Risk Factors for Non-Albicans *Candidemia* Focusing on Prior Antifungal and Immunosuppressive Therapy

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ABSTRACT: **Background:** With the widespread use of antifungal agents, the frequency of non-albicans *Candida* (NAC) blood-stream infections (BSI) is increasing.

Objectives: To describe the epidemiology, clinical manifestations, and risk factors for NAC BSI, focusing on prior antifungal and immunosuppressive therapy.

Methods: The authors conducted an observational, retrospective cohort study among adult patients with candidemia at the Rambam Health Care Campus, a tertiary medical center in Israel, between 2009 and 2015. Comparisons between patients with *Candidemia albicans* and NAC candidemia were performed. Regression analysis, with NAC BSI as the dependent variable and significant risk factors for NAC as independent variables, was performed.

Results: A total of 308 episodes of candidemia were included. *C. albicans* was isolated in 30.8% of patients (95/308), while NAC spp. were isolated in the rest. Significant independent risk factors for NAC included immunosuppression therapy (odds ratio [OR] 0.38, 95% confidence interval [95%CI] 0.19–0.76) and previous azole use (OR 0.2, 95%CI 0.06–0.710). The interaction between prior azole and immunosuppression therapy in the model was not significant, and after its inclusion in the model only immunosuppression remained significantly associated with NAC. In the subgroup of patients who did not receive prior azoles, immunosuppression therapy, neutropenia, and bone marrow transplantation were significantly associated with NAC.

Conclusions: Independent of previous azole treatment, immunosuppressive therapy was a significant risk factor for NAC in our cohort.

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KEY WORDS: azole, *Candidemia albicans*, immunosuppression therapy, non-albicans *Candida* (NAC)

The epidemiology of candidemia has changed in the last decades, with rising incidence and changing distribution of Candida species [1-4]. As Candidemia-attributed mortality is still common, offering appropriate empiric treatment is critical. Such treatment plans include the assessment of differences between *Candida albicans* and non-albicans Candida (NAC) and are based on known risk factors. In most cases, *C. albicans* are susceptible to fluconazole, while more variability is seen with the NAC spp. [5]. As most cases of invasive candidiasis, including candidemia, arise from the gastrointestinal tract (GIT) [6], factors altering the gut flora, like antimicrobial treatment (antifungal and antibacterial agents) were frequently observed to affect the distribution of Candida spp. and cause candidemia. The role of other potential modifiers of GIT flora such as chemotherapy and other immunosuppressive drugs have been studied less.

In the present study, we examined the risk factors for non-albicans species in cases of candidemia and focused on immunosuppressive treatment.

PATIENTS AND METHODS

This single-center retrospective observational cohort study was conducted at Rambam Health Care Campus, a tertiary hospital with 960 beds. This facility includes surgical and medical intensive care units, a burns unit, and a hematology division with a bone marrow transplantation department.

The study was approved by the hospital ethics committee.

INCLUSION CRITERIA

The study comprised adult patients (age >18 years) with at least one positive blood culture for *Candida* spp. between the years 2009 and 2015. *Candida* spp. growing within 14 days of each other were considered a single candidemia episode. A new episode was defined as isolation of a new *Candida* spp. at least 14 days after the last isolate of *Candida* in blood or the same species growing more than 2 months after the last isolate from a previous episode. Patients were considered for each separate episode of candidemia. We accepted patients with polymicrobial infections, including concomitant bacteremia.

We excluded clinically non-significant cases defined as blood culture that grew *Candida* from patients who survived for at least one month without antifungal treatment.

STUDY VARIABLES

The dependent variable was candidemia caused by NAC species. The primary exposure factors included prior azole therapy, defined as at least 4 days of azole treatment within the last month before candidemia onset; immunosuppressive treatment of steroids for more than 2 weeks; chemotherapy in the last 3 months; and current usage of other immunosuppressive drugs. We also collected data on factors altering the gastrointestinal flora such as previous antibiotic use (given for at least 7 days within the 30 days preceding candidemia onset), surgical intervention (within 3 months before candidemia), and other GIT pathology such as leak, mucositis, and graft-versus-host disease. In addition, we collected demographic data as well as information on co-morbidities, risk factors for candidemia, and mortality. We documented data on the minimum inhibitory concentration for antifungal agents tested, duration of positive blood cultures, antifungal treatment given, source control, and complications.

DATA SOURCES

Cases of candidemia were identified from the microbiology database. Clinical data were collected from the hospital's electronic medical record system, which is a complete patient healthcare record.

STATISTICAL ANALYSIS

Risk factors for non-albicans candidemia were assessed by univariate and multivariate analysis. Categorical variables were compared using chi-square or Fisher's exact test. Ordinal variables were assessed by linear-on-linear chi-square and continuous variables using *t*-test or the Mann–Whitney U non-parametric test, as appropriate. Variables significant ($P < 0.05$) on univariate analysis and not clinically or statistically correlated were entered into a bivariate regression analysis using all variables entered. The model's predictive ability was assessed as the area under-the-receiver operating characteristics curve (AUC) of its probabilities. The interaction between previous antifungal therapy and immunosuppressive therapy was tested and subgroup analysis was performed for patients without previous azole exposure. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 23 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

During the 7-year study period, 316 separate episodes of *Candida* growth in blood cultures in adults were identified. Eight episodes were excluded as clinically non-significant. The study comprised 302 patients with 308 separate episodes of candidemia. The 30-day mortality was 168/308 (55%). *C. albicans* was isolated in 95 (30.8%), *C. glabrata* in 71 (23.1%), *C. tropicalis* in 53 (17.2%), *C. parapsilosis* in 45 (14.6%), *C. krusei* in 36 (11.7%), and other species in 8 patients. The characteristics of patients with albicans versus NAC candidemia are shown in Table 1.

Patients with NAC were younger with a mean of age of 62 ± 19.34 years compared to 67 ± 16.63 years ($P = 0.017$) with *C. albicans* candidemia. No significant differences were found for most background conditions. While all conditions related to malignancy, bone marrow transplantation, neutropenia and malignancy, and immunosuppressive therapy were clearly more common among patients with NAC. Prior antibacterial treatment was administered in most cases, 72 (75.8%) and 162 (76.1%) for albicans and NAC candidemia, respectively. Other GIT disturbances were recorded in 77 (25%) cases with similar rates in both groups.

Prior antifungal exposure in the month before candidemia onset was recorded in 51 cases (16.5%). Forty-seven cases included azole agent: 30 cases of fluconazole alone, 8 of voriconazole alone, and the rest treated with a combination of antifungal agents including azoles. Indications for antifungal treatments included prophylaxis in 28 cases, empiric treatment in 7, and treatment of previous invasive fungal infections in 13. Prior azole exposure was documented in 44/213 patients (20.7%) with NAC compared to only 3 of 95 cases (3.1%) of albicans candidemia ($P < 0.001$).

The clinical presentations of the candidemia treatment and outcomes are presented in Table 2.

A higher rate of patients with NAC received appropriate antifungal treatment within 24 hours of candidemia onset, 74/213 (34.7%) compared to 18/95 (18.9%) in patients with *C. albicans* candidemia, $P = 0.005$. The difference decreased and was no longer statistically significant by 48 hours after candidemia onset. No statistically significant difference in 3-day mortality was seen in either group.

On multivariable analysis [Table 3], only two variables remained independently significantly associated with NAC: prior to azole exposure (odds ratio [OR] 0.20, 95% confidence interval [95%CI] 0.06–0.71) and immunosuppressive treatment (OR 0.38, 95%CI 0.19–0.76). Due to the small number of patients with microvascular complications caused by diabetes, this variable was dichotomized to yes/no diabetes, which was not significantly associated with NAC.

When included, the interaction term prior to azole exposure immunosuppressive treatment was not significant and only immunosuppressive treatment remained significantly associated with NAC, OR 0.48, 95%CI 0.24–0.95. The models had moderate prediction (AUC 0.68, 95%CI 0.62–0.74 for the model with the interaction).

In the subgroup of patients without previous azole exposure, immunosuppressive treatment was given to 49/169 patients (29%) with NAC compared to 14/92 patients (15.2%) with *C. albicans* candidemia ($P = 0.013$). Neutropenia and

Table 1. Characteristics of patients with *Candidemia albicans* (*C. albicans*) versus non-albicans candidemia

Characteristics	Albicans N=95 (%)	Non-albicans N=213 (%)	*P* value
Age, years (mean ± SD)	67 ± 16.63	62 ± 19.34	0.017
Male	59 (62.1)	119 (55.9)	0.306
Baseline functional status			0.793
Normal	55 (57.9)	132 (62)	
Limited	17 (17.9)	35 (16.4)	
Bedridden	23 (24.2)	46 (21.6)	
Dementia	14 (14.7)	21 (9.9)	0.213
Admission from			0.167
Home	57 (60)	145 (68.1)	
Long-term care facilities, nursing homes	21 (22.1)	29 (13.6)	
Other hospital	17 (17.9)	39 (18.3)	
Previous hospitalization in the preceding 90 days	55 (57.9)	142 (66.7)	0.139
Healthcare-associated candidemia	93 (97.9)	210 (98.6)	0.655
Nosocomial candidemia	83 (87.4)	177 (83.1)	0.34
Charlson Comorbidity Index (median, min–max)	2 (0–9)	2 (0–9)	0.981
Diabetes mellitus			
None	63 (66.3)	156 (73.2)	‹ 0.001
Diabetes without microvascular complications	23 (24.2)	56 (26.3)	‹ 0.001
Diabetes with microvascular complications	9 (9.5)	1 (0.5)	
Myocardial infarction	27 (28.4)	36 (16.9)	0.021
Peptic ulcer disease	10 (10.5)	13 (6.1)	0.173
Liver disease			0.341
None	92 (96.8)	205 (96.2)	
Mild cirrhosis	2 (2.1)	0 (0)	
Moderate to severe cirrhosis	1 (1.1)	8 (3.8)	
Hemodialysis	1 (1.1)	6 (2.8)	0.273
Bone marrow transplantation	1 (1.1)	41 (19.2)	‹ 0.001
Solid organ transplantation	1 (1.1)	2 (0.9)	1
Immunosuppressive treatment	14 (14.7)	86 (40.4)	‹ 0.001
Proton-pump inhibitor / H2 blocker treatment	54 (56.8)	122 (57.3)	0.794
Gastrointestinal tract disturbance			0.733
None	70 (73.7)	161 (75.6)	
Perforation/anastomosis leak	15 (15.7)	27 (12.6)	
Mucositis	2 (2.1)	13 (6.1)	
Other	8 (8.4)	12 (5.6)	
Intravenous drug user	5 (5.3)	6 (2.8)	0.285
Chronic renal failure (creatinine › 1.5 mg/dl)	18 (18.9)	22 (10.3)	0.038
Malignancy			‹ 0.001
None	62 (65.3)	91 (42.7)	
Non-metastatic solid	13 (13.7)	32 (15)	
Metastatic solid	12 (12.6)	16 (7.5)	
Hematologic: lymphoma	6 (6.3)	29 (13.6)	
Hematologic: AML, MDS, ALL	2 (2.1)	45 (21.1)	
Neutropenia at day 0 (‹ 500 cells/mm3)	3 (3.2)	53 (24.9)	‹ 0.001
Burns	0 (0)	5 (2.3)	0.329
Prosthetic heart valve	8 (8.4)	10 (4.7)	0.198
Implantable cardioverter defibrillator or pacemaker	4 (4.2)	7 (3.3)	0.686
Vascular graft	3 (3.2)	4 (1.9)	0.486
Prosthetic joint	2 (2.1)	1 (0.5)	0.226
Other prosthetic devices	6 (6.4)	9 (4.5)	0.278
Recent intensive care unit admission (1 month before)	35 (36.8)	60 (28.2)	0.128
Total parenteral nutrition	39 (41.1)	79 (37.1)	0.509
Prior antibiotic therapy*	72 (75.8)	162 (76.1)	0.96
Recent abdominal surgery (2 months before)	19 (20)	29 (13.6)	0.154
Prior azole treatment**	3 (3.2)	44 (20.7)	‹ 0.001
Intravascular catheter	54 (56.8)	140 (65.7)	0.136
Concomitant bacterial blood: stream infection (n=307)	11 (11.6)	27 (12.7)	0.776

*At least one agent more than 7 days during last month before candidemia onset

**More than 4 days of treatment during last month before candidemia

ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, MDS = myelodysplastic syndrome

bone marrow transplantation were also significantly associated with NAC [Table 4].

DISCUSSION

In our study, we examined risk factors for NAC. Our results showed that, in addition to azole exposure before candidemia, immunosuppressive treatment is an independent risk factor for NAC candidemia. No other major risk factor differentiated between patients with *C. albicans* and NAC candidemia.

The association between immunosuppressive treatment and NAC was observed in previous studies [7,8], although these investigations did not attempt to separate the variables representing immune suppression (malignancies, neutropenia, and immunosuppressive medications) from previous antifungal therapy. Our variable of immunosuppressive treatment included patients with various forms of immune suppression. We attempted to isolate the various forms from their correlation with prior antifungal therapy by assessing the interaction and subgroup analysis. In both analyses, immunosuppressive treatment was associated with NAC candidemia. The effect of immunosuppressive agents on the gut flora has been reported in mice models [9], which showed varying effects of different immunosuppressive medications, including cyclophosphamide, methotrexate, and steroids on *C. albicans* growth in the GIT. This effect may be related to heterogeneous susceptibility of different *Candida* species to environmental changes, allowing NAC spp. to predominate in the gut flora.

Previous studies have repeatedly observed the strong association between azole exposure and NAC candidemia [8,10-14]

Table 2. Clinical presentation, management and mortality: *Candidemia albicans* versus non-albicans candidemia

Characteristics	Albicans N=95 (%)	Non-albicans N=213 (%)	*P* value
Temperature › 38°C or ‹ 36°C	69 (73.4)	147 (70.3)	0.585
Hypotension at day 0*	26 (27.4)	49 (23)	0.41
Mental status changes within 48 hours	10 (10.5)	19 (8.9)	0.656
Use of vasopressors day 0	33 (35.1)	62 (29.2)	0.307
New mechanical ventilation within 48 hours	14 (10.1)	28 (16.7)	0.094
New hemodialysis within 48 hours	3 (3.2)	9 (4.2)	0.65
Central line-associated candidemia	22 (23.2)	59 (27.7)	0.403
Appropriate treatment for candidemia within 48 hours of candidemia onset	45 (47.4)	121 (56.8)	0.125
Appropriate treatment for candidemia within 24 hours of candidemia onset	18 (18.9)	74 (34.7)	0.005
30 day mortality	57 (60)	111 (52.1)	0.199

*Hypotension was defined as systolic blood pressure of ‹ 90 mmHg, mean arterial pressure of ‹ 65 mmHg, or systolic blood reduction of more than 40 mmHg

Table 3. Multivariate model of risk factors for *Candidemia albicans* (*C. albicans*) candidemia

Variable	Odds ratio	95% confidence interval	*P* value
Diabetes mellitus	0.84	0.47–1.5	0.554
Myocardial infarction	1.54	0.81–2.93	0.184
Chronic renal failure	1.49	0.71–3.14	0.297
Age, year	1	0.98–1.02	0.979
Prior azole treatment	0.2	0.06–0.71	0.013
Immunosuppressive treatment	0.38	0.19–0.76	0.006

Table 4. Characteristics of patients without recent azole exposure: *Candidemia albicans* versus non-albicans candidemia

Characteristics	Albicans N=92 (%)	Non-albicans N=169 (%)	*P* value
Age, years (mean ± SD)	67.39 ± 16.56	64.69 ± 18.35	0.242
Diabetes mellitus None Diabetes without microvascular complications Diabetes with microvascular complications	 60 (65.2) 23 (25) 9 (9.8)	 116 (68.6) 52 (30.8) 1 (0.6)	0.001
Bone marrow transplantation	1 (1.1)	13 (7.7)	0.024
Immunosuppressive treatment	14 (15.2)	49 (29)	0.013
Malignancy None Non-metastatic solid Metastatic solid	 60 (65.2) 13(14.1) 11(12)	 88 (52.1) 31(13.3) 16(9.5)	0.054
Hematologic: lymphoma Hematologic: AML, MDS, ALL	6 (6.5) 2(2.2)	15 (8.9) 19(11.2)	
Neutropenia at day 0 (‹ 500 cells/mm3)	3 (3.3)	28 (16.6)	0.002

ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, MDS = myelodysplastic syndrome

risk factors, and outcome in hospitalized patients with *Candida* albicans (C. albicans or fluconazole-resistant *Candida* spp. [15,16]. In contrast to previous studies, we did not find an association between antibacterial treatment and NAC candidemia [10,12,17]. These findings may be related to the high rate of patients in our cohort who had received previous antibacterial treatment. Neither variable represented healthcare exposure associated with NAC candidemia in our cohort, which was likely due to the high rate of healthcare acquired and nosocomial candidemias in our cohort.

Our study has several limitations. Our main finding was dependent on the quality of our data regarding prior antifungal therapy and immunosuppressive therapy. These variables were easily extracted from the electronic patient files as all medications on admission, during hospital stay, and at discharge are documented, in addition to the diagnoses. The retrospective data collection may have affected our ability to precisely document candidemia presentation. Our center cares for many immune compromised patients, as we are the only center in northern Israel with hemato-oncology and oncology departments. As a single-center study, our results might not be applicable to other centers. The small sample size limited our ability to analyze specific immunosuppressive agents that may have variable associations on specific *Candida* species [16]. We did not investigate specific antibacterial agents that were found to be associated with different *Candida* species.

CONCLUSIONS

Candidemia ranks high among infection-related causes of mortality in Israel [18] and the use of immunosuppressive treatment continues to increase. The fact that immunosuppressive treatment is independently associated with NAC should be considered when prescribing empirical antifungal therapy for immune compromised patients with suspected invasive candidiasis or for those with preliminary isolation of *Candida* in blood before species identification. This finding is especially significant due to the importance of appropriate early antifungal treatment on survival [19]. Our finding should be assessed in future studies and the reasons for this association, if proven empirically, should be evaluated.

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Capsule

DNA damage and parental age

Mutations in the sperm and eggs of humans have been attributed to errors in DNA replication. More than 75% of human germline mutations are paternal in origin. This condition is thought to be a result of male gametes undergoing more rounds of cell division than female gametes and thus having a greater probability of replication error. **Gao** et al. examined datasets of de novo mutations in the human germline and found that the mutation bias is not driven by spermatogenesis. They observed a surprising degree of C-to-G transversions and CpG transitions, indicative of DNA damage. The authors deduced that most mutations in early embryos are more likely to result from factors associated with maternal age at conception and accumulated damage in oocytes and embryos than from replication error.

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Eitan Israeli

Capsule

Biologic roles of human autoreactive B cells in rheumatoid arthritis revealed by RNA-sequencing

Mahendra and colleagues obtained the comprehensive transcriptome profile of human citrulline-specific B cells from patients with rheumatoid arthritis (RA). Citrulline- and hemagglutinin-specific B cells were sorted by flow cytometry using peptide–streptavidin conjugates from the peripheral blood of RA patients and healthy individuals. The transcriptome profile of the sorted cells was obtained by RNA-sequencing, and expression of key protein molecules was evaluated by aptamer-based SOMAscan assay and flow cytometry. The ability of these proteins to effect differentiation of osteoclasts and proliferation and migration of synoviocytes was examined by in vitro functional assays. Citrulline-specific B cells, in comparison to citrulline-negative B cells, from patients with RA differentially expressed the interleukin-15 receptor α (IL-15Rα) gene as well as genes related to protein citrullination and cyclic AMP signaling. In analyses of an independent cohort of cyclic citrullinated peptide–seropositive RA patients, the expression of IL-15Rα protein was enriched in citrulline-specific B cells from the patients' peripheral blood, and surprisingly, all B cells from RA patients were capable of producing the epidermal growth factor ligand amphiregulin (AREG). Production of AREG directly led to increased migration and proliferation of fibroblast-like synoviocytes, and, in combination with anti–citrullinated protein antibodies, led to the increased differentiation of osteoclasts.

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