MAJOR ARTICLE

Impact of Treatment Strategy on Outcomes in Patients with Candidemia and Other Forms of Invasive Candidiasis: A Patient-Level Quantitative Review of Randomized Trials

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(See the Editorial Commentary by Clancy and Nguyen, on pages 1123–5.)

Background. Invasive candidiasis (IC) is an important healthcare-related infection, with increasing incidence and a crude mortality exceeding 50%. Numerous treatment options are available yet comparative studies have not identified optimal therapy.

Methods. We conducted an individual patient-level quantitative review of randomized trials for treatment of IC and to assess the impact of host-, organism-, and treatment-related factors on mortality and clinical cure. Studies were identified by searching computerized databases and queries of experts in the field for randomized trials comparing the effect of ≥2 antifungals for treatment of IC. Univariate and multivariable analyses were performed to determine factors associated with patient outcomes.

Results. Data from 1915 patients were obtained from 7 trials. Overall mortality among patients in the entire data set was 31.4%, and the rate of treatment success was 67.4%. Logistic regression analysis for the aggregate data set identified increasing age (odds ratio [OR], 1.01; 95% confidence interval [CI], 1.00–1.02; $P = .02$), the Acute Physiology and Chronic Health Evaluation II score (OR, 1.11; 95% CI, 1.08–1.14; $P = .0001$), use of immunosuppressive therapy (OR, 1.69; 95% CI, 1.18–2.44; $P = .001$), and infection with *Candida tropicalis* (OR, 1.64; 95% CI, 1.11–2.39; $P = .01$) as predictors of mortality. Conversely, removal of a central venous catheter (CVC) (OR, 0.50; 95% CI, .35–.72; $P = .0001$) and treatment with an echinocandin antifungal (OR, 0.65; 95% CI, .45–.94; $P = .02$) were associated with decreased mortality. Similar findings were observed for the clinical success end point.

Conclusions. Two treatment-related factors were associated with improved survival and greater clinical success: use of an echinocandin and removal of the CVC.

Epidemiologic studies from the last 2 decades have identified *Candida* species as the fourth most common cause of nosocomial bloodstream infection [1–4]. Despite recognition of disease risk factors and advances in infection prevention, candidemia-related hospitalizations and mortality have continued to rise [1, 5]. Mortality rates associated with invasive candidiasis (IC) approach 50% [6–13]. Moreover, longitudinal studies have detected a global shift in epidemiology toward non-*albicans Candida* species, particularly *Candida glabrata* [14–22]. The changing epidemiology of *Candida* bloodstream infection is of concern, because these species exhibit variable susceptibility to antifungal drugs with some of these emerging species [13, 23–26].

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The number of antifungal drugs for IC has increased during the last 2 decades [27–32]. Several large randomized trials have compared these antifungal drug therapies for this disease state. However, these studies, powered for noninferiority, have not identified an optimal treatment strategy. The goal of the present study was to analyze individual patient data from these trials to determine mortality and clinical cure in patients with candidemia and other forms of IC across treatment regimens. We hypothesized that the increased sample size of a pooled analysis of patient-level data would allow detection of differences in patient outcomes.

METHODS

Inclusion Criteria

We identified randomized clinical trials that compared antifungal treatments for candidemia and IC. Criteria for trial selection included the availability of data on mortality and clinical success with each *Candida* species. As our focus was on the use of individual patient-level data, we considered only studies in which individual patient data were available [33]. We searched multiple databases (10/1010, repeated 1 January 2011, and 1 June 2011) using the terms "candidemia," "invasive candidiasis," "antifungal," and the names of each specific antifungal drug. Trials of biologic agents were excluded.

Outcomes

The primary outcome was 30-day all-cause mortality. The secondary outcome was clinical and microbiologic success, defined as symptom resolution and negative cultures at the end of therapy (typically 14 days). The rationale for these measures includes consistency of definition and data availability across trials.

Host-, Organism-, Disease-, and Treatment-Related Data

The rationale for choice of factors was based on prior association with outcome [2, 6, 34–37]. Demographics included sex and age. Information was collected on comorbid conditions, including malignancy, organ transplantation, and surgery within 30 days of infection, renal (creatinine level >3.0 mg/dL or hemodialysis) or hepatic dysfunction (laboratory values >5 times the upper limit of normal), neutropenia within 30 days of infection, use of parenteral nutrition at the time of infection, immunosuppressive therapy (corticosteroids or chemotherapy) at diagnosis, antibiotics within 30 days of infection, the presence of a central venous catheter (CVC) at the time of enrollment, the need for mechanical ventilation, and intensive care unit stay at diagnosis. Infection and organism factors included the site of infection, *Candida* species, and a measure of severity of illness, the Acute Physiology and Chronic Health Evaluation (APACHE) II score. Data from cases with missing fungal species information and multiple *Candida* species were excluded from analysis. The treatment variables evaluated included specific antifungal therapy and removal of CVCs at any time during the treatment phase. Data from combination antifungal therapy were excluded. Information regarding the timing of start of therapy relative to disease diagnosis and the timing of CVC removal were not available for all patients.

Data Source and Management

The data from the modified intent-to-treat patient populations were provided by the industry sponsor or principal investigator. The similarity of the trials, including design, disease, and host factor definitions; treatment initiation and duration strategy; and the availability of identical outcome data based on both definition and timing (Table 1) provided a strong rationale to pool individual patient-level data. Data extraction and transformation process involved 2 core stages: preprocessing stage and the data integration stage. Preprocessing involved the extraction of raw laboratory files and conversion into SAS software (version 9.1.3; SAS Institute) data sets. A set of programs were developed to assess and validate the content quality of the source data (eg, missing values, frequency, and format consistency). In the data integration stage, each cleaned source file was transformed and restructured into a SAS data set with standardized naming conventions and value formats used in the study.

Data Analysis

Frequencies of each *Candida* spp, host, and treatment variable were determined. Missing data were treated as missing. Antifungal therapy was considered at the level of the individual drug and drug class. The rationale for consideration of drug class (polyenes [amphotericin B and liposomal amphotericin B], triazoles [fluconazole and voriconazole], echinocandins [anidulafungin, caspofungin, micafungin]) included the similarity of drug mechanism, spectrum of activity, and reported efficacy in experimental and treatment comparisons. To evaluate factors associated with mortality or clinical success, univariate analyses were performed using the χ^2 test, or Fisher's exact test for categorical variables and unpaired Student's t test for continuous variables. Multivariable modeling was undertaken using stepwise logistic regression. All variables significant at $\alpha = .20$ in univariate analyses were considered as possible predictor variables for the multivariable analyses. The criterion for entry into the model was significance at $\alpha = .20$ or clinical relevance, whereas the criterion for remaining in the model was significance at $\alpha = .05$. All tests of significance were 2 tailed. The study trial number was included in every model to assess for heterogeneity and study effect. Model fit was assessed using the Hosmer–Lemeshow test for goodness of fit, the Pearson χ^2, and the C statistic. Analyses were undertaken for the entire

Table 1. Characteristics of Randomized Controlled Candidemia Trials Fulfilling Criteria for Inclusion in Analysis

Reference (Patient No.; Enrollment Dates)	Drugs and Maintenance Regimens	Design	Inclusion	Host or Disease Factor Exclusion	Treatment Duration	Modified Intent-to-Treat Population	Primary Outcome	Secondary Outcome
Rex et al, 1994 [46] (237; 1989–1993)	Fluconazole 400 mg/d vs amphotericin B 0.5–0.6 mg/kg/d	Randomized, double blinded	Candidemia and fever or hypotension	Neutropenia, hematologic malignancy, HIV, transplant, pregnancy	≥14 d after last positive blood culture	Receipt of ≥1 d of antifungal drug	Clinical and microbiologic success at EOT	All-cause death at EOT
Mora-Duarte et al, 2002 [48] (239; 1997–2001)	Caspofungin 50 mg/d vs amphotericin B 0.6–0.7 mg/kg/d (0.7–1.0 for neutropenic patients)	Randomized, double blinded	Candidemia or invasive candidiasis	Endocarditis, osteomyelitis, meningitis	10 d intravenous and all therapy >14 d after last positive culture	Receipt of ≥1 d of antifungal drug	Clinical and microbiologic success and absence of toxicity-required change in therapy at EOT	All-cause death at EOT
Rex et al 2003 [45] (236; 1995–1999)	Fluconazole 800 mg/d vs amphotericin B 0.6–0.7 mg/kg/d and fluconazole 800 mg/d	Randomized, double blinded	Candidemia and fever or hypotension	Neutropenia, pregnancy, *Candida krusei*	≥14 d after last positive blood culture, amphotericin B component 5–8 d	Receipt of ≥1 d of antifungal drug	Clinical and microbiologic success at EOT	All-cause death at EOT
Kullberg et al 2005 [47] (422; 1998–2003)	Voriconazole 3 mg/kg every 12 h for 3 d, then possible switch to 200 mg oral twice daily vs amphotericin B 0.7–1.0 mg/kg/d followed by fluconazole 400 mg/d	Randomized, double blinded	Candidemia and fever or hypotension	Neutropenia, AIDS, chronic granulomatous disease, aplastic anemia, hepatic and renal dysfunction, pregnancy	≥14 d after last positive blood culture	Receipt of ≥1 d of antifungal drug	Clinical and microbiologic success at 12 wk and EOT	All-cause death at 30 d
Reboli et al 2007 [43] (245; 2003–2004)	Anidulafungin 100 mg/d vs fluconazole 400 mg/d	Randomized, double blinded	Candidemia or invasive candidiasis	Pregnancy	≥14 d after last positive blood culture	Receipt of ≥1 d of antifungal drug and document fungal infection	Clinical and microbiologic success at EOT	All-cause death within 30 d
Kuse et al 2007 [41] (264; 2003–2004)	Micafungin 100 mg/d vs liposomal amphotericin B 3 mg/kg/d	Randomized, double blinded	Candidemia or invasive candidiasis	Hepatic dysfunction	>14 d	Receipt of ≥1 d of antifungal drug	Clinical and microbiologic success at EOT	All-cause death within 30 d
Pappas et al 2007 [49] (595; 2004–2006)	Micafungin 100 or 150 mg/d for ≥10 d then possible switch to fluconazole 400 mg/d vs caspofungin 50 mg/d for ≥10 d then possible switch to fluconazole 400 mg/d	Randomized, double blinded	Candidemia or invasive candidiasis	Hepatic dysfunction, pregnancy, cyclosporin use, endocarditis, osteomyelitis, meningitis	≥14 d after last positive blood culture	Receipt of ≥1 d of antifungal drug and documentation of fungal infection	Clinical and microbiologic success at EOT	All-cause death within 30 d

Abbreviation: EOT, end of therapy; HIV, human immunodeficiency virus.

Table 2. Frequency of Host, Disease, and Organism Factors in Patients With Invasive Candidiasis

Factors	Variable	Patients, No.[a]	Patients, %[b]
Demographics	Age, mean ± SD, y	55.1 ± 17.64	…
	Male sex	1102	57.5
	Female sex	813	42.5
Risks and comorbid conditions	Central venous catheters[c]	1492	78.0
	Surgery[d]	659	34.4
	Neutropenia[d]	139	9.0
	Malignancy	410	28.2
	Transplantation	69	4.8
	Immunosuppressive therapy[c]	440	28.6
	ICU[c]	531	54.1
	TPN[c]	410	31.9
	Mechanical ventilation[c]	410	31.9
	Renal dysfunction[c] (creatinine >3.0 mg/L or hemodialysis)	223	12.4
	Hepatic dysfunction[c] (laboratory values >5 times upper limit of normal)	47	4.3
	Antibiotics[d]	534	52.0
Disease information	Sites of infection	1590	
	BSI	1349	84.8
	Urine	2	0.1
	Abdominal	16	1.0
	CNS	14	0.9
	Eye	58	3.7
	Heart	7	0.4
	Joint	2	0.1
	Other	67	4.2
	Multiple	75	4.7
Severity	APACHE II score, mean ± SD	14.9 ± 7.2	…
Candida organisms	All organisms	1915	
	C. albicans	837	43.7
	C. glabrata	206	10.7
	C. tropicalis	352	18.3
	C. krusei	40	2.0
	C. parapsilosis	299	15.6
	Other	181	9.5
Antifungal	Amphotericin B	254	13.3
	Liposomal amphotericin B	218	11.4
	Fluconazole	271	14.2
	Voriconazole	254	13.3
	Anidulafungin	128	6.7
	Caspofungin	249	13.0
	Micafungin	541	28.3

Table 2 continued.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BSI, bloodstream infection; CNS, central nervous system; ICU, intensive care unit; SD, standard deviation. TPN, total parenteral nutrition.

[a] Data represent No. of patients unless otherwise specified.

[b] Percentages among patients in whom data were available (not missing).

[c] Present at time of *Candida* diagnosis.

[d] Present within 30 days of *Candida* diagnosis.

study population and subgroup analyses were completed for each *Candida* species alone, for the aggregated non-*albicans* *Candida* species, and for bloodstream infection site.

RESULTS

Description of Studies

Nine randomized trials met the inclusion criteria. Patient-level data were available for 7 studies (Table 1). One trial was excluded due to inclusion of a biologic agent [38]. Data from 1 trial were not available despite attempts to contact the authors and industry sponsors [39]. The majority of trials served as US Food and Drug Administration or European Medicines Agency licensing studies. Antifungal regimens included 2 polyenes, 2 triazoles, and 3 echinocandins. One trial included combination therapy and this arm was excluded from analysis by our a priori inclusion criteria.

Host-, Organism-, and Treatment-Related Variables

The analysis included 1915 patients with IC for the mortality end point (1895 for the composite success end point). The frequency of disease, host, and organism variables in the data set are presented in Table 2. The mean patient age was 55.1 year, and 57.5% of the patients were men. *C. albicans* was the most frequent *Candida* species (n = 837; 43.7% of cases), followed by *C. tropicalis* (n = 352; 18.3%), *C. parapsilosis* (n = 299; 15.6%), *C. glabrata* (n = 206; 10.7%), and *C. krusei* (n = 40; 2.0%). The mean APACHE II score was 14.9. The majority of patients (n = 1492; 78%) had a CVC in place at enrollment.

Factors Associated With Mortality and Treatment Response

The overall 30-day mortality was 31.4%, and composite treatment success at the end of treatment was 67.4%. Univariate analyses identified multiple factors significantly associated with mortality and treatment success (Table 3). Demographic, disease, and host factors associated with higher risk of death in the entire cohort included increasing APACHE II score,

Table 3. Univariate Analysis of the Host, Disease, Organism, and Treatment Factors and Outcome in Patients With Invasive Candidiasis

	Alive (n = 1313)		Dead (n = 602)			Success (n = 1277)		Failure (n = 618)		
Variables	No.	%	No.	%	*P*	No.	%	No.	%	*P*
APACHE II score, mean ± SD	13.4 ± 6.5	…	18.6 ± 7.4	…	<.0001	14.0 ± 6.8	…	16.9 ± 7.5	…	<.0001
Age, mean ± SD, y	53.2 ± 17.6	…	59.4 ± 16.9	…	<.0001	54.8 ± 15.6	…	55.6 ± 17.6	…	.3
Male sex	755	57.5	374	62.1	.9	744	58.3	343	55.5	.25
Female sex	558	42.5	255	42.4	…	533	41.7	275	44.5	…
Surgery	465	35.4	194	32.2	.17	449	35.2	199	32.2	.20
Malignancy	272	26.5	138	32.4	.02	264	27.2	145	31.0	.13
Neutropenia	81	7.5	58	12.6	.001	75	7.3	63	12.7	.0006
Transplantation	50	4.9	19	4.5	.73	49	5.1	20	4.3	.52
Immunosuppressive therapy	275	25.6	165	35.8	<.0001	276	26.9	158	31.9	.04
ICU	304	47.1	227	67.6	<.0001	323	25.3	204	33.0	<.0001
TPN	263	29.4	147	37.4	.004	249	29.1	157	37.7	.002
Renal dysfunction	127	10.2	92	17.3	<.0001	145	11.9	77	13.6	.29
Hepatic dysfunction	26	3.3	21	6.7	.01	25	3.3	27	6.4	.02
Mechanical ventilation	209	18.3	201	39.3	<.0001	246	22.3	159	29.8	.001
Antibiotics	366	53.3	168	49.6	.26	327	48.9	197	58.5	.004
Candida organism					<.0001[a]					.003[a]
C. albicans	587	44.7	250	41.5		562	44.0	268	43.4	
C. glabrata	142	10.8	64	10.6		142	11.1	61	10.0	
C. tropicalis	209	15.9	143	23.8		225	17.6	125	20.2	
C. krusei	24	1.8	16	2.7		21	1.6	19	3.1	
C. parapsilosis	231	17.6	68	11.3		215	16.8	77	12.5	
C. guilliermondii	19	1.4	3	0.5		17	1.3	5	0.8	
C. lusitaniae	11	0.1	7	1.2		15	1.2	3	0.5	
Other	90	6.9	51	8.5		80	6.3	60	9.7	
Therapy					.001[a]					.004[a]
Amphotericin B	159	12.1	95	15.8		171	13.4	80	12.9	
Liposomal amphotericin B	146	11.1	72	12.0		143	11.2	75	12.1	
Fluconazole	171	13.0	100	16.6		151	11.8	110	17.8	
Voriconazole	164	12.5	90	15.0		162	12.7	87	14.1	
Anidulafungin	99	7.5	29	4.8		97	7.6	31	5.0	
Caspofungin	186	14.2	63	10.5		175	13.7	72	11.7	
Micafungin	388	30.0	153	25.4		378	29.6	163	26.4	
Polyene	305	23.2	167	27.7	<.001	314	24.6	155	25.1	.81
Triazole	335	25.5	190	31.6	.005	313	24.5	197	31.9	.0007
Echinocandin	673	51.3	245	40.7	<.001	650	50.9	266	43.0	.001
CVC removal	817	62.2	317	52.6	<.001	795	78.5	334	71.6	.001
CVC retained	213	16.2	145	24.1		218	21.5	134	28.9	

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CVC, central venous catheter; ICU, intensive care unit; SD, standard deviation; TPN, total parenteral nutrition.

Unless otherwise specified data represent number of patients and percentage with the variable among those in the outcome category. Missing data for each variable can be determined by adding the number in each outcome category and subtracting from the total number of patients with outcomes for mortality (n = 1915) and success (n = 1895).

[a] χ^2 test comparing across categories.

advancing age, the presence of malignancy, neutropenia, immunosuppressive therapy, total parenteral nutrition (TPN), mechanical ventilation, and renal and hepatic dysfunction. Among the infecting *Candida* species, *C. tropicalis* was associated with higher mortality (*C. tropicalis* 41% vs other species 29%; $P < .0001$). Conversely, *C. parapsilosis* infection was associated with lower mortality than non-*parapsilosis* infection (*C. parapsilosis* 22.7 % vs other species 33.0%; $P < .001$). A comparison of patient, disease, treatment, and outcome variables across individual *Candida* species demonstrated higher APACHE II scores and more frequent neutropenia in the *C. tropicalis* subgroup (APACHE II in the

C. tropicalis subgroup, 16.4 ± 7.6 vs 14.6 ± 7.1 among other species; $P = .001$ and neutropenia in the *C. tropicalis* subgroup, 14% vs 6% among other species; $P < .0001$). Conversely, the APACHE II scores were lower for the *C. parapsilosis* subgroup compared with other species (12.8 ± 6.6 vs 15.4 ± 7.3; $P < .0001$).

With respect to antifungal regimens, patients randomized to receive an echinocandin had significantly better survival rates than those who received either a polyene or a triazole (mortality, 27% for echinocandins vs 36% for other regimens [$P < .0001$], 36% for triazoles vs 30% for other drugs [$P = .006$], and 35% for polyenes vs 30% for other drugs [$P = .04$]).

Survival was significantly better for those who underwent CVC removal during the treatment phase (mortality for CVC removal, 28% vs 41% for CVC retention; $P < .0001$). Analysis of these variables using composite success instead of mortality as the treatment end point revealed very similar associations (Table 3). In subgroup analysis, the impact of the same host-, organism-, and treatment-related variables remained statistically similar for the entire non-*albicans Candida* population as well as individual species, including *C. albicans*, *C. tropicalis*, and *C. glabrata*.

Logistic regression analysis for the aggregate data set identified increasing age (odds ratio [OR], 1.01; 95% confidence interval [CI], 1.00–1.02; $P = .02$), greater APACHE II score (OR, 1.11; 95% CI, 1.08–1.14; $P = .0001$), use of immunosuppressive therapy (OR, 1.69; 95% CI, 1.18–2.44; $P = .001$), and infection with *C. tropicalis* (OR, 1.64; 95% CI, 1.11–2.39; $P = .01$) as associated with greater mortality (Table 4). Conversely, removal of CVC at any time during treatment (OR, 0.50; 95% CI, .35–.72; $P = .0001$) and echinocandin treatment (OR, 0.65; 95% CI, .45–.94; $P = .02$) were associated with reduced mortality. A similar model was demonstrated for the *C. albicans* cohort. For the non-*albicans Candida* subgroup, only echinocandin treatment, CVC removal, and APACHE II scores remained independently associated with the mortality. For the *C. glabrata* subgroup, CVC removal continued to influence outcome. However, for *C. tropicalis* and *C. parapsilosis*, only disease severity predicted survival. Examination of the data for a study effect by inclusion of trial number into the final model did not affect analyses outcome.

Similar multivariable models were explored for the secondary composite success end point. Echinocandin therapy remained associated with increased response for the entire cohort, and for the *C. albicans* and *C. glabrata* groups. CVC removal also favorably affected response for the entire population, the non-*albicans Candida* group and for *C. tropicalis*. APACHE II scores also remained a strong predictor of response in each of these models. Additional subgroup multivariate analyses for patients with candidemia were concordant with the aggregate results. Specifically, the use of an echinocandin (OR, 0.50; 95% CI, .35–.72; $P = .0001$) and CVC removal (OR, 0.45; 95% CI, .31–.67; $P = .0001$) remained similarly protective from death.

In a sensitivity analysis, we explored whether the impact of CVC removal and antifungal drug class on outcomes was affected by other variables. We repeated multivariable analyses incorporating interaction terms between CVC removal or antifungal drug class and each of the relevant variables (based on significance in univariate analysis). We also calculated and compared the frequency of each variable's statistical significance in univariate analyses in patients with or without CVC removal and for each drug class. Furthermore, we examined the impact of CVC removal and drug class in a number of APACHE II cohorts. The impact of CVC removal was similar and significant for the lowest 3 APACHE II quartiles (Figure 1). For the highest APACHE II quartile (>34), CVC removal was not associated with improved outcome. Receipt of an echinocandin antifungal was associated with a favorable outcome in the first 2 APACHE II quartiles. For the higher quartiles (>24), drug class did not affect outcome. Incorporation of interaction terms in the multivariate models did not affect the value of either CVC removal or echinocandin therapy (data not shown).

COMMENT

IC is largely a disease of medical progress and its incidence parallels the progress in healthcare technology [2, 37, 40–42]. Despite advances in drug development [41, 43–48] the incidence

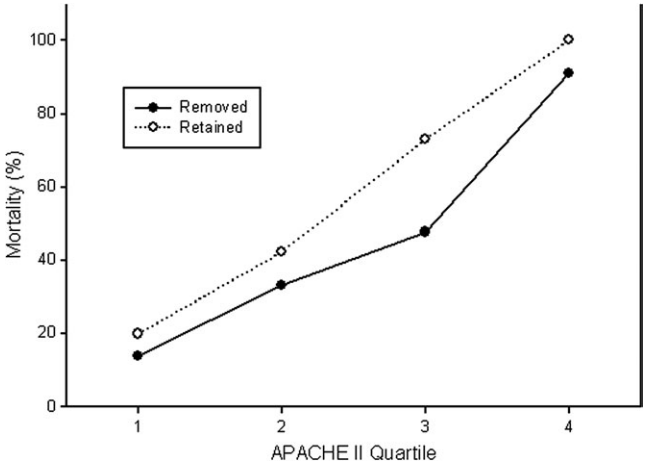

Figure 1. Impact of severity of illness and central venous catheter (CVC) management on patient mortality. Each symbol represents the mortality rate as a percentage for patients in 1 of 4 Acute Physiology and Chronic Health Evaluation (APACHE) II score quartiles: quartile 1, 0–11; 2, 12–23; 3, 24–35; and 4, 36–47. Closed symbols represent patients with CVC removal; open symbols, patients with CVC retention. Differences in mortality were statistically significant for quartiles 1, 2, and 3 (quartile 1, $P = .05$; 2, $P = .01$; 3, $P = .002$; and 4, $P = .41$).

Table 4. Multivariate Analysis of Host, Disease, and Treatment Factors and Outcome in Patients With Invasive Candidiasis

	Mortality				Success		
Organisms[a]	Factor	*P*	OR	95% CI	Factor	*P*	OR	95% CI
All organisms (n = 978)	Age	.02	1.01	1.00–1.02	APACHE II	.0001	0.94	.93–.96
	APACHE II score	.0001	1.11	1.08–1.14	Echinocandin	.01	2.33	1.27–4.35
	Immunosuppressive therapy	.001	1.69	1.18–2.44	CVC removed	.001	1.69	1.23–2.33
	Candida tropicalis	.01	1.64	1.11–2.39	Study	NS		
	Echinocandin	.02	0.65	.45–.94				
	CVC removed	.0001	0.50	.35–.72				
	Study	NS						
Candida albicans (n = 408)	APACHE II score	.0001	1.09	1.05–1.13	APACHE II score	.005	0.92	.92–.99
	Immunosuppressive therapy	.002	2.22	1.30–3.70	Echinocandin	.005	3.70	1.49–9.09
	Surgery	.05	0.58	.34–.98	Study	NS		
	Malignancy	.03	1.89	1.05–3.45				
	Echinocandin	.03	0.55	.32–.95				
	CVC removed	.01	0.52	.31–.90				
	Study	NS						
Non-*albicans* species (n = 570)	APACHE II score	.0001	1.14	1.1–1.17	Age	.004	1.02	1.01–1.03
	Echinocandin	.04	0.52	.36–.78	APACHE II score	.0001	0.93	.91–.96
	CVC removed	.05	0.69	.48–.98	CVC removed	.007	1.74	1.16–2.61
	Study	NS			Study	NS		
Candida glabrata (n = 104)	CVC removed	.001	0.13	.04–.45	APACHE II score	.05	0.95	.90–.99
	Study	NS			Echinocandin	.05	2.63	1.10–625
					Study	NS		
Candida tropicalis[b]	APACHE II score	.0001	1.13	1.08–1.18	Age	.04	0.98	.96–.99
	Study	NS			APACHE II score	.0001	0.93	.89–.96
					CVC removed	.02	1.97	1.10–3.52
					Study	NS		
Candida parapsilosis[c]	APACHE II score	.001	1.11	1.04–1.19	APACHE II score	.01	0.95	.90–.99
	ICU admission	.02	2.63	1.12–6.25	Study	NS		
	Study	NS						

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; CVC, central venous catheter; ICU, intensive care unit; NS, not significant ($P > .05$); OR, odds ratio; Study = individual study publication.

[a] Parenthetical numbers represent number of individuals available for each model.

[b] For *Candida tropicalis,* n = 262 for analysis of mortality and 261 for analysis of success.

[c] For *Candida parapsilosis,* n = 158 for analysis of mortality and 212 for analysis of success.

and mortality associated with IC have not changed substantially in the last 2 decades [12, 13]. Thus, a great deal of investigation and the goal of the current study has centered on identification of treatment factors to improve management of IC. Previous retrospective analyses have demonstrated that early administration of antifungal drug and removal of CVCs in candidemia improve outcome [34, 42, 50–56].

Our analysis identified 2 modifiable management strategies to improve patient outcomes. The first was the identification of optimal antifungal therapy. Use of an echinocandin was associated with reduced mortality compared with use of a drug from either the triazole or polyene classes. Comparative trials designed to assess superiority of one antifungal class over another for treatment of IC are unavailable and barring development of new antifungals, are unlikely to be undertaken in the future. Study level meta-analyses have corroborated the findings of the individual trials but have not yielded additional knowledge. [57, 58]. For example, they identified significantly greater toxicity associated with amphotericin B than triazole or echinocandin therapy but, not any differences in efficacy. The pooled analysis of individual patient-level data may, however, discern the impact of treatment strategies and take into account potentially confounding influences, such as host- and organism-related factors [59]. From this quantitative review, we identified that echinocandin therapy was associated with reduced mortality.

These findings support recent treatment guidelines that recommend an echinocandin as a first-line choice for IC [44], particularly for the critically ill, those with prior triazole exposure, and those infected with less susceptible *Candida* spp such as *C. glabrata* and *C. krusei*. Our results support an expansion of these first-line recommendations to most patients with IC and candidemia. Notably, the superiority of the echinocandin class was evident among patients with a wide range of severity of illness (up to an APACHE II score of 24) and for both *C. albicans* and non-*albicans* groups. The species for which an echinocandin appeared least effective in univariate analysis was *C. parapsilosis*. This previously described observation is not surprising, given the higher minimum inhibitory concentrations of echinocandins with *C. parapsilosis*. However, that higher mortality has not been definitively demonstrated for *C. parapsilosis* when treated with an echinocandin in these trials, which in the current analysis may be explainable by the organisms's relatively lower virulence [18, 42, 44].

The second observation from our analyses involves management of CVCs. Numerous studies have identified intravascular catheters as a risk factor for candidemia. Catheters, like other medical devices, can serve as a substrate for *Candida* biofilm infection, which exhibits a drug-resistant phenotype [60, 61], necessitating biofilm extirpation for treatment success [62, 63]. Retrospective analyses, with their inherent limitations, have demonstrated that CVC removal can shorten the duration of candidemia and enhance the likelihood of survival. Many investigations have been unable to control for other disease variables, most importantly severity of illness (eg, APACHE II). In several of the studies in which CVC removal was found to improve outcome, APACHE II scores were higher in the cohort for which the devices were retained [11, 55, 64–66], perhaps because of the critical need of CVCs for therapy or the hesitancy of clinicians to expose some patients to the risk associated with device replacement. In addition, a recent analysis demonstrated that early CVC removal did not influence outcome [66]. Despite the limitations of available studies, consensus guidelines support removal of vascular catheters, when feasible, in nonneutropenic patients with candidemia [44, 52]. In the current investigation CVC removal was not randomized and specific data regarding the exact timing of CVC removal were not available for all patients. Therefore, we could not explore the impact of early CVC removal on the outcome. However, our analysis does attempt to account for other patient and disease variables that affect patient outcome in IC. We did not identify a preponderance of these factors in either the CVC removal or CVC retention cohorts. Furthermore, interaction analyses in multivariable modeling were not statistically significant. Interestingly, in analysis of the impact of severity of illness, we identified an APACHE II group for which CVC removal was not helpful. However, for patients with scores in this range (>30), very few treatments of any type rescue patients from death. In the absence of a randomized trial of early CVC removal versus retention, it is likely this component of management will remain controversial.

Several limitations in our analysis merit mention. First, these trials often exclude patients who fall into the extremes of the clinical spectrum, such as those who are ambulatory and only mildly ill and those who are immunocompromised and/or severely ill. Tangible evidence of this difference is clear in comparison of APACHE II scores and mortality rates in retrospective and randomized treatment trials. Thus, caution must be exercised in extrapolation of the observations for all patients. Second, there are important, management and outcome questions that we are unable to address. For example, the trials excluded or provided limited information in several populations for which IC is important, including neonates and patients with neutropenia. In addition, the data are insufficient to address critical issues regarding prior antifungal therapy, the specific timing of antifungal administration, and CVC removal relative to IC diagnosis. Available data permitted only assessment of all-cause mortality and not that attributable to IC or other outcomes of importance, such as duration of candidemia and relapse. Furthermore, because these studies were undertaken during a 15-year period, the standard of care may have changed. However, the APACHE II scores and overall mortality throughout the study period were remarkably similar.

These limitations notwithstanding, the strengths of these observations warrant consideration. This is the largest patient-level quantitative review undertaken for this important and emerging infectious disease. The results extend those of previous investigations including the identification of numerous host and disease state variables that affect the outcome of IC. However, host and disease state factors are often immutable. The most important finding from the current study is demonstration of 2 management strategies that were associated with improved survival (>10%). First, the findings lend support for the hypothesis that CVC retention has a negative impact on outcome in patients with candidemia. The second observation identified a choice of an antifungal from the echinocandin drug class as optimal for patient survival and patient success. In contrast to the current guidelines, the findings of our analysis suggest that this drug choice should be considered as initial therapy for most patient groups and not only those with severe illness, immunocompromised status, or suspected infection with a non-*albicans Candida* species.

Notes

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