase in the incidence

7 of less susceptible *Candida* species such as *C* glabrata.[2, 3] A previous study

8 suggested this was not the case, but this was published some years ago.[2]

9

10 Non-albicans infections frequently do not respond to standard azole antifungal

11 treatments.[3] Intravaginal nystatin is an option but this treatment became

12 unavailable in the UK during 2007.[4] Four case reports suggested that amphotericin

13 and flucytosine vaginal cream (amp/flu VC) was an effective treatment for non-

- albicans VVC [5, 6] and this has been used in our clinic since nystatin becameunavailable.
- 16

17 In this paper we review the prevalence of *Candida* species within our clinic over the 18 past five years, with particular emphasis on non-albicans species, and assess the

efficacy of amp/flu VC in the treatment of VVC caused by non-albicans species.

20

21 Methods

A retrospective review was performed of all vaginal yeast isolates collected from vaginal samples taken from all women with symptoms attending the Leeds Centre for Sexual Health between 2004 and 2008. Positive cultures were quantified and the isolates identified. The germ tube test was used to identify *C. albicans*. All germ

tube negative isolates were identified using Auxacolor 2, Dalmau agar and, where necessary, API 32C kits.

28

The amphotericin 100mg with flucytosine 1g in Aquagel per vagina nightly for 14

30 nights was obtained from the Pharmacy Manufacturing Unit, North Staffordshire

31 Hospital, Stoke-on-Trent. The women prescribed amp/flu VC were identified through

32 the Leeds General Infirmary hospital pharmacy records and their clinical notes

33 reviewed for the outcome of treatment.

34

35 <u>Results</u>

The numbers and prevalence of *C. albicans, C. glabrata* and other yeasts isolated

37 from the women are shown in table 1.

1 2

	2004	2005	2006	2007	2008
Total number of cultures	2359	3837	3690	4569	6456
C albicans	561	897	880	1141	1756
Prevalence of <i>C. albicans</i>	24%	23%	24%	25%	27%
C. glabrata	17	29	22	30	31
Prevalence of C. glabrata	0.72%	0.76%	0.60%	0.66%	0.48%
Other yeasts	5	7	17	15	25
Prevalence of other	0.21%	0.18%	0.46%	0.33%	0.39%
yeasts					
Total numbers of non-	22	36	39	45	56
albicans yeasts					
Prevalence of all non-	0.93%	0.94%	1.06%	0.98%	0.87%
albicans yeasts					
Percentage non-albicans	3.8%	3.9%	4.2%	3.8%	3.1%
isolates of all yeasts					
Total numbers of all yeasts	583	933	919	1186	1812

3

4 Table 1. Prevalence of yeasts isolated from women attending the Leeds Centre for

5 Sexual Health between 2004 and 2008

6

7 The number of isolates of non-albicans yeasts has increased but this is

8 proportionate to the increase in workload of the clinic and the prevalence has

9 remained stable at between 0.87-1.06%. In 2008 there were 31 isolates of

C. glabrata and 25 isolates of other non-albicans yeasts. Of these, 24 (43%) were 10

asymptomatic at review so did not require any medication. Eighteen (32%) women 11

had been treated with azoles at their initial visit and did not return for follow-up. 12

- 13 Fourteen were treated with amp/flu VC.
- 14

15 During the two-years from 2006, 18 women were prescribed amp/flu VC. All had had previous episodes of VVC. The yeasts isolated were C. glabrata from 15, and one 16 each of S. cerevisiae, C. parapsilosis and C. dubliniensis. The women had all 17 received clotrimazole or fluconazole initially but remained symptomatic and so were 18 prescribed amp/flu VC. They were followed up 2-4 weeks later with repeat cultures. 19 20 No significant side effects were reported. At follow up all 18 were clear of their initial yeast isolate on culture but two had persistent symptoms and positive cultures for C. 21 22 albicans. There was partial symptomatic improvement in three women but some 23 residual vulval irritation remained despite being persistently culture negative. These 24 residual symptoms were attributed to irritant dermatitis and settled with emollients 25 and soap substitutes.

- 26

27 Discussion

28 It has been suggested that the widespread use of azoles, particularly fluconazole,

may lead to a pathogen shift and increase the incidence of resistant Candida 29

30 species such as C glabrata.[2, 3] However, a previous paper from our clinic showed

no increase in the prevalence of non-albicans yeasts between 1993 to 1998.[2] This 31

32 study has also shown a stable prevalence of non-albicans yeasts between 2004 to

2008, confirming those findings. 33

34

1 The national guidelines for the treatment of VVC recommend nystatin pessaries for 2 non-albicans yeast infections [4], but nystatin is no longer available in the UK. 3 Amphotericin is a fungistatic polyene active against many fungi. Flucytosine is a 4 fluorinated pyrimidine antifungal agent which is fungicidal but with a low genetic 5 barrier for resistance. When combined together they act synergistically with 6 amphotericin B enhancing cellular penetration of flucytosine and thereby potentiating 7 the activity of flucytosine. In addition, if resistance develops to flucytosine, the 8 amphoteracin B has activity against the yeasts. 9 10 On the basis of successful case reports using amp/flu VC [5, 6] we introduced it for 11 the treatment of non-albicans VVC. The treatment is well tolerated but is 12 considerably more expensive than nystatin. The cost of amp/flu VC is approximately 13 £206 per course compared with nystatin at approximately £10 per course. Also, as 14 the shelf life is unknown the treatment needs to be started within 48 hours of 15 manufacture. The duration of the intravaginal treatment is 14 days and ideally should be avoided during menstruation. Consequently, the ordering and delivery 16 17 requires co-ordination with the woman's menstrual cycle to ensure it can be started 18 within 48 hours of manufacture at a time when menstruation is not expected for at 19 least 14 days. However, we have now successfully treated 18 women with non-20 albicans VVC using amp/flu VC with 100% clearance of the non-albicans yeasts. 21 22 Key Messages 23 It has been thought that widespread use of "over-the-counter" azoles may 24 increase the incidence of resistant Candida species such as C glabrata. 25 26 Between 2004 – 2008, the prevalence of non-albicans yeasts remained stable • 27 with no increase in non-albicans Candida species such as C glabrata. 28 29 Infections with species other than C. albicans frequently do not respond to • 30 standard azole treatments. 31 32 Treatment of 18 women with non-albicans VVC using amphotericin and • 33 flucytosine vaginal cream achieved clearance of the non-albicans species in all 34 of them. 35 36 **Competing interests** None of the authors have any competing interests. 37 38 39 Funding None 40 41 42 **Copyright licence statement** The Corresponding Author has the right to grant on behalf of all authors and does 43 44 grant on behalf of all authors, an exclusive licence (or non exclusive for government 45 employees) on a worldwide basis to the BMJ Publishing Group Ltd to permit this 46 article (if accepted) to be published in STI and any other BMJPGL products and sub-47 licences such use and exploit all subsidiary rights, as set out in our licence

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Contributors

NH collected the patient data. HRA collected the mycology data and supervised the laboratory testing. HRA and JDW initiated the project. NH and JDW analysed the

- data. All authors contributed to the preparation of the manuscript.

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