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The predictors of outcome in immunocompetent patients with hematogenous candidasis

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Ischemic heart disease

Summary *Objective:* Clinical parameters that predict outcome in non-immunosuppressed candidemic patients are not fully understood.

Methods: Eighty-one consecutive episodes of candidemia were retrospectively evaluated in 75 patients during 1998–2000.

Results: Infection due to *Candida albicans* was common ($n = 30$; 37%) followed by *Candida glabrata* ($n = 25$; 31%), *Candida parapsilosis* ($n = 14$; 17%), *Candida tropicalis* ($n = 6$; 7%), *Candida krusei* ($n = 5$; 6%), and *Candida lusitaniae* ($n = 1$; 1%). Among 70 evaluable patients, 31 (44%) had fungemia-associated mortality; advanced age ($P < 0.004$), underlying malignancy ($P < 0.025$), coronary artery disease ($P < 0.01$), and concurrent non-*Candida* species fungal infection ($P < 0.047$) were significant prognosticators of compromised short-term survival by multivariate analysis. Mortality was higher in patients with *Candida glabrata* (60%) and *C. tropicalis* (75%) infection compared to 44% deaths in individuals with *C. albicans* infection ($P > 0.1$). 11/25 (44%) of non-immunocompromised individuals died and 20/45 (44%) immunosuppressed patients succumbed to fungemia: persistent vs. non-persistent (<3 days) *Candida* bloodstream invasion, neutropenia, diabetes mellitus, renal insufficiency, prior antimicrobial therapy, cirrhosis of liver, abdomino-pelvis surgery, and critical-care-unit vs. non critical-care-unit admission did not significantly impact outcome in either group. All 11 infants, including nine with prematurity survived *Candida* species bloodstream infection ($P < 0.025$).

Conclusions: Short-term mortality in candidemic non-immunocompromised patients was comparable to fungemia-associated deaths in immunosuppressed patients. Ischemic heart disease has appeared as a new predictor of unfavorable outcome in patients with hematogenous candidiasis.

Introduction

Candidemia is a serious complication in patients undergoing treatment for cancer.[1,2] In hospitalized non-oncology patients, admission to a medical or

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surgical critical care unit increases the risk of systemic yeast invasion,[3,4] especially in the setting of recent surgery, hyperalimentation, or acute renal failure.[3] This rise in hematogenous candidiasis[5,6] is in part attributed to the near universal use of implantable and semi-implantable indwelling intravascular devices[7,8] and prolonged appropriate and/or inappropriate broad-spectrum antimicrobial therapy with vancomycin, imipenem, etc. given pre-emptively or empirically to susceptible individuals.[9]

In fungemic cancer patients, predictors of unfavorable outcome include prolonged and severe granulocytopenia, multi-organ yeast dissemination, advanced malignancy, leukemia, hematopoietic stem cell transplantation and intensive care unit stay at the time of fungemia diagnosis.[10–12] However, in non-immunosuppressed patients, predictors of short-term survival with candidemia are less certain. In this retrospective evaluation, we analyzed host- and microorganism-associated predictors of short-term survival in immunocompromised and non-immunosuppressed patients with blood-borne candidiasis.

Materials and methods

Study design

All consecutive episodes of *Candida* species bloodstream invasion were evaluated from 1 January 1998 to 1 January 2000. Patient and laboratory information was retrieved from patients' charts and the computerized hospital data system. All blood culture specimens were processed at the Microbiology Laboratory, Department of Pathology, Palmetto-Richland Memorial Hospital, South Carolina, United States. *Candida* species isolation and identification was performed by methods described elsewhere.[13]

Definitions

Candidemia was defined as a clinical illness associated with the presence of *Candida* species in the patient's bloodstream. All positive blood cultures for *Candida* species during the same hospitalization were considered as a single episode. If more than one *Candida* species was isolated, infection due to each was considered as a separate episode.[13] Persistent or sustained fungemia was defined as blood isolation of yeast for >3 days.[13–15]

Neutropenia was defined as either absolute neutrophil count <500 cells/μl, or total white cell count of <1000 cells/μl; severe neutropenia and granulocytopenia are used interchangeably. Patients with underlying malignancy, hematopoietic stem cell transplantation, neutropenia, and/or prolonged (>2 weeks) systemic corticosteroid therapy were considered immunosuppressed. Advanced age was defined as >55 years.

Fungemia-associated mortality was defined as death within 30 days of initial blood culture yeast isolation, and absence of known terminal events, such as intracranial or gastrointestinal hemorrhage or pulmonary embolism.[1,13]

Fungemia, candidemia, hematogenous candidiasis, blood-borne candidiasis and *Candida* species bloodstream invasion are used interchangeably.

Statistical analysis

In the univariate analysis, the Pearson χ^2 test was used to compare categorical variables in patients with fungemia. For the multivariate analysis, a logistic regression was employed to compare categorical and continuous populations. A comparison was declared significant if the P value was <0.05.

Results

Patient and disease characteristics

Patient characteristics are presented in Table 1. Eighty-one episodes of fungemia occurred in 75 patients; 69 individuals (92%) had infection due to a single *Candida* species and in six patients (8%) multiple yeast species were isolated from blood culture samples. *Candida albicans* was common ($n = 30$; 37%); in 51 (63%) episodes due to non-*albicans* candidemia, nearly half had *C. glabrata* ($n = 25$; 49%) hematogenous invasion, followed by *C. parapsilosis* ($n = 14$; 17%), *C. tropicalis* ($n = 6$; 7%), *C. krusei* ($n = 5$; 6%), and *C. lusitaniae* ($n = 1$; 1%).

Among 70 evaluable patients, overall fungemia-associated short-term mortality was 44% ($n = 31$). Twenty-three of 70 patients (33%) had *C. albicans* infection and ten of these (44%) died. Mortality was 50% (1/2), 60% (12/20), and 75% (3/4) in patients with *C. krusei*, *C. glabrata*, and *C. tropicalis* bloodstream infections, respectively (Table 3). In patients with persistent or prolonged (>3 days) yeast blood isolation, mortality was 44%, whereas 40% died in the setting of non-persistent *Candida* bloodstream invasion. Similarly, in six patients (9%) with ≥ 2 *Candida* species, fungemia mortality was 33% ($n = 2$) compared to 45% ($n = 29$) mortality in 64 patients with a single yeast species infection. A

Table 1 Characteristics of patients with *Candida* species bloodstream infection during 1998 to 2000.

	N (%)	Mortality (%)[a]
Patients	75	
Male	37 (49)	
Female	38 (51)	
Age[b]		
Adults (>17 y)	56 (75)	30/51 (59)
Pediatric (>1 y)	8 (11)	1/8 (13)
Infants and neonates	11 (15)	0 (0)
WBC[c,d]		
Normal leukocyte count ($4 - 10 \times 10^9$/L)	26/74 (35)	7/24 (29)
Neutropenia ($<1 \times 10^9$/L)	8/74 (11)	5/8 (63)
Leukopenia ($\geq 1 - < 4 \times 10^9$/L)	9/74 (12)	5/9 (56)
Leukocytosis ($>12 \times 10^9$/L)	31/74 (42)	14/28 (50)
Evaluable patients	70	31/70 (44)
Single positive blood culture	25/70 (36)	
Multiple site positive blood culture	45/70 (64)	
Central venous catheter[e]	37/71 (52)	18/35 (51)
Total parentral nutrition	47/73 (64)	22/45 (49)
Fever (>100.5 °F)	45/70 (64)	19/43 (44)
Afebrile	25/70 (36)	12/25 (48)
Antimicrobial use[f]	60/71 (85)	26/60 (43)
Single antimicrobial	10 (14)	7/10 (70)
Two antimicrobials	23 (32)	8/23 (35)
Three antimicrobials	9 (13)	3/9 (33)
Four or more antimicrobials	18 (25)	8/17 (47)
Penicillins	19 (27)	6/18 (33)
Cephlosporins	42 (59)	21/41 (51)
Vancomycin	22 (31)	8/21 (38)
Carbapenem	6 (8)	0/6 (0)
Aminoglycosides	24 (34)	6/23 (26)
Fluoroquinolones	18 (25)	8/18 (44)
Trimethoprim-sulfamethoxazole	8 (11)	0/11 (0)
Clindamycin	8 (11)	0/11 (0)
Monobactam	2 (3)	0/2 (0)
Macrolides/azolides	4 (6)	0/4 (0)
Tetracyclines	1 (1)	0/1 (0)
Antifungal use	22/71 (31)	11/20 (55)
Triazole-based antifungal	15 (21)	8/14 (57)
Amphotericin B	5 (7)	3/4 (75)
Nystatin	2 (3)	0/2 (0)

[a] In 5 patients, final outcome was not available and their information was excluded from the analysis of mortality; Mortality percentage was calculated according to the number of patients that died in within 30 days of fungemia diagnosis/number of evaluable patients within specific category.
[b] Median age $\pm$SD $= 48 \pm 29$ years.
[c] Median WBC $\pm$SD $= 10 \pm 9 \times 10^9$/L.
[d] WBC analysis not available for one patient.
[e] Central venous catheters were not routinely removed in patients with no evidence of catheter-related fungemia; duration of CVC prior to fungemia diagnosis was median 8 ± 7 days.
[f] Antimicrobial therapy including antibiotics and antifungals that patients received within 30 days of bloodstream *Candida* species isolation.

single death (5%) occurred in 19 pediatric patients; all 11 infants, including nine that were premature at birth and three receiving care in neonatal ICU, survived blood-borne candidiasis ($P < 0.025$).

Ten of 70 evaluable patients (14%) received fluconazole alone within 30 days of fungemia diagnosis, five of these ten (50%) developed *C. glabrata* infection.

Univariate analysis

In the immunosuppressed patients, higher mortality was seen in the presence of profound granulocytopenia (63%), cirrhosis of liver (100%), diabetes mellitus (67%), and prior exposure to multiple-broad-spectrum antimicrobials (83%). In non-immunosuppressed patients, higher mortality was observed in the setting of persistent non-*albicans* candidemia (78%), renal dysfunction (57%) and concurrent bacteremia (53%).

Case-control analysis comparing these two patient groups is presented in Table 2, which shows no significant differences in outcome. Similarly, short-term mortality in patients with *C. albicans* infections was compared with outcomes in individuals with non-*albicans* candidemia and presented in Table 3; there was no statistically significant difference in short-term mortality in either group.

Multivariate analysis

A logistic regression model was employed to compare discrete and continuous variables, adjusted for the other variables in the model. Candidemic patients with advanced age ($P < 0.004$), underlying malignancy ($P < 0.025$), and concomitant non-*Candida* systemic mycosis ($P < 0.047$) had significantly poor outcomes. Among 15 patients (21%) with a history of coronary artery disease, 12 (80%) died, compared to 19 (35%) deaths in 55 patients with no known history of coronary artery disease (significant by multivariate analysis ($P < 0.01$)). All other clinical parameters shown in Table 2, including stay in ICU did not significantly increase short-term mortality in these fungemic patients.

Discussion

Systemic candidiasis has evolved as a serious complication in critically ill non-immunosuppressed patients.[3,4,14,15] Most systemic yeast infections, especially due to *Candida albicans*, *C. tropicalis*, *C. glabrata* and *C. krusei* arise from existing endogenous orointestinal microflora.[15,16] During the last decade, a substantial increase in non-*albicans*

Table 2 Case-control analysis of predictors of survival in 70 evaluable patients with fungemia during 1998—2000.

Confounding variables	Non-compromised ($n = 25$)		Immunosuppresssed ($n = 45$)		*P* value
	n (%)	Mortality (%)	*n* (%)	Mortality (%)	
Overall mortality		11/25 (44)		20/45 (44)	>0.5
Neutropenia (ANC < 500 cells/mm^3)	0 (0)	0 (0)	8 (18)	5/8 (63)	NC
Leukocytosis (WBC > 11 000 cells/mm^3)	14 (56)	7/14 (50)	15 (33)	7/15 (47)	>0.5
Fever (>100.5 °F)	12 (48)	4/12 (33)	31 (69)	16/31 (52)	>0.1
Central venous catheter	20 (80)	10/20 (50)	41 (91)	19/41 (46)	>0.5
Cancer[a]	1 (4)	1/1 (100)	31 (69)	18/31 (58)	>0.1
AIDS	0 (0)	0 (0)	2 (44)	0/2 (0)	NC
Diabetes mellitus	8 (32)	4/8 (50)	6 (13)	4/6 (67)	≥0.5
Coronary artery disease	10 (40)	8/10 (80)	5 (11)	4/5 (80)	>0.5
Persistent non-*albicans* candidemia	9 (36)	7/9 (78)	8 (18)	5/8 (63)	≥0.5
Renal dysfunction	7 (28)	4/7 (57)	5 (11)	2/5 (40)	>0.5
Cirrhosis	0 (0)	0 (0)	1 (2)	1/1 (100)	NC
Abdomino-pelvic surgery	11 (44)	4/11 (36)	12 (27)	7/12 (58)	>0.1
Concurrent bacterial infection	17 (68)	9/17 (53)	21 (47)	9/21 (43)	≥0.5
Concurrent non-*Candida* fungal infection	2 (8)	1/2 (50)	4 (9)	4/4 (100)	≥0.1
Prior antifungal exposure[b]	3 (12)	1/3 (33)	14 (31)	7/14 (50)	>0.5
Prior antibiotic exposure[b]	5 (20)	2/5 (40)	6 (13)	5/6 (83)	≥0.1

NC: non-calculatable.

[a] One patient with remote history of cancer in clinical remission was regarded as non-immunosuppressed.

[b] Prior antibiotic and antifungal therapy was considered in patients with antimicrobial exposure in <3 months of fungemia diagnosis.

Table 3 Impact on short-term mortality in patients with *Candida albicans* versus non-*albicans* bloodstream candidiasis is compared.

	Fungemia episodes in 70 evaluable patients *N* (mortality; %)	*P* value
Candida albicans vs non-*albicans* spp.	23 (10; 44%) vs 47 (21; 45%)	NS
Candida albicans vs *C. glabrata*	23 (10; 44%) vs 20 (12; 60%)	NS
Candida albicans vs *C. parapsilosis*	23 (10; 44%) vs 14 (3; 21%)	NS
Candida albicans vs *C. tropicalis*	23 (10; 44%) vs 4 (3; 75%)	NS
Candida albicans vs *C. krusei*	23 (10; 44%) vs 2 (1; 50%)	NS
Candida albicans vs ≥2 *Candida* species	23 (10; 44%) vs 6 (2; 33%)	NS

One patient with *C. lusitaniae* infection who died is not included in comparative *Candida* species analysis, although he is included in the overall analysis of *C. albicans* versus non-*albicans* candidemia. *N* is the number of patients with each organism; in parenthesis the number of patients that died and the percentage of patients in whom mortality was associated with specific *Candida* species is presented. NS = not significant.

Candida species infection in oncology patients and those with acquired immune deficiency syndrome was, in part, attributed to a shift in colonizing yeast species resulting from triazole-based antifungal-induced selection of less-susceptible microorganisms.[13,17–20] A similar pattern of *Candida* species shift was recently observed in critically ill, non-immunosuppressed hospitalized patients.[14,21] In this report, nearly one-third (31%) of bloodstream infections were due to *C. glabrata*, an observation consistent with current species re-distribution trends observed in the USA,[17] albeit most of our patients with *C. glabrata* infections did not receive prior fluconazole therapy.[17,22,23] It was interesting to note that recent exposure (<30 days) to fluconazole was seen in one-quarter (5 of 20) of patients with *C. glabrata* fungemia, but only 10% (5/50) of patients with non-*glabrata* candidemia, although this difference was not significant ($P>0.1$).

Advanced age, underlying malignancy and concomitant non-*Candida* fungal infections were associated with increased fungemia-associated deaths in our group, which was in concert with adverse prognosticators noted in oncology patients.[10–12] The presence of coronary artery or ischemic heart disease appeared as a new predictor in patients with significantly compromised short-term survival with systemic candidiasis. Existing ischemic heart disease is a well-recognized co-morbidity, which predicts compromised survival in patients with serious systemic infections; this association in patients with candidemia was not unexpected. The presence of leukocytosis, fever, central venous catheter and prior exposure to antifungal drugs were not associated with a significant negative impact on survival in either group. It was encouraging to note that candidemia-related mortality in the pediatric population was markedly low (5%), compared to 44% mortality in adult patients with hematogenous candidiasis.

The significant difference in response among all high-risk candidemic infants including those with prematurity ($P < 0.025$) was probably associated with intact peripheral blood neutrophil count, absence of prolonged exposure to multiple broad-spectrum antimicrobials, in some, prompt removal of infected indwelling intravascular catheter, and appropriate therapeutic intervention.

In patients with persistent-prolonged fungemia, mortality (44%) was comparable to candidemia-related deaths (40%) in the non-sustained setting.[24,25] Similarly, mortality was comparable in patients with *C. albicans* infection (44%); the higher death rates seen in patients with *C. glabrata* (60%) and *C. tropicalis* (75%) infection were not significantly different from fungemia outcome in patients with *C. albicans* infection ($P>0.1$). Systemic *C. albicans* dissemination is often a severe illness, compared to hematogenous invasion due to non-*albicans Candida* species, including *C. parapsilosis*, and *C. glabrata*.[26–28] This observation was reproduced in animal studies; systemic *C. albicans* infection resulted in fulminant and universally fatal disease in untreated non-immunosuppressed animals, whereas a sub-acute, non-fatal infection was commonly observed in animals infected with *C. glabrata*.[29]

Conclusion

In conclusion, hematogenous candidiasis was a serious complication associated with comparably high mortality in non-immunosuppressed patients. Candidemic patients with advanced

age, underlying malignancy, and concomitant non-*Candida* species systemic mycosis had higher mortality. The presence of coronary artery disease appeared as a significant predictor of unfavorable short-term survival and may further help to identify fungemic patients at increased risk of death.

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Conflict of interest: No conflict of interest declared.

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