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ORIGINAL ARTICLE

The association between fluconazole dose and MIC with mortality and persistence in candidemia

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Abstract

To evaluate the association between fluconazole exposure parameters and clinical outcomes in patients with candidemia. We retrospectively included all adults with candidemia in a single center from January 2009 to December 2017, treated initially with fluconazole for fluconazole-susceptible candidemia. We assessed the association between fluconazole exposure parameters and 30-day mortality or 14-day clinical failure, a composite of mortality at day 14 or persistent candidemia ≥ 72 h, in all patients and in patients with *C. glabrata* candidemia. During the study period, 158 patients fulfilled the inclusion criteria. Main species were *C. albicans* 66 (41.8%), *C. glabrata* 35 (22.2%), and *C. parapsilosis* 31 (19.6%). Sixty patients (38%) died within 30 days. Sixty-one patients (38.6%) experienced 14-day failure. In 30-day survivors, the median AUC_{24}/MIC was 2279 [398, 5989] versus 1764 [238, 6714] h in non-survivors, $p = 0.75$. Median fluconazole MIC was 0.75 [0.25, 4] and 1 [0.22, 5.50] mg/L, $p = 0.54$, respectively. Similar non-significant differences were found for other fluconazole exposure parameters and in the 14-day clinical failure analysis. For *C. glabrata*, a higher AUC_{24}/MIC was observed among 30-day survivors with a median of 230 [77, 539] compared to 96 [75, 164] h in non-survivors, $p = 0.008$, in parallel with a trend for lower MIC values (median 7 [1, 2] versus 16 [8, 24] mg/L, $p = 0.06$, respectively). Currently used fluconazole dosing has no association with clinical outcome in *Candida* with low MIC values. For *Candida* species with high MICs, attention to dosing is needed.

Keywords Candidemia · Fluconazole · Mortality · Area under curve · Minimal inhibitory concentration

Introduction

Fluconazole has an essential role in the treatment of candidemia. It is recommended as the drug of choice for candidemia in hemodynamically stable patients without azole exposure or as a continuation drug for susceptible *Candida* species candidemia [3].

Optimizing the dosing of fluconazole is recommended. The Infectious Diseases Society of America (IDSA) recommends a standard maintenance dose of 6 mg/kg daily for susceptible species and double this dose for susceptible dose-dependent (SDD) *Candida* species and *C. glabrata* [3]. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommends attaining an area under curve above the minimal inhibitory concentration (AUC/MIC) of at least 100 for invasive candidiasis [4, 5]. This recommendation is based on clinical data that included only 126 patients with candidemia. The Clinical and Laboratory Standards Institute (CLSI) recommends standard dosing (6 mg/kg/day) for *Candida* spp. with a fluconazole MIC ≤ 2 mg/L. For *C. glabrata* with MIC ≤ 32 mg/L and other *Candida* spp. with

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an intermediate MIC of 4 mg/L, the maximum dosage regimen of fluconazole is recommended [1]. Clinical studies that evaluated fluconazole pharmacokinetic (PK) and pharmacodynamics (PD) parameters in candidemia showed variable results [6–11].

In the present study, we examined the association between fluconazole dose and MIC with clinical outcomes of patients with candidemia focusing on *C. glabrata*, which typically has higher MIC values than other *Candida* species treated with fluconazole.

Methods

We retrospectively identified adult patients (age ≥ 18 years) with candidemia between January 2009 to December 2017 at Rambam Health Care Campus, a 960-bed primary and tertiary hospital.

Candidemia was defined as the growth of *Candida* in at least one blood culture and patients were identified through the records of the microbiology laboratory. Patients who survived without directed treatment were excluded. For the current analysis, we included only patients that were treated with fluconazole as the initial antifungal drug, as monotherapy, for at least two consecutive days. Patients with *C. krusei* were excluded.

The exposure parameters included the dose/MIC, AUC_{24}/MIC, and AUC_{24}/MIC ≥ 400, focusing on AUC_{24}/MIC as the primary exposure variable. We calculated creatinine clearance (CLcr) by the Modification of Diet in Renal Disease (MDRD) equation [12] using serum creatinine on the start day of treatment. We calculated fluconazole clearance according to the following equation: Fluconazole clearance (ml min^{-1} kg^{-1}) = 0.064 + 0.003 × CLcr (ml min^{-1}) [13]. Fluconazole AUC_{24} was calculated as the ratio of fluconazole maintenance dose and clearance.

The outcomes assessed were 30-day all-cause mortality and 14-day clinical failure, a composite of mortality by day 14 or persistent candidemia ≥ 72 h after start of fluconazole. We recorded the date of death and duration of candidemia. Post-discharge mortality data were available.

We reviewed patients' electronic medical records and extracted clinical data focusing on risk factors for the outcomes investigated, including demography, comorbidities, severity of disease, source of the candidemia, source control, and concomitant bacteremia with its treatment. We documented whether a loading dose of fluconazole was used, its dose, the maintenance doses, and the *Candida* species with MIC. *Candida* species identification was performed using Vitek MS or Vitek-2 systems (bioMeriouex, France). Susceptibility testing was performed using E-test or Vitek-2.

Univariate analysis was performed for both outcomes. Variables clinically and statistically ($p < 0.05$) associated with the outcome and the exposure variable were entered into a logistic regression analysis. The analysis was performed for all patients with candidemia and separately for patients with *C. glabrata* candidemia.

Results

During a 10-year period, we identified 394 cases of clinically-significant candidemia out of 405 cases with *Candida* growth in blood cultures. Excluded cases included 39 cases with *C. krusei*, 114 cases treated with other than fluconazole initial treatment, 64 cases received no treatment, 15 cases of fluconazole initial treatment with less than 48 h, and 5 cases with missing MIC values. Eventually, 158 patients with candidemia were treated with fluconazole as the first antifungal agent for at least 48 h and included in the present study. The *Candida* species were *C. albicans* in 66 (41.8%), *C. glabrata* in 35 (22.2%), *C. parapsilosis* in 31 (19.6%), *C. tropicalis* in 22 (13.9%), and 4 (2.5%) in other species. Fluconazole was started within a median of 3 days [1, 5]from candidemia onset and given for a duration of 11 days [6, 14]. Overall, 60 patients (38%) died within 30 days and 61 (38.6%) experienced 14-day clinical failure.

All patients

The median fluconazole AUC_{24}/MIC for 30-day survivors was 2279 [398, 5989] compared to 1764 [238, 6714] h in non-survivors, $p = 0.75$ (Table 2). Among survivors, the median MIC for fluconazole was 0.75 [0.25, 4] compared to 1 [0.22, 5.50] mg/L among non-survivors, $p = 0.54$ with mean fluconazole daily dose of 389 ± 153 versus 386 ± 121 mg, $p = 0.38$, respectively. The fluconazole AUC was 1250 [946, 1978] versus 1449 [944, 2161] mg h/L, $p = 0.34$. There were no significant differences in fluconazole dose/MIC between survivors and non-survivors. Most patients had AUC/MIC ≥ 400 h with no significant difference between groups.

Unadjusted risk factors for 30-day mortality included basic functional status, malignancy, neutropenia, recent ICU admission (within 1 month proceeding candidemia), presence of a central venous catheter (CVC), appropriate treatment within first 24 h for concomitant bacteremia, mental status change, and tachycardia at candidemia onset (Table 1). On multivariate analysis, recent ICU admission was associated with survival, while presence of line catheter, mental status change, and tachycardia on candidemia onset was associated with mortality. Adjusted to these, the fluconazole AUC/MIC was not associated with survival (Table 1).

Similar non-significant associations between fluconazole exposure and the outcome were observed for 14-day clinical failure. Bone marrow transplantation, neutropenia, malignancy, CVC, tachycardia, and inappropriate antifungal treatment

Table 1 Comparison between 30-day survivors and non-survivors – all patients treated initially with fluconazole

Variable	Survivors $n = 98$ (62%) median [Q1, Q3] mean ± S.D. n (%)	Non-survivors $n = 60$ (38%) median [Q1, Q3] mean ± S.D. n (%)	Univariate p value	Multivariate OR [95% CI], p value
Age	69.54 [57, 81]	71.5 [61.70, 81.36]	0.41	
Male	65 (66.3)	38 (63.3)	0.70	
Admission from home	67 (68.4)	41 (68.3)	0.30	
Previous hospitalization (90 days)	56 (57.1)	37 (61.7)	0.57	
Health care associated	83 (97.6)	51 (98.1)	0.86	
Nosocomial acquired	82 (83.7)	48 (80)	0.55	
Basic functional status			0.02	
Normal	57 (58.2)	24 (40)		Reference
Limited	18 (18.4)	13 (21.7)		1.28 [0.46–3.56], 0.63
Bedridden	23 (23.5)	23 (38.3)		1.85 [0.75–4.51], 0.17
Dementia	11 (11.2)	11 (18.3)	0.21	
Bone marrow transplantation	2 (2%)	2 (3.3%)	0.61	
Malignancy	31 (31.6)	29 (48.3)	0.03	1.47 [0.69–3.16], 0.31
Charlson comorbidity score	1.94 [1, 3]	2 [1, 3]	0.68	
Recent ICU admission (last month)	31 (31.6)	8 (13.3)	*0.01*	0.26 [0.1–0.67], 0.005
Total parenteral nutrition	23 (23.5)	18 (30)	0.36	
Recent antibiotic RX [1]	77 (78.6)	39 (65)	0.06	
Recent abdominal surgery (within 2 months)	19 (19.4)	11 (18.3)	0.87	
Previous antifungal RX (> 4 days in last month)	4 (4.1)	2 (3.3)	0.81	
Neutropenia at candidemia onset	1 (1%)	4 (6.7%)	0.04	
Central vascular catheter				
No catheter	54 (55.1)	17 (28.3)	0.003	Reference
Exists, not extracted	12 (12.2)	15 (25)		3.75 [1.65–8.54], 0.002
Exists, extracted	32 (32.7)	28 (46.7)		4.46 [1.57–12.67], 0.005
Hypotension at onset	18 (18.4)	18 (30)	0.09	
New mechanical ventilation	6 (6.2)	7 (11.7)	0.22	
New mental status change	4 (4.1)	8 (13.3)	0.03	7.26 [1.62–32.45], 0.009
Tachycardia at onset	64 (65.3)	50 (83.3)	0.01	3.25 [1.29–8.18], 0.01
Empirical treatment (24 h) for concomitant bacteremia [2]				
No bacteremia	83 (85.6)	41(68.3)	0.035	Reference
Inappropriate	13 (13.4)	18 (30)		1.64 [0.61–4.38], 0.31
Appropriate	1 (1)	1 (1.7)		4.87 [0.86–27.6], 0.07

Table 1 (continued)

Variable	Survivors $n = 98$ (62%) median [Q1, Q3] mean ± S.D. n (%)	Non-survivors $n = 60$ (38%) median [Q1, Q3] mean ± S.D. n (%)	Univariate p value	Multivariate OR [95% CI], p value
Candida species				
C. albicans	39 (39.8)	27 (45)	0.58	
C. glabrata	20 (20.4)	15 (25)		
C. parapsilosis	23 (23.5)	8 (13.3)		
C. tropicalis	14 (14.3)	8 (13.3)		
Other	2 (2.0)	2 (3.3)		
Appropriate antifungal treatment within 24 h	24 (24.5)	14 (23.3)	0.86	
Appropriate antifungal treatment within 48 h	63 (64.3)	34 (56.7)	0.34	
Fluconazole MIC (mg/L)	0.75 [0.25, 4]	1 [0.22, 5.50]	0.54	
Fluconazole loading dose	57 (58.2)	34 (56.7)	0.85	
Fluconazole daily dose (mg)	389 ± 153	386 ± 121	0.38	
Fluconazole AUC mg h/L	1250 [946, 1978]	1449 [944, 2161	0.34	
Fluconazole AUC/MIC h	2279 [398, 5989]	1764 [238, 6714]	0.75	1 [1–1], 0.73
Fluconazole dose/MIC ratio	400 [150, 1600]	400 [87, 1852]	0.64	
Fluconazole AUC/MIC ≥400 h	73 (74.5)	41 (63.8)	0.40	

[1] For at least for 7 days in the month before the candidemia

[2] Clinically-significant bacteremia occurring within 7 days before to 7 days after the culture taken date of the candidemia

within the first 24 h of start of candidemia were significantly associated with 14-day clinical failure on univariate analysis (Table 2). On multivariate analysis, only malignancy and the presence of a CVC that was not extracted were associated with failure and fluconazole AUC/MIC remained non-significant (Table 2).

C. glabrata candidemia

Thirty-five (22.2%) patients had candidemia with *C. glabrata* species that fulfilled inclusion criteria. Fifteen patients (43%) died within 30 days. Nine patients (25.7%) experienced 14-day clinical failure.

Thirty-day survivors of *C. glabrata* candidemia had prominently lower fluconazole MICs compared to non-survivors, median 7 [1, 2] versus 16 [8, 24] mg/L, $p = 0.06$. The mean fluconazole daily dose was 470 ± 197 versus 386 ± 91 mg, $p = 0.39$, respectively. The adjusted fluconazole daily dose, as expressed by the AUC was not significantly different among survivors (1325 [971, 2008] mg h/L) and non-survivors (1200 [931, 15,460] mg h/L), $p = 0.36$. Higher values of fluconazole AUC/MIC and dose/MIC were observed in survivors compared to non-survivors, not reaching statistically significant differences (Table 3). A minority of patients reached AUC/MIC values ≥400 h in both groups. Similar, though less prominent trends, were observed for the 14-day clinical failure (Table 3). Due to the small sample size, we did not proceed to multivariate analyses in the subgroup of patients with *C. glabrata* candidemia.

Discussion

In the present study analyzing fluconazole PK/PD parameters and clinical outcome in patients with candidemia treated initially with fluconazole, we found no significant association between fluconazole MICs, drug exposure with 30-day mortality, or early clinical failure. Most MICs were low and consequently high AUC/MICs were achieved, regardless of the fluconazole dose. In *C. glabrata* candidemia, although higher doses of fluconazole were administered compared to other patients, lower AUC/MIC values were observed due to high MIC values. In this group of patients, a trend for survival with higher AUC/MIC values was observed, although the small sample size did not allow sufficient confidence in this result.

Table 2 Comparison between 14-day success and failure (14 day mortality or persistent candidemia)—all patients

Variable	Success $n = 97$ (61.4%) median [Q1, Q3] mean ± S.D. n (%)	Failure $n = 61$ (38.6%) median [Q1, Q3] mean ± S.D. n (%)	Univariate p value	Multivariate OR [95% CI], p value
Age	71 [60.95, 80]	71 [57, 82]	0.55	
Male	58 (59.8)	45 (73.8)	0.07	
Admission from home	66 (68)	42 (68.9)	0.30	
Previous hospitalization (90 days)	42 (43.3)	23 (37.7)	0.48	
Health care associated	86 (97.7)	48 (98)	0.92	
Nosocomial acquired	78 (80.4)	52 (85.2)	0.43	
Basic functional status			0.39	
Normal	53 (54.6)	28 (45.9)		
Limited	17 (17.5)	14 (23)		
Bedridden	27 (27.8)	19 (31.1)		
Dementia	12 (12.4)	10 (16.4)	0.47	
Bone marrow transplantation	0 (0)	4 (6.6)	0.01	
Malignancy	27 (27.8)	33 (54.1)	0.001	2.83 [1.39–5.76], 0.004
Charlson score (median)	2 [1, 3]	2 [1, 3]	0.93	
Recent ICU admission (last month)	27 (27.8)	12(19.7)	0.24	
Total parenteral nutrition	22 (22.7)	19 (31.1)	0.23	
Recent antibiotic RX [1]	72 (74.2)	44 (72.1)	0.77	
Recent abdominal surgery (within 2 months)	18 (18.6)	12 (19.7)	0.86	
Previous antifungal RX (> 4 days in last month)	3 (3.1)	3 (4.9)	0.55	
Neutropenia at candidemia onset	0 (0)	5 (8.2)	0.004	
Central vascular catheter				
No catheter	52 (53.6)	17 (28.3)	0.02	Reference
Exists, not extracted	13 (13.4)	14 (23)		2.4 [1.1–5.22], 0.02
Exists, extracted	32 (33)	28 (45.9)		2.49 [0.92–6.69], 0.07
Hypotension at onset	19 (19.6)	17 (27.9)	0.22	
New mechanical ventilation	7 (7.3)	6 (9.8)	0.57	
New mental status change	5 (5.2)	7 (11.5)	0.14	
Tachycardia at onset	64 (66)	50 (82)	0.02	1.91 [0.81–4.48], 0.13
Empirical treatment (24 h) for concomitant bacteremia [2]				
No bacteremia	80 (83.3)	44 (72.1)	0.07	
Inappropriate	14 (14.6)	17 (27.9)		
Appropriate	2 (2.1)	0 (0)		
Candida species				
C. albicans	36 (37.1)	30 (49.2)	0.17	
C. glabrata	26 (26.8)	9 (14.8)		
C. parapsilosis	22 (22.7)	9 (14.8)		

Table 2 (continued)

Variable	Success $n = 97$ (61.4%) median [Q1, Q3] mean ± S.D. n (%)	Failure $n = 61$ (38.6%) median [Q1, Q3] mean ± S.D. n (%)	Univariate p value	Multivariate OR [95% CI], p value
C. tropicalis	11 (11.3)	11 (18)		
Other	2 (2.1)	2 (3.3)		
Appropriate antifungal treatment within 24 h	17 (17.5%)	21 (34.4)	0.01	2.18 [0.97–4.88], 0.05
Appropriate antifungal treatment within 48 h	60 (61.9)	37 (60.7%)	0.88	
Fluconazole MIC (mg/L)	0.75 [0.25, 4]	1 [0.19, 2]	0.19	
Fluconazole loading dose	60 (61.9)	31 (50.8)	0.17	
Fluconazole daily dose (mg)	399 ± 147	370 ± 130	0.68	
Fluconazole AUC (mg h/L)	1239 [946, 2009]	1546 [946, 2139]	0.30	
Fluconazole AUC/MIC (h)	1524 [266, 5929]	1995 [698, 6868]	0.16	1 [1–1], 0.43
Fluconazole dose/MIC ratio	400 [100, 1600]	400 [200, 2105]	0.25	
Fluconazole AUC/MIC ≥ 400 h	66/97 (68)	48/61 (78.7)	0.14	

[1] For at least for 7 days in the month before the candidemia

[2] Clinically significant bacteremia occurring within 7 days before to 7 days after the culture taken date of the candidemia

Our findings are different from earlier studies (Supplementary Table 1). Clancy and colleagues [6] reported better microbiological success with fluconazole 24-h dose/MIC ratio above 50 in 32 patients with candidemia. The dose in this small cohort was low in the majority of patients, ranging between 100 and 200 mg/d and the cohort included only two episodes of *C. glabrata* candidemia. Pfaller and colleagues [15] reviewed data from three studies reporting fluconazole dose and MIC in patients with

Table 3 Fluconazole exposure parameters among patients *C. glabrata* candidemia and clinical outcomes

30-day mortality, medians [IQR]			
	Alive 20 (57.1%)	Dead 15 (42.9%)	p value
MIC (mg/L), median [Q1, Q3]	7 [4, 14]	16 [8, 24]	0.06
Fluconazole loading dose, n (%)	12 (60)	7 (46.7)	0.43
Daily dose (mg) mean ± SD	470 ± 197	386 ± 91	0.39
AUC (mg h/L), median [Q1, Q3]	1325 [971, 2088]	1200 [931, 1546]	0.36
AUC/MIC (h), median [Q1, Q3]	230 [77, 539]	96 [75, 164]	0.08
Dose/MIC ratio, median [Q1, Q3]	41 [25, 200]	25 [16, 50]	0.11
AUC/MIC ≥ 400 (h), n (%)	6/20 (30)	1/15 (6.7)	0.08
Clinical failure, medians [IQR]			
	Success 26 (74.3%)	Failure 9 (25.7%)	p value
MIC (mg/L), median [Q1, Q3]	8 [4, 16]	16 [4, 24]	0.32
Fluconazole loading dose, n (%)	15 (57.7)	4 (44.4)	0.49
Daily dose (mg), mean ± SD	453 ± 183	377 ± 66	0.47
AUC (mg h/L), median [Q1, Q3]	1283 [976, 2009]	1152 [887, 1546]	0.42
AUC/MIC (h), median [Q1, Q3]	150 [75, 348]	104 [78, 203]	0.47
Dose/MIC ratio	41 [25, 150]	25 [16, 100]	0.35
AUC/MIC ≥ 400 (h), n (%)	6 (23.1)	1 (11.1)	0.43

candidemia and invasive candidiasis (including the previously mentioned study of Clancy et al. [6]). They found a ratio of dose/MIC≥ 25 as the best threshold for treatment success, achieving successful treatment in 70% (181/257) of patients compared to 43% (23/47) with a dose/MIC ratio of less than 25. In a cohort of 77 non-neutropenic patients with candidemia [7], a significantly higher dose/MIC was observed for patients surviving in-hospital, yet the fluconazole dose used was low in general, as reflected by a mean dose/MIC of 13.3 ± 10.5 in survivors and 7.0 ± 8.0 in non-survivors, $P = 0.03$. This cohort included 11 episodes of *C. glabrata* candidemia [7]. Another study included 126 patients with candidemia and 110 patients with oropharyngeal candidiasis finding a dose/MIC threshold of 35.5 to best discriminate between cure and failure, where cure was defined by the eradication of the candidemia and resolution of the associated signs and symptoms [8]. Baddley and colleagues found an association between AUC/MIC< 11.5 (translated to dose/MIC of < 12.5) with all-cause mortality in a cohort of 84 patients with candidemia [9].

Two studies from recent years failed to show an association between fluconazole PK/PD parameters and relevant clinical outcomes, similar to our findings. In a cohort of 77 patients with candidemia, no association between fluconazole exposure and 30-day mortality was observed for non-albicans candidemia (compromising almost half of the cohort), while in *C. albicans* an association between AUC/MIC or dose/MIC > 400 h and 30-day survival was found [10]. The most recent and largest cohort included 257 patients with candidemia from a multicenter population-based surveillance project of yeast fungemia in Spain (CANDIPOP); this study could not demonstrate any association between fluconazole PK/PD parameters and a composite outcome of 30-day mortality and persistent candidemia [11]. Most *Candida* species in this cohort were highly susceptible to fluconazole with a MIC ≤ 2. *C. glabrata* occurred in 23 cases, compromising only 9% of the cohort, but the majority of *Candida* spp. with MIC > 2 belonged to this species. As in our study, the fluconazole doses were significantly higher than those used in previous studies, leading to very high fluconazole exposures in the majority of patients and no association between exposure and clinical outcome.

Our study has limitations. First, the retrospective data collection might have affected data quality, although all clinical and microbiological data were in electronic format in the study period in our institution. Second, being conducted in a single center, our study might reflect local epidemiology and local policies of treatment including adherence to fluconazole dosing. Our cohort included a heterogeneous patient population, as all studies on candidemia, including patients with solid tumors, hematological malignancies, and ICU patients that might need different PK/PD targets. *Candida* susceptibilities were not tested by broth microdilution, the recommended gold standard method, yet fluconazole testing with both E-test and VITEK is the most commonly used method in clinical laboratories, it directs our practice, and results were found to have a good correlation with the reference method in *Candida* susceptibility testing [2, 14, 16]. Finally, the relatively small number of patients with *C. glabrata* or *Candida* species with high MICs limited our analysis of this subgroup. Yet, compared to previous studies it is one of the largest series of *C. glabrata* candidemia.

To summarize, targeting PK/PD parameters in the treatment of *Candida* species with low MICs seems to have no importance when using standard recommended doses of fluconazole. For *C. glabrata* that usually had high MIC values, clinicians should give the maximal dose, possibly directed by AUC/MIC ratios. Fluconazole has an important role in the treatment of candidemia, especially as a stepdown agent after clearance of candidemia [3]. At this point, the clinician has information on the *Candida* species and MIC. More studies are needed that associate exposure with clinical outcomes to determine optimal PK/PD targets per species.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval The study was approved by the ethics committee at Rambam Hospital.

Informed consent Not required; not applicable.

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