

Vaginal *Candida albicans*: High frequency of *in vitro* fluconazole resistance in a select clinical population.

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Abstract

Introduction: *In vitro* fluconazole resistance in vaginal *C. albicans* has rarely been reported in the U.S. Little is known about characteristics of patients who demonstrate fluconazole resistance vs. sensitivity, or how likely resistant strains are to persist over time. **Objective:** We sought to describe the frequency of fluconazole resistance and associated factors in a select population of patients with vaginal cultures positive for *C. albicans*. **Methods:** We conducted a chart review of patients with clinician ordered vaginal cultures positive for *C. albicans* undergoing clinician requested fluconazole susceptibility testing in our medical center's clinical mycology lab from January 2017-April 2021. Patient characteristics were compared using chi-squared and anova tests and associations with fluconazole resistance assessed using modified Poisson regression models with robust standard errors. **Results:** Of N=92 patients with vaginal *C. albicans*, 3.3% were sensitive dose dependent (SDD: minimal inhibitory concentration (MIC)=4) to fluconazole, and 30.4% were resistant (R: MIC>=8). Amongst those with at least 2 previous episodes of vulvovaginal candidiasis (VVC) in the past 6 months (N=46), 50% had R and 6.5% had SDD isolates. Compared to those with sensitive (S: MIC<=2) isolates, patients with SDD or R were younger and more likely to have the following characteristics: chart designated Black or African American race, bacterial vaginosis (BV) in the past year, high or multi dose azole treatment, fluconazole suppressive therapy in the past 6 months, and more VVC and BV episodes in the previous 6 months (Table 1). Of N=7 patients who had a follow up culture with initial R isolates, 28.6% had a sensitive *C. albicans* vaginal isolate. **Conclusions:** The frequency of *C. albicans* vaginal isolates with *in vitro* resistance to fluconazole in this select population was high. Our findings highlight the importance of considering azole resistance in patients with refractory VVC or breakthrough symptoms while on suppressive therapy. Clinicians should not necessarily assume that a patient found to have fluconazole resistance on one occasion will inevitably exhibit resistant strains during future symptomatic VVC episodes. Prospective studies to verify associations with demographic and clinical factors as well as to correlate *in vitro* resistance with treatment response and longitudinal resistance patterns are needed.

Introduction

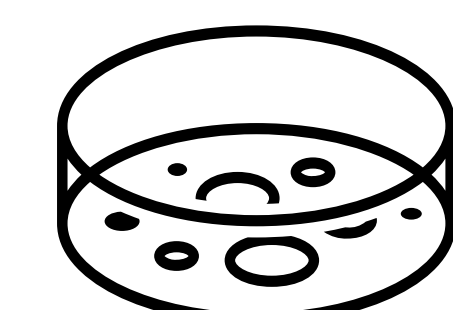
- Over 50% of US women will experience at least one episode of VVC, 9% experience recurrent VVC.
- >90% of VVC is caused by *C. albicans*.
- Little is known about characteristics of women who demonstrate fluconazole resistance.

Objective

To describe frequency of fluconazole resistance and associated factors in a select population of patients with clinician ordered vaginal fungal cultures positive for *C. albicans* undergoing AST in a single-center study.

Methods

- Positive vaginal fungal cultures with AST in patients ≥ 18 years.

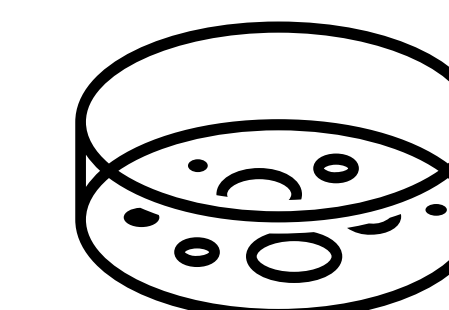


C. albicans +ve

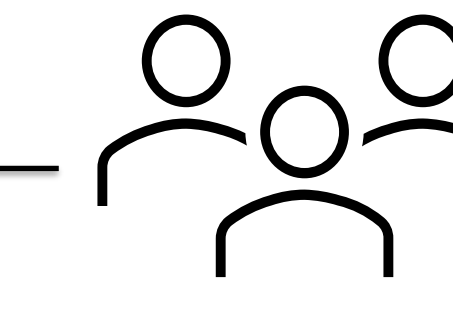
Fluconazole Susceptibility Test

- MIC ≤ 2: Susceptible (S)
- MIC = 4: Susceptible dose-dependent (SDD)
- MIC ≥ 8: Resistant (R)

- Clinical data abstracted from electronic medical records, 2017-2021.
- Patient characteristics compared via ANOVA and Chi-Squared tests.
- Modified Poisson regression to assess associations with *in vitro* fluconazole resistance.
- Analyses conducted using STATA v. 17.



131 +ve cultures



112 people

First cultures:
82.0% (92) *C. albicans*
11.6% (13) *C. glabrata*

- Amongst the 92 first vaginal *C. albicans* isolates: 30.4% R, 3.3% SDD, and 66.3% S to fluconazole.
- 46 out of 92 people with a first *C. albicans* vaginal culture had ≥2 tx VVC episodes in prior 6 months; of these, 50% R, 6.5% SDD to fluconazole.
- Fluconazole R in blood *C. albicans* isolates = 0.5%; in urine *C. albicans* isolates = 7.2%.

Conclusions

- In vitro* fluconazole resistance in vaginal *C. albicans* isolates may be more common than previously assumed.
- Azole resistance should be considered in individuals with refractory VVC or those presenting with breakthrough symptoms while on suppressive therapy.
- Clinicians should not assume that a patient found to have fluconazole resistance on one occasion will inevitably exhibit resistant strains during future symptomatic VVC episodes.
- More research needed to understand how *in vitro* resistance correlates with *in vivo* treatment response, longitudinal resistance patterns and to understand the role of the organism, host immunity, the vaginal microbiome, pharmacokinetics, and pharmacodynamics in contributing towards treatment response.

Results

Table 1: Characteristics of N=93 women with first vaginal culture positive for *C. albicans*, comparing those with S vs. R or SDD to fluconazole based on *in vitro* MICs

	Overall <i>C. albicans</i> only (N=92)	Fluconazole S <i>C. albicans</i> (N=61)	Fluconazole R or SDD <i>C. albicans</i> (N=31)	P-value
Age mean (SD)	33.5 (12.0)	35.6 (13.6)	29.6 (6.7)	0.02
Race				0.02
White	24 (26.1)	22 (36.1)	2 (6.5)	
Black	61 (66.3)	34 (55.7)	27 (87.1)	
Latinx	4 (4.4)	3 (4.9)	1 (3.2)	
Other/Unknown	3 (3.3)	2(3.3)	1 (3.2)	
Hx VVC tx past year	70 (76.1)	39 (63.9)	31 (100.0)	<0.01
# Episodes VVC tx last 6m	2.1 (2.0)	1.3 (1.6)	3.5 (2.0)	<0.01
High/multi dose azole tx last 6m				<0.01
No/NA	52 (56.5)	44 (72.1)	8 (25.8)	
Yes	31 (33.7)	12 (19.7)	19 (61.3)	
Unknown	9 (9.8)	5 (8.2)	4 (12.9)	
Fluconazole sup last 6m				0.03
No/NA	84 (91.3)	59 (96.7)	25 (80.7)	
Yes	7 (7.6)	2 (3.3)	5 (16.1)	
Unknown	1 (1.1)	0 (0.0)	1 (3.2)	
History of BV tx in last year	49 (53.3)	26 (42.6)	23 (74.2)	<0.01
# Episodes BV tx last 6m	1.2 (1.8)	0.6 (1.0)	2.4 (2.3)	<0.01
Boric acid tx in last 6m				0.17
No/NA	82 (89.1)	57(93.4)	25 (80.7)	
Yes	8 (8.7)	3 (4.9)	5 (16.1)	
Unknown	2 (2.2)	1 (1.6)	1 (3.2)	
Hormonal contraception	34(37.0)	25(41.0)	9 (29.0)	0.26
History immunocompromise	8 (8.7)	6(9.8)	2(6.5)	0.71
HIV positive	1 (1.1)	1 (6.4)	0 (0.0)	0.47
Diabetes	17 (18.5)	16(26.3)	1(3.2)	<0.01
Menopause	12 (13.0)	12(19.7)	0(0.0)	<0.01
Subsequent <i>C. albicans</i> (N=10)				0.25
Fluc S	5 (50.0)	3(100%)	2 (28.6%)	
Fluc SDD	1 (10.0)		1 (14.3%)	
Fluc R	4 (40.0)		4 (57.1%)	
Symptoms				
Itch	46(50.0)	33(54.1)	13(41.9)	0.27
Discharge	38 (41.3)	19 (31.2)	19(61.3)	<0.01
Burning/pain/dyspareunia	19(20.7)	17(27.9)	2(6.5)	0.02
Irritation	20 (21.7)	11(18.0)	9(29.0)	0.23
Odor	14(15.2)	8(13.1)	6(19.4)	0.43
Other	6(6.5)	4 (6.6)	2 (6.5)	0.99
None	10 (10.9)	7 (11.5)	3 (9.7)	0.79