

Epidemiology and Risk Factors for Fluconazole Resistance and Mortality among Adults with Candidemia in Atlanta and Baltimore

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Background

Candidemia, a leading cause of blood stream infections, causes significant morbidity and mortality. *C. albicans* remains the most common cause of candidemia, but blood stream infections due to *Candida* non-*albicans* species, which are more likely to be resistant to fluconazole, have been increasing. Fluconazole resistant candidemia has been classified as a serious threat level in the report of "Antibiotic Resistant Threats in the United States, 2013" by CDC, however the impact of fluconazole resistance on mortality remains poorly defined.

Methods

Active population-based surveillance for candidemia was conducted in Atlanta and Baltimore as part of the Center for Disease Control (CDC)-sponsored Emerging Infections Program. Case-isolates were sent to CDC for speciation and susceptibility testing. Independent risk factors associated with fluconazole resistance and all-cause 2-30-day mortality were identified using logistic regression in patients with incident candidemia.

Table 1: Selected Characteristics for Candidemia Cases in GA and MD from 2008-2013

Demographics		N	%	
Age (yrs)	20-44	603	(18.5)	
	24-64	1341	(41)	
	≥65	1324	(40.5)	
Male Sex		1684	(51.6)	
		1926	(58.9)	
Race	Black	1926	(58.9)	
	White	1198	(36.7)	
	Other/Unknown	144	(4.4)	
Co-morbid Conditions	Diabetes	1212	(37.1)	
	Surgery	1131	(34.6)	
	Chronic Kidney Disease	578	(17.7)	
	Solid organ malignancy	524	(16)	
	Chronic liver disease	404	(12.4)	
	HIV	195	(6)	
	Pancreatitis	126	(3.9)	
	Hematologic malignancy	112	(3.4)	
Clinical Characteristics	Solid organ transplant	69	(2.1)	
	HST	14	(0.4)	
	Acquisition	CO	253	(7.7)
		HACO	870	(26.6)
		HO	2145	(65.6)
	Nursing home resident	614	(22)	
	Critical care	2052	(64)	
Systemic antibiotics	2609	(79.8)		
TPN	1008	(30.8)		
CVC	2705	(83.9)		
Azole Exposure	298	(9.4)		

HST hematopoietic stem cell transplant, CO community onset, HACO hospital associated community onset, HO hospital onset, TPN total parenteral nutrition, CVC central venous catheter

Table 2: Independent Factors Associated with Fluconazole Resistance

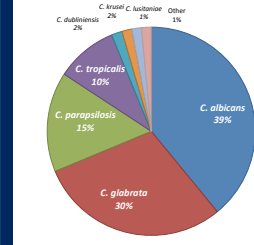
	Adjusted OR	95% CI
Azole Exposure before culture	3.93	(2.67-5.76)
Black Race	1.45	(1.02-2.07)
HIV	2.81	(1.66-4.75)
Hematologic Malignancy	3.63	(2.04-6.44)
Solid Organ Transplant	2.99	(1.35-6.62)
Chronic Liver Disease	0.41	(0.22-0.76)

Fluconazole resistant cases in incident blood culture in first episode of candidemia, N=2586
Other variables included in the model: hospital onset infection, presence of central venous catheter, hematopoietic stem cell transplant

Results

A total of 3,553 cases of candidemia were identified between 2008 and 2013, with an average yearly incidence of 18.9 cases/100,000. *C. albicans* remains the most common species (39.1%, Figure 1), however it is surpassed by *C. glabrata* among recurrent cases and those with previous azole exposure (34.5% and 36.2% respectively). Overall, 65.6% of incident cases were hospital-onset; 93% had at least one of the following risk factors: a central venous catheter, total parenteral nutrition, or antibiotics within 14 days (Table 1). A total of 21.1% of patients died between 2-30 days. Overall, 6.9% of case-isolates were resistant to fluconazole (Figure 2); 26.6% of cases with fluconazole resistance died between 2-30 days. Independent risk factors associated with fluconazole resistance and all cause 2-30 day mortality are shown in Tables 2 and 3. No association was found between fluconazole resistance and mortality.

Figure 1: Epidemiology of *Candida* Species



Cases with species identification N=3546(99.8%), cases with antifungal susceptibility testing N=2913 (82%)

Figure 2: Fluconazole Susceptibility of *Candida* Species

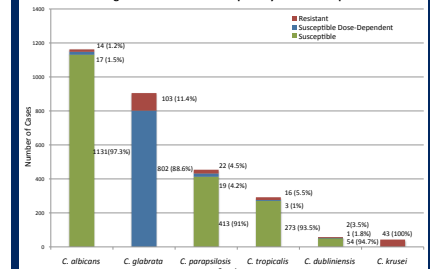


Table 3: Independent Factors Associated with Mortality

	Adjusted OR	95% CI
Age ≥65 years	1.70	(1.35-2.14)
Chronic Liver Disease	1.73	(1.25-2.39)
HIV	1.63	(1.06-2.52)
Malignancy	1.66	(1.28-2.16)
Hospital Onset Infection	1.87	(1.42-2.47)
Critical Care	3.57	(2.69-4.73)
Central Venous Catheter Removed	0.42	(0.33-0.53)
Treatment with Azole	0.45	(0.36-0.57)
Treatment with Amphotericin B	2.77	(1.72-4.46)
Infection with <i>C. tropicalis</i>	1.67	(1.19-2.35)

All cause mortality between 2-30 days after incident blood culture in first episode of candidemia, N=2230
Other variables included in the model: systemic antibiotics, central venous catheter, prior azole therapy, treatment with echinocandin, fluconazole resistance, infection with *C. parapsilosis* and *C. trusei*, interaction term between fluconazole resistance and age≥65 years.

Summary and Conclusions

Fluconazole resistance was increased in immunocompromising conditions associated with prior azole exposure. Chronic liver disease was associated with decreased resistance, possibly secondary to avoidance of azoles in this patient population. Adherence to treatment guidelines, specifically removal of CVCs, may improve candidemia outcomes. However, further investigation is needed to evaluate impact of health status on the association between CVC removal and mortality.

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