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MAJOR ARTICLE

Impact of Infectious Disease Consultation in Patients With Candidemia: A Retrospective Study, Systematic Literature Review, and Meta-analysis

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Background. Morbidity and mortality from candidemia remain unacceptably high. While infectious disease consultation (IDC) is known to lower the mortality from *Staphylococcus aureus* bacteremia, little is known about the impact of IDC in candidemia.

Methods. We conducted a retrospective observational cohort study of candidemia patients at a large tertiary care hospital between 2015 and 2019. The crude mortality rate was compared between those with IDC and without IDC. Then, we systematically searched 5 databases through February 2020 and performed a meta-analysis of the impact of IDC on the mortality of patients with candidemia.

Results. A total of 151 patients met the inclusion criteria, 129 (85%) of whom received IDC. Thirty-day and 90-day mortality rates were significantly lower in the IDC group (18% vs 50%; $P = .002$; 23% vs 50%; $P = .0022$, respectively). A systematic literature review returned 216 reports, of which 13 studies including the present report fulfilled the inclusion criteria. Among the 13 studies with a total of 3582 patients, IDC was performed in 50% of patients. Overall mortality was 38.2% with a significant difference in favor of the IDC group (28.4% vs 47.6%), with a pooled relative risk of 0.41 (95% CI, 0.35–0.49). Ophthalmology referral, echocardiogram, and central line removal were performed more frequently among patients receiving IDC.

Conclusions. This study is the first systematic literature review and meta-analysis to evaluate the association between IDC and candidemia mortality. IDC was associated with significantly lower mortality and should be considered in all patients with candidemia.

Keywords. candidemia; *Candida* bloodstream infection; infectious disease consultation; mortality.

Candida species are the most common cause of fungal bloodstream infection, with a crude mortality rate of ~35% [1, 2]. Clinical practice guidelines from the Infectious Disease Society of America (IDSA) and the European Society of Clinical Microbiology and Infectious Diseases provide evidence-based recommendations for the management of patients with candidemia [3, 4]. While a delay in treatment can increase mortality, adherence to these guideline recommendations is associated with lower mortality in patients with candidemia [5–7]. Recent studies suggest that patients with candidemia receiving an infectious disease consultation (IDC) have lower mortality, compared with those without IDC [8, 9]. However, these reports were single-center studies, and many had small sample sizes, limiting the generalizability of the findings. Therefore, we aimed to add to the existing evidence base with a new retrospective cohort study at our institution, and then by performing a systematic literature review and meta-analysis to evaluate the impact of IDC on mortality in patients with candidemia.

METHODS

Study Design

A retrospective, observational cohort study was conducted at The University of Iowa Hospitals and Clinics (UIHC), an 811-bed academic hospital located in Iowa City, Iowa. All patients aged ≥18 years with blood cultures positive for *Candida* species from January 1, 2015, to November 31, 2019, were included. We only included the first episode of candidemia. Exclusion criteria were death or transfer to the palliative care unit within 48 hours from the time cultures became positive. IDC included chart review, physical examination of the patient, and written recommendations for therapy based on published IDSA guidelines and expert opinion [3]. Data collected included demographics,

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comorbidities, the involvement of an ID specialist (IDC), microbiology data, source of the infection, ophthalmological examination, removal of central venous catheter (CVC) if it was the likely source, transthoracic or esophageal echocardiogram, length of hospital stay (LOS), and treatment duration. Recent chemotherapy and recent abdominal surgery were defined as <3 months from the positive blood culture. The primary outcome was 90-day mortality. Secondary outcomes were overall in-hospital mortality and 30-day mortality. The primary source of candidemia was determined through chart review. The chart review was performed by T.K. This study was approved by the Institutional Review Board at the UIHC.

Search Strategy and Selection Criteria for the Systematic Literature Review

A systematic literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [10] and the Meta-Analysis Of Observational Studies in Epidemiology (MOOSE) guidelines [11]. The study protocol has been approved by the International Prospective Register for Systematic Reviews (PROSPERO) database (CRD42020156939). The searches were developed and conducted by a health sciences librarian (H.H.). Search strategies employing subject headings and keywords were created for Ovid MEDLINE, Embase (Elsevier), CINAHL (EBSCOhost), Scopus (Elsevier), and Cochrane CENTRAL (Wiley). The Ovid MEDLINE strategy was peer-reviewed by another health sciences librarian. That strategy was translated to the other databases (Supplementary Table 1). The searches were conducted on March 3, 2020. No date limitations were applied. The results in Ovid MEDLINE and Embase were limited to studies in English. All database results were exported to EndNote and de-duplicated [12]. Inclusion criteria were as follows: (1) original research manuscripts (ie, randomized control trials, cross-sectional, case–control, and cohort studies); (2) published in English; (3) assessed impact of IDC on mortality in patients with *Candida* bloodstream infection. Exclusion criteria were as follows: (1) studies including only children; (2) editorials and commentaries; (3) animal studies. All potentially relevant studies collected by H.H. were screened by T.K.

Data Abstraction and Quality Assessment

Two independent reviewers (T.K. and A.R.M.) abstracted data from the included studies using a standardized abstraction form, and a third (M.A.) arbitrated discrepancies. The following data were collected from each study: study design, study period, population characteristics, source of candidemia, *Candida* species, proportion of ICD, proportion of ophthalmology consultation, proportion of echocardiogram performed, proportion of CVC removal, and mortality.

We used the Downs and Black scale to evaluate study quality [13]. Each reviewed paper was assessed and the total score calculated. All questions were answered as intended except for question #27 (a single item on the Power subscale, which was scored 0 to 5), which we changed to a yes/no answer. The 2 reviewers performed component quality analysis independently, reviewed all inconsistent assessments, and achieved consensus by discussion.

Statistical Analysis

Continuous variables were shown as the mean ± SD and compared using the Student *t* test or Mann-Whitney *U* test. Categorical variables were shown as absolute and relative frequencies and compared using Pearson's χ^2 test or the Fisher exact test. We compared demographic characteristics, clinical factors, and outcomes between episodes with and without IDC. We started by fitting a saturated logistic regression model to create the propensity score for the dependent variable receipt of IDC. All potential predictors of IDC or mortality were included as independent variables. The propensity scores were added to the rest of the analysis data set for our next set of models. Multivariable survival analysis with Cox hazards models was performed, and a predictive model for 90-day all-cause mortality was built with inverse weighting by the propensity score. IDC was analyzed as a time-dependent variable, as the time of consultation was not fixed across subjects. We screened potential predictive factors, considering those with a *P* value of <.10 in the univariate analysis for inclusion in the multivariate model. A *P* value <.05 was considered significant, and all reported *P* values are 2-tailed for multivariate models.

We included our observational study in this meta-analysis as the Iowa Study. To meta-analyze the extracted data, all-cause mortality was assessed using a random-effects model to estimate the pooled odds ratio (OR) and 95% confidence interval with inverse variant weights as described by DerSimonian and Laird [14]. We performed stratified analyses by definition of mortality (28–42- and 90-day morality). We also evaluated the associations between ICD and rate of ophthalmology consult and echocardiogram order. Heterogeneity between studies was evaluated with I^2 estimation and the Cochran Q statistic test. We used the Cochrane Review Manager, version 5.3. Publication bias was assessed using a funnel plot.

RESULTS

Retrospective Cohort Study

We identified 194 patients who had candidemia at UIHC during the study period. Forty-three patients were excluded; 19 patients were <18 years old, and 24 patients either died or were transferred to the palliative care unit within 48 hours after the blood culture became positive. A total of 151 patients met the criteria for study inclusion. One hundred twenty-nine patients (85%) received IDC, and 22 (15%) did not. Baseline characteristics including patient demographics, comorbidities, and *Candida* species were similar between groups except for the source of

candidemia (Table 1). Though the most common source was CVC-associated infection in both groups, the second most common source was a "gastrointestinal issue" in the IDC group and "unknown" in the non-IDC group ($P = .013$). Patients who received IDC were significantly more likely to have ophthalmological examination (88% vs 27%; $P < .001$) and echocardiogram performed (60% vs 36%; $P = .015$). Of patients with CVCs, those in the IDC group were more likely to have their CVC removed (95% vs 56%; $P < .001$). In-hospital, 30-day, and 90-day mortality rates were significantly lower in the IDC group (20% vs 46%; $P = .015$; 18% vs 50%; $P = .002$; 25% vs 50%; $P = .022$, respectively). There was no difference in overall LOS (mean, 31 vs 23 days; $P = .31$), treatment duration (mean, 27 vs 10 days; $P = .063$), or evidence of endophthalmitis (5% vs 0%; $P = .6$), respectively. In multivariable analysis (Table 2), IDC was significantly associated with lower 90-day mortality (adjusted hazard ratio [HR], 0.27; 95% CI, 0.16–0.46; $P < .001$).

Systematic Review Study Selection

A flowchart outlining our article selection is shown in Figure 1. We identified 344 publications from the initial database searches. After the removal of duplicate studies, 216 articles were screened by titles and abstracts, of which 36 studies were identified for full-text review. Twelve studies published between 2005 and 2019 met our inclusion criteria [7–9, 15–23]. We added our retrospective cohort study as the 13th study (Iowa Study). All 13 studies combined had a total of 3582 patients (Table 3). This included 1789/3582 (50%) patients with IDC and 1793/3582 (50%) controls without IDC.

Study Characteristics

All included studies were retrospective single-center cohort studies. Most studies were conducted in the United States (n = 9) [7, 8, 15, 16, 19–22], followed by Japan (n = 2) [9, 18], Italy (n = 1) [17], and Germany (n = 1) [23]. The number of enrolled patients in each study ranged from 40 to 1691. The mean or median age ranged from 52 to 70 years. The proportion of male patients ranged between 43% to 69%. IDC was performed in 28% to 88% of patients. *Candida* species identification was available in 12 studies. *C. albicans* was the most common pathogen in all studies except for 1 study of patients with only *C. glabrata* fungemia [16] and 1 study of patients with CVC-associated bloodstream infection [22]. The source of candidemia was described in 4 studies (not including a study by John et al. focusing only on CVC-associated bloodstream infection), and CVC-associated bloodstream infection was the most common source [8, 9]. Seven studies evaluated 30-day mortality [8, 9, 17, 18, 20, 22], 5 studies evaluated 90-day mortality [9, 15, 19, 21], 2 studies evaluated 42-day mortality [7, 15], 1 study evaluated 60-day mortality [8], 1 study evaluated 28-day mortality [16], and 1 study did not specify the time frame for mortality [23]. The mortality rate was lower in patients with IDC compared with non-IDC in all 13 studies (Table 3). When we assessed the quality of the included studies, we found that 12 studies scored ≥17 on the 28-point quality assessment checklist and 1 study scored 16.

Meta-analysis

Three studies included in the systematic review were excluded from meta-analysis because of unclear mortality numbers depending on IDC [20, 22] or an unknown time frame for mortality [23]. Ten studies were included in the meta-analysis [7–9, 15–19, 21]. The overall mortality rate within 28–90 days was 38.2% (1156/3025). There was a significant difference in favor of the IDC group with 28.4% mortality, vs 47.6% in the control group ($P < .001$). The pooled odds ratio (OR) was 0.41 (95% CI, 0.35–0.49), as shown in the forest plot (Figure 2). After performing a stratified analysis, we observed a similar trend in 28–42-day mortality (OR, 0.39; 95% CI, 0.27–0.56) and 90-day mortality (OR, 0.45; 95% CI, 0.33–0.60). Rates of ophthalmological examination were documented in 6 studies [8, 9, 15, 21, 23]. Ophthalmology consults were placed more frequently in the IDC group (62%; 790/1279) compared with the control group (21%; 273/1304). The pooled OR was 6.1 (95% CI, 4.61–8.07) (Figure 3A). Rates of echocardiogram were documented in 5 studies [8, 9, 15, 23]. Echocardiograms were performed more frequently in the IDC group (54%; 662/1219) compared with the control group (28%; 369/1296). The pooled OR was 3.01 (95% CI, 2.10–4.33) (Figure 3B). Rates of CVC removal were documented in 5 articles [8, 9, 15, 18]. CVC removal was performed more frequently in the IDC group (78%; 830/1069) compared with the control group (61%; 686/1116). The pooled OR was 3.27 (95% CI, 1.23–8.69) (Figure 3C).

Heterogeneity

The between-study heterogeneity varied according to the different outcome analyses. We calculated low heterogeneity for overall mortality, ophthalmology consult, and echocardiogram order with I^2 estimates of 3%, 26%, and 38%, respectively. Heterogeneity in CVC removal was high, with an I^2 estimate of 87%.

Publication Bias

There was no publication bias seen in the funnel plot (Supplementary Figure 1).

DISCUSSION

Our retrospective observational cohort study revealed that IDC was associated with lower mortality in patients with candidemia. Our systematic literature review demonstrated that the rate of IDC varied significantly across institutions, and our meta-analysis confirmed that IDC was associated with a

Table 1. Baseline Characteristics, Impact of Management, and Clinical Outcomes in Patients With Candidemia

Characteristic	No IDC (n = 22)	IDC (n = 129)	*P* Value
Demographics			
Age, mean (SD), y	58.8 (16.6)	54.5 (15.5)	.24
Male sex	13 (59.1)	69 (53.5)	.65
Injection drug user	1 (4.5)	7 (5.4)	.9
Comorbidities			
Alcoholic	3 (13.6)	10 (7.8)	.41
Transplant	1 (4.5)	10 (7.8)	.9
Morbid obesity	3 (13.6)	19 (14.7)	.9
HIV	0	1(0.8)	.9
Chronic kidney disease	5 (22.7)	27 (20.9)	.78
Hepatitis	2 (9.1)	8 (6.2)	.64
Cirrhosis	2(9.1)	12 (9.4)	.9
Coronary artery disease	5 (22.7)	21 (16.3)	.54
Hypertension	10 (45.5)	64 (49.6)	.82
Heart failure	2 (9.1)	19 (14.7)	.74
Type 2 diabetes mellitus	4 (18.2)	41 (31.8)	.31
Autoimmune disease	1 (4.5)	15 (11.6)	.47
Malignancy	7 (31.8)	52 (40.3)	.49
Recent chemotherapy	1 (4.5)	23 (17.8)	.20
Recent abdominal surgery	5 (22.7)	36 (27.9)	.8
Total parental nutrition	6 (27.3)	26 (20.2)	.57
Central line present >2 d	16 (72.7)	84 (65.1)	.63
Candida species			
C. albicans	12 (54.5)	55 (42.6)	.36
C. glabrata	6 (27.3)	47 (36.4)	.48
C. parapsilosis	3 (13.6)	16 (12.4)	.9
C. tropicalis	2 (9.1)	8 (6.2)	.64
C. krusei	0	4 (3.1)	.9
Other	1 (4.5)	7 (5.4)	.9
Primary source			
Line	9 (40.9)	63 (48.8)	.013
Gastrointestinal issue	4 (18.2)	26 (20.2)	
Urinary	1 (4.5)	21(16.3)	
Unknown	7 (31.8)	6 (4.7)	
Endocarditis	0	7 (5.4)	
Bone and joint	0	3 (2.3)	
Skin and soft tissue	1 (4.5)	1 (0.8)	
IVDU	0	1 (0.8)	
LVAD	0	1 (0.8)	
Clinical management			
Removal of catheter[a]	9 (56.2)	80 (95.2)	<.001
Echocardiogram performed	8 (36.4)	77 (59.7)	.061
Ophthalmologic examination	6 (27.3)	114 (88.4)	<.001
Evidence of eye disease	0	6 (4.7)	.59
Treatment duration, mean (SD), d	9.5 (6.1)	27.0 (43.7)	.063
Clinical outcomes			
In-hospital mortality	10 (45.5)	26 (20.2)	.015
30-d mortality	11 (50.0)	23 (17.8)	.002
90-d mortality	11 (50.0)	32 (24.8)	.022
LOS, mean (SD), d	23.0 (21.7)	30.7 (34.3)	.31

Data are presented as No. (%) unless otherwise presented.

[a]Within patients who had a central line catheter.

Abbreviations: IDC, infectious disease consult; IVDU, intravenous drug use; LOS, length of stay; LVAD, left ventricular assist device.

substantial (59%) reduction in all-cause mortality. Importantly, patients with candidemia receiving IDC had more ophthalmic exams, echocardiograms, and CVC removals.

While improvement in the mortality associated with IDC is likely multifactorial, the most likely explanations are that ID physicians optimize antifungal prescribing, facilitate earlier

Table 2. Propensity Score–Weighted Factors Associated With 90-Day Mortality in Patients With *Candida* Bloodstream Infection Accounting for Time-Dependent IDC (Iowa Study)

	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age	1.04 (1.02–1.05)	<.0001	1.05 (1.02–1.07)	<.0001
Male sex	0.31 (0.20–0.48)	<.0001	0.52 (0.30–0.9)	.0194
Injection drug user	0.21 (0.03–1.39)	.1049		
Alcoholic	0.36 (0.12–1.07)	.0666	1.66 (0.39–7.12)	.4923
Transplant	0.29 (0.07–1.13)	.0738	0.67 (0.16–2.91)	.5944
Morbid obesity	0.37 (0.16–0.87)	.0226	0.88 (0.33–2.35)	.8040
HIV	N/A			
Chronic kidney disease	0.67 (0.42–1.06)	.088	0.95 (0.53–1.71)	.8586
Hepatitis	0.17 (0.03–0.97)	.0463	0.24 (0.03–2.08)	.1949
Cirrhosis	2.23 (1.59–3.13)	<.0001	1.88 (0.81–4.35)	.1409
Coronary artery disease	0.79 (0.46–1.36)	.3988		
Hypertension	1.07 (0.77–1.48)	.7047		
Heart failure	0.78 (0.41–1.48)	.4543		
Type 2 diabetes mellitus	0.74 (0.49–1.12)	.1524		
Autoimmune disease	0.40 (0.16–1.00)	.0489	0.89 (0.30–2.64)	.8300
Malignancy	3.54 (2.43–5.15)	<.0001	0.78 (0.38–1.62)	.5084
Recent chemotherapy	3.21 (2.24–4.58)	<.0001	7.56 (3.37–16.93)	<.0001
Recent abdominal surgery	1.21 (0.87–1.68)	.2623		
Total parental nutrition	0.28 (0.15–0.53)	<.0001	1.38 (0.64–3.01)	.4124
Central line present >2 d	0.77 (0.55–1.06)	.1084		
C. albicans	1.29 (0.93–1.79)	.1249		
C. glabrata	3.86 (2.64–5.64)	<.0001	2.32 (1.34–3.99)	.0025
C. parapsilosis	0.17 (0.07–0.45)	.0004	0.27 (0.09–0.78)	.0156
C. tropicalis	0.37 (0.10–1.33)	.1272		
C. krusei	0.48 (0.07–3.46)	.4689		
Catheter-related infection	0.76 (0.54–1.07)	.1151		
Removal of catheter	0.76 (0.55–1.05)	.1002		
Echocardiogram performed	0.59 (0.43–0.84)	.0027	2.05 (1.07–3.96)	.0316
Ophthalmologic examination	1.31 (0.82–2.09)	.2539		
Evidence of eye disease	0.64 (0.16–2.57)	.5254		
IDC	0.25 (0.17–0.36)	<.0001	0.27 (0.16–0.46)	<.0001

Abbreviations: HR, hazard ratio; IDC, infectious disease consultation.

identification and control of infectious sources, and recommend removal of central lines. Farmakiotis et al. recently reported that the mortality associated with candidemia decreases with early initiation of appropriate therapy in patients with *C. glabrata* [16]. Another study by Takakura et al. has shown higher rates of appropriate empiric therapy in patients with IDC, compared with those without IDC [18]. Although we did not evaluate the selection of antifungal medication or timing of appropriate therapy, both likely contribute to the better outcomes associated with IDC.

CVC removal was also more frequent in patients with candidemia who were followed by ID, compared with those who were not, in our retrospective observation study and in the meta-analysis. IDSA guidelines recommend removal of CVC if it is suspected to be the source of candidemia, and previous studies have demonstrated CVC removal to be associated with lower mortality in patients with candidemia [24, 25]. Nevertheless, 1 meta-analysis demonstrated no survival benefit from CVC removal [26]. In addition, considerable heterogeneity in the association between IDC and CVC removal was present in our meta-analysis as well. Interestingly, our retrospective study found that the source of candidemia was not detected or clearly addressed in 32% of the non-IDC group and 5% of the IDC group. Furthermore, treatment duration was shorter in the non-IDC group, although this difference did not reach statistical significance. It is possible that lack of identification and/or control of the source of candidemia, especially when CVC-related, along with shorter treatment duration, may explain the higher mortality rate in patients with candidemia who did not receive IDC.

We also demonstrate that IDC was associated with an increased likelihood of ophthalmology referral in our observational study. The meta-analysis revealed that the IDC group was 6 times more likely to receive ophthalmological examination, with low heterogeneity. According to IDSA guidelines, ophthalmological examination is recommended for all non-neutropenic patients with candidemia [3]. The

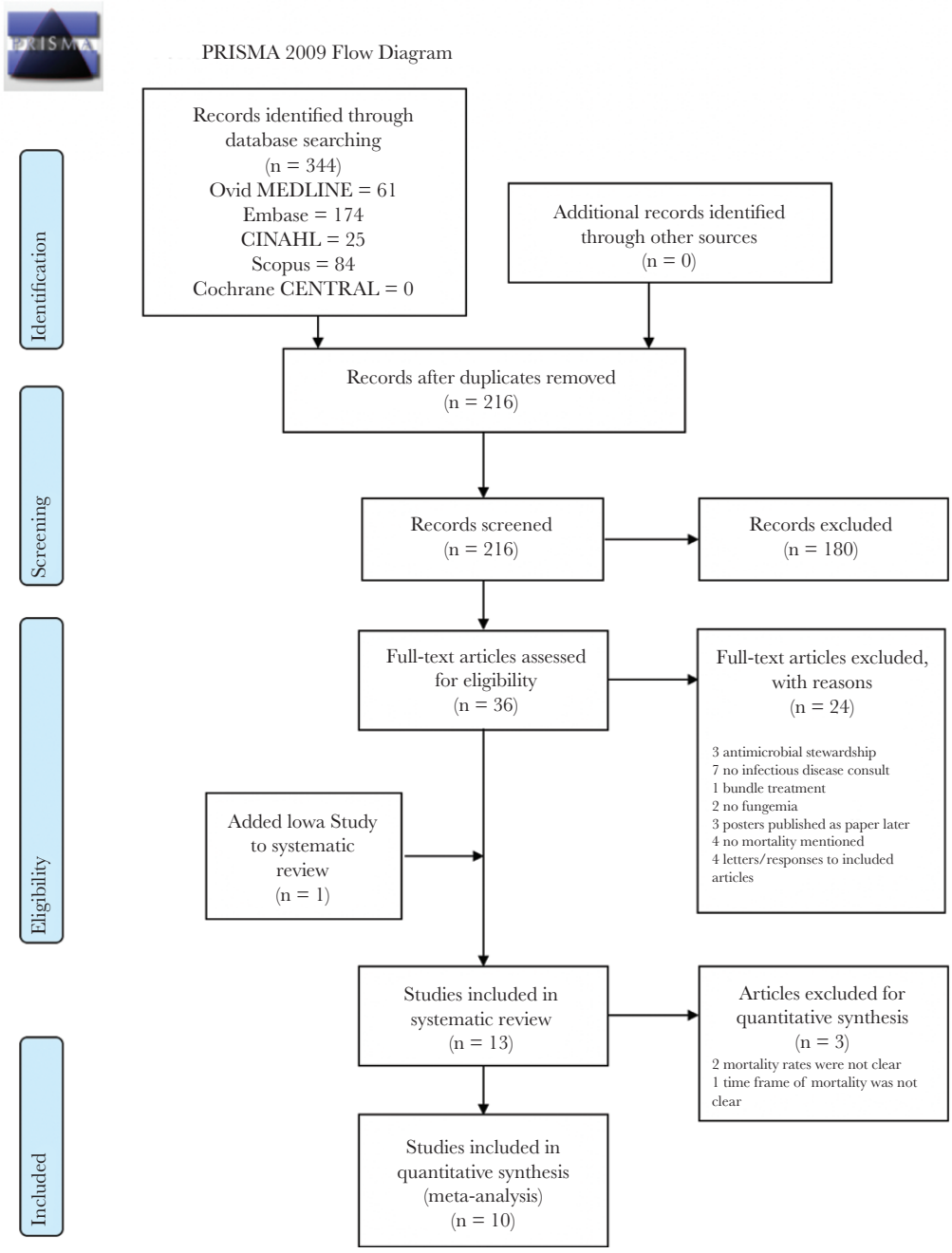


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2009 flow diagram.

evaluation for endophthalmitis contributes to an appropriate choice and duration of antifungal therapy. While not statistically significant in our observational study, the proportion of endophthalmitis was higher in the IDC group than the non-IDC group (4.6% vs 0%). Taken together, these findings suggest that IDC may lead to more diagnoses of endophthalmitis.

Candidemia patients who receive IDC also have an increased likelihood of echocardiogram performed when compared with those in whom IDC is not obtained. In our retrospective cohort study, the rate of endocarditis was similar between patients with and without IDC (0% vs 5.3%), and the overall rate of endocarditis (4.6%) was similar to a previous finding of 4.2% [27]. Our chart review showed that echocardiograms were also frequently done in those without IDC for evaluation of hypotension and not specifically for ruling out infective endocarditis (36.4% in the non-IDC group vs 59.7% in the IDC group). The meta-analysis demonstrated that the IDC group was 3 times more likely to have an echocardiogram with relatively low heterogeneity. Identifying patients with more severe infection such

Table 3. Summary of Study Characteristics

First Author/ Year	Study Design, Period, Region	No.	Age	Male Gender	Patient Population	*Candida* Speciation	Source of Candidemia	Rate of IDC	Rates of Eye Exam	Rates of ECHO	Rate of CL Removal	Mortality in Patients With IDC and Without IDC	D & B Score
Amado et al. 2017 [19]	Retrospective single-center study, 2008–2013, USA	163	Mean, 58 y	59.5%	TPN 20%, malignancy 27%, diabetes 17%, abdominal surgery 14%	*C. albicans* (35%), *C. parapsilosis* (30%), *C. glabrata* (19%), *C. tropicalis* (9%), *C. krusei* (3%), other (4%)	n/a	124/163 (76%)	n/a	n/a	n/a	90-d mortality available in 124 patients; 38/88 (43%) vs 22/36 (61%)	17
Babazadeh et al. 2013 [20]	Retrospective single-center study, 2007–2012, USA	181	n/a	n/a	APACHE-II scores were 16.2 in IDC and 15.6 in non-IDC	n/a	n/a	136/181 (75%)	n/a	n/a	89% vs 54%	30-d mortality; "IDC was associated with lower morality when controlling for APACHE score" (HR, 0.5.; 95% CI 0.27–0.92; $P = .026$)	18
Chesdachiai et al. 2020 [21]	Retrospective single-center study, 2016–2018, USA	68	n/a	n/a	n/a	*C. albicans* 38%, *C. glabrata* 34%, *C. parapsilosis* 15%, other 13%	n/a	60/68 (88.2%)	42/60 (70%) vs 3/8 (38%)	"IDC was associated with obtaining echo $P = .005$"	n/a	90-d mortality 21/60 (35%) vs 5/8 (63%)	18
Farmakiotis et al. 2014 [16]	Retrospective single-center study, 2005–2013, USA	146	Mean, 55 y	51%	Solid tumor 68%, hematological malignancy 32%, diabetes 16%, CKD 16%, liver disease 12%, abdominal surgery 18%, TPN 25%	*C. glabrata* 100%	n/a	58/146 (40%)	n/a	n/a	n/a	28-d mortality 19/58 (33%) vs 39/88 (44%)	22
Ishikane et al. 2019 [9]	Retrospective single-center study, 2002–2013, Japan	275	Mean, 70 y	68.6%	HIV 7.1%, transplant 2.4%, diabetes 28.6%, solid organ cancer 33.3%, hematological malignancy 10.3%, CKD 7.9%, liver disease 2.4%	*C. albicans* 49%, *C. glabrata* 23%, *C. parapsilosis* 17%, *C. tropicalis* 10%, others 6%	Within patients with IDC central line–associated infection 78%, peripheral line–associated 12%, intra-abdominal 5%, unknown 5%	126/275 (44.5%)	98/126 (77.8%) vs 54/157 (34.4%)	TTE 22/126 (17.5%) vs 1/157 (0.6%)	86/126 (68%) vs 120/157 (76%)	30-d mortality 23/126 (18%) vs 44/157 (28%), 90-d mortality 41/126 (33%) vs 64/157 (41%)	24
John et al. 2017 [22]	Retrospective single-center study, 2011–2016, USA	82	Median age of pediatric patients, 2.25 y; median age of adult patients, 59 y	n/a	n/a	*C. albicans* 32%, *C. glabrata* 40%, *C. parapsilosis* 9%, other 19%	Cather-associated bloodstream infection	56/82 (68%)	n/a	n/a	n/a	30-d mortality; "patients with IDC who received standard of care had lower morality compared with those who did not (35% vs 67%; $P = .03$)"	16
Lee et al. 2019 [8]	Retrospective single-center study, 2015–2016, USA	145	Median, 57 y	59%	HIV 2%, malignancy 24%, diabetes 30%, CKD 16%, cirrhosis 6%	*C. albicans* 42%, *C. glabrata* 23%, *C. krusei* 3%, *C. parapsilosis* 19%, *C. tropicalis* 8%	Catheter 58%, skin and soft tissue 9%, bone and joint 3%, endocarditis 5%, prosthetic material 2%, intra-abdominal 11%, other 6%, unknown 6%	111/145 (77%)	72/111 (65%) vs 10/34 (29%)	84/111 (76%) vs 18/34 (53%)	57 /62 (92%) vs 6/12 (50%)	30-d mortality 22/111 (20%) vs 17/34 (50%), 60-d mortality 27/111 (24%) vs 20/34 (59%)	22

Table 3. Continued

First Author/ Year	Study Design, Period, Region	No.	Age	Male Gender	Patient Population	*Candida* Speciation	Source of Candidemia	Rate of IDC	Rates of Eye Exam	Rates of ECHO	Rate of CL Removal	Mortality in Patients With IDC and Without IDC	D & B Score
Meija-Chew et al. 2019 [15]	Retrospective single-center study, 2002–2015, USA	1691	Mean, 56.2 y	53%	Diabetes 24%, CKD 18%, liver disease 6%, solid tumors 33%, hematological malignancy 14%, bone marrow transplant 1%, solid organ transplant 1%	*C. albicans* 48%, *C. glabrata* 20%, *C. parapsilosis* 15%, *C. tropicalis* 7%, *C. krusei* 3%, other 9%	n/a	776/1691 (45.9%)	412/776 (53%) vs 160/915 (17%)	Any echo 442/776 (57%) vs 305/915 (33%)	587/776 (76%) vs 538/915 (59%)	6-wk mortality 173/776 (22%) vs 431/915 (47%), 90-d morality 222/776 (29%) vs 468/915 (51%)	21
Menichetti et al. 2018 [17]	Retrospective single-center study, 2012–2014, Itary	276	Age >65, 61%	43%	n/a	*C. albicans* 51%, *C. parapsilosis* 25%, *C. glabrata* 11%, *C. tropicalis* 7%, *C. krusei* 1%, other 1%	n/a	76/276 (27.5%)	n/a	n/a	n/a	30-d mortality 15/76 (20%) vs 73/200 (37%)	20
Mohr et al. 2020 [23]	Retrospective single-center study, 2006–2008 and 2016–2018, Germany	245	59 in 2006–2008, 63 in 2016–2018	62% in 2006–2008, 62% in 2016–2018	n/a	2006–2008: *C. albicans* 63%, *C. glabrata* 16%; 2016–2018: *C. albicans* 51%, *C. glabrata* 32%	n/a	77/245 (31.4%)	52/77 (67.5%) vs 40/168 (23.8%)	TEE 37/77 (48.1%) vs 37/168 (22%)	n/a	Mortality (unknown time frame) 28/77 (36.4%) vs 85/168 (50.6%)	18
Patel et al. 2005 [7]	Retrospective single-center study, 2002–2003, USA	119	Mean, 51.8 y	50%	CKD 48%, immunosuppression 34%, TPN 31%, abdominal surgery 29%, diabetes 29%	*C. albicans* 41%, *C. parapsilosis* 24%, *C. glabrata* 20%, *C. tropicalis* 8%, *C. krusei* 4%, *C. lusitaniae* 2%, *C. guilliermondii* 1%	n/a	37/119 (32%)	n/a	n/a	n/a	6-wk mortality available in 102 patients, 6/34 (18%) vs 27/68 (39%)	17
Takakura et al. 2006 [18]	Retrospective single-center study, 2002–2003, Japan	40	Mean, 55.9 y	61%	n/a	*C. albicans* 48%, *C. glabrata* 22%, *C. parapsilosis* 22%, *C. tropicalis* 4%, other 4%	n/a	23/40 (57.5%)	n/a	n/a	20/21 (95%) vs 13/16 (81%)	30-d mortality available in 39 patients, 5/23 (22%) vs 9/16 (56%)	17
Iowa Study 2019	Retrospective single-center study, 2015–2019, USA	151	Mean, 53 y	54%		*C. albicans* 44%, *C. glabrata* 35%, *C. parapsilosis* 12%, *C. tropicalis* 7%, *C. krusei* 3%, other 5%	Line 48%, GI issue 20%, urinary 14%, unknown 8%, endocarditis 5%, bone 2%, skin soft tissue 3%, IVDU 2%	129/151 (85.4%)	114/129 (88%) vs 6/22 (27%)	Any echo 77/129 (60%) vs 8/22 (36%)	80/84 (95%) vs 9/16 (56%)	30-d mortality 23/129 (18%) vs 11/22 (50%), 90-d morality 32/129 (25%) vs 11/22 (50%)	n/a

Abbreviations: CKD, chronic kidney disease; CL, central line; D & B score, Downs and Black score; ECHO, echocardiogram; GI, gastrointestinal; IDC, infectious disease consult; IVDU, intravenous drug use; TPN, total parental nutrition; TTE, transthoracic echocardiogram.

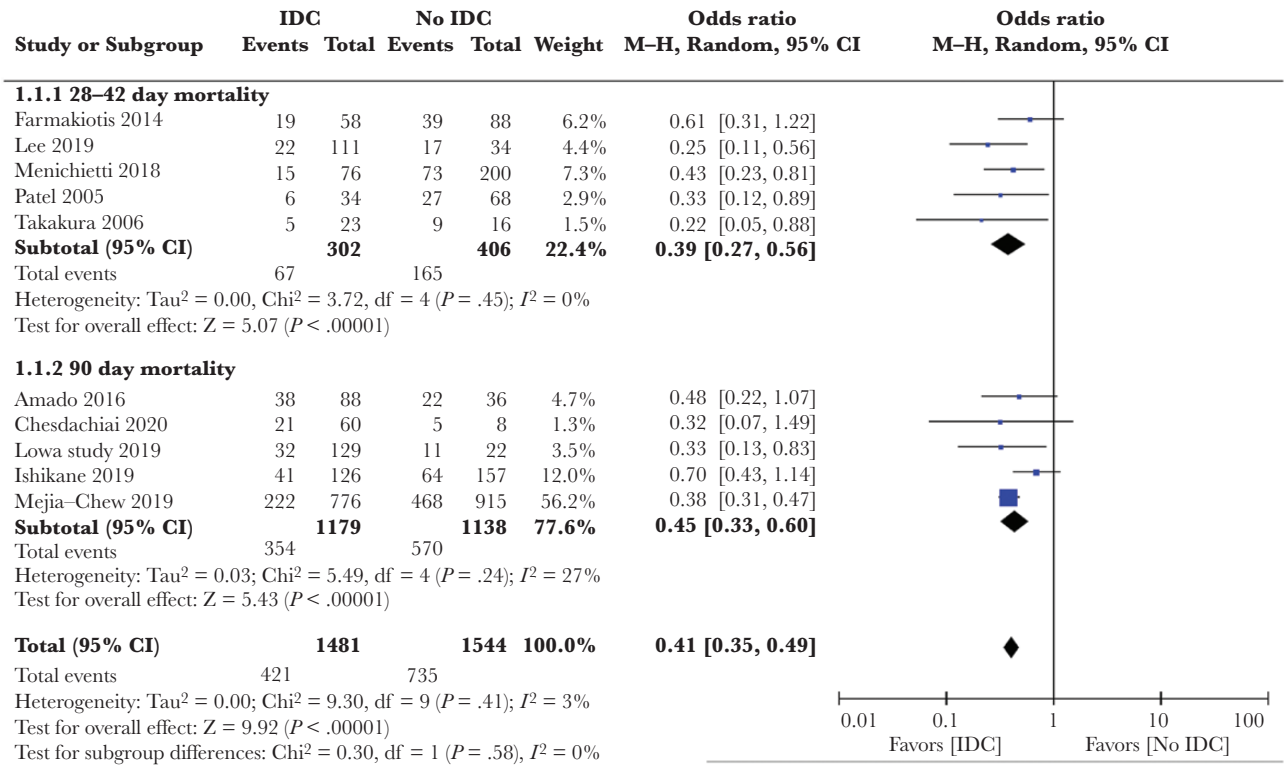


Figure 2. Overall mortality. Abbreviation: IDC, infectious disease consult.

as endocarditis could also explain the lower mortality seen in the IDC group.

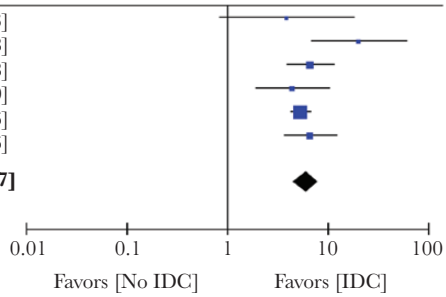
IDC in patients with *Staphylococcus aureus* bacteremia (SAB) is known to be associated with a decrease in 30-day mortality, 90-day mortality, length of stay, SAB relapse rates, and more frequent adherence to standards of care (antibiotic choice, antibiotic duration, and follow-up blood cultures) [28, 29]. Favorable effects of IDC have also been described in patients with endocarditis and pneumonia, with higher rates of appropriate therapy, and also in ICU patients and solid organ transplant recipients [30–33]. While IDC occurs for all or the vast majority of patients with SAB, this is not the case for patients with candidemia at all institutions. Specifically, our systematic literature review revealed that the rate of IDC for patients with candidemia ranged from 28% to 88%. Given the significant survival benefit demonstrated in our study and meta-analysis, IDC should be considered in all patients with candidemia, where ID specialists are available. In fact, a recent study reported the implementation of the automatic IDC for candidemia in their institution after confirming this trend [8]. Moreover, Mellinghoff et al. proposed a scoring system in 2018 for the management of candidemia as a tool to measure guideline adherence [34]. Given that management of candidemia can be complicated, a standardized evaluation to investigate whether each institution is adherent to guidelines is needed to improve the quality of care.

This work has several limitations. First, the retrospective cohort study was at a single center; therefore, *Candida* species distribution may not reflect that of other hospitals, especially those with a high frequency of potentially resistant non-*albicans Candida* species, such as *C. glabrata*. Nonetheless, benefits from IDC were documented in another study focusing exclusively on patients with *C. glabrata* fungemia [16]. Second, in our systematic literature review and meta-analysis, all studies included were retrospective single-center studies. However, these designs are frequently used when it is not logistically feasible or ethical to conduct randomized controlled trials. More research is needed to understand which aspects of IDC contribute the most to a decrease in mortality. In addition, further research is needed to investigate the impact of an antimicrobial stewardship team instead of IDC, especially for places where IDC is not available. Third, the mortality difference observed between those with and without ID consultation could be due to the benefits of ID consultation, or could be explained by unmeasured confounders or by immortal time bias or selection bias. For example, ID may not have been consulted because patients were too sick or did not survive long enough to receive IDC. In cases where IDC occurred after candidemia, we know that patients were alive to receive IDC; otherwise they would not have met inclusion criteria for cohort entry. Immortal time bias refers to the time between cohort entry and exposure, whereby a patient is guaranteed to be alive because of the way

A

Study or Subgroup	IDC Events	IDC Total	No IDC Events	No IDC Total	Weight	Odds ratio M–H, Random, 95% CI
Chesdachiai 2020	42	60	3	8	3.2%	3.89 [0 .84, 18.03]
Iowa study 2019	114	129	6	22	6.1%	20.27 [6.87, 59.78]
lshikane 2019	98	126	54	157	19.2%	6.68 [3 .92, 11.38]
Lee 2019	72	111	10	34	9.6%	4.43 [1.92, 10.20]
Mejia-Chew 2019	412	776	160	915	45.5%	5.34 [4.28, 6.66]
Mohr 2020	52	77	40	168	16.5%	6.66 [3 .67, 12.06]
Total (95% CI)		**1279**		**1304**	**100.0%**	**6.10 [4.61, 8.07]**
Total events	790		273			

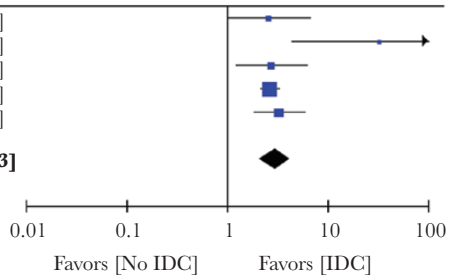
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 6.80$, df = 5 ($P = .24$); $I^2 = 26\%$
Test for overall effect: Z = 12.64 ($P < .00001$)



B

Study or Subgroup	IDC Events	IDC Total	No IDC Events	No IDC Total	Weight	Odds ratio M–H, Random, 95% CI
Iowa study 2 019	77	129	8	22	11.8%	2.59 [1.02, 6.62]
lshikane 2019	22	126	1	157	3.0%	33.00 [4.38, 248.59]
Lee 2019	84	111	18	34	14.9%	2.77 [1.24, 6.16]
Mejia-Chew 2019	442	776	305	915	47.3%	2.65 [2. 17, 3.23]
Mohr 2020	37	77	37	168	23.0%	3.27 [1.84, 5.83]
Total (95% CI)		**1279**		**1296**	**100.0%**	**3.01 [2.10, 4.33]**
Total events	662		369			

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 6.47$, df = 4 ($P = .17$); $I^2 = 38\%$
Test for overall effect: Z = 5.97 ($P < .00001$)



C

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds ratio M–H, Random, 95% CI
Iowa study 2019	80	84	9	16	17.8%	15.56 [3 .80, 63.62]
Ishikane 2019	86	126	120	157	26.2%	0.66 [0.39, 1.12]
Lee 2019	57	62	6	12	17.4%	11.40 [2 .66, 48.83]
Mejia–Chew 2019	587	776	538	915	28.0%	2.18 [1.76, 2.69]
Takakura 2006	20	21	13	16	10.6%	4.62 [0 .43, 49.30]
Total (95% CI)		**1069**		**1116**	**100.0%**	**3.27 [1.23, 8.69]**
Total events	830		686			

Heterogeneity: $Tau^2 = 0.88$; $Chi^2 = 31.70$, df = 4 ($P < .00001$); $I^2 = 87\%$
Test for overall effect: Z = 2.38 ($P = .02$)

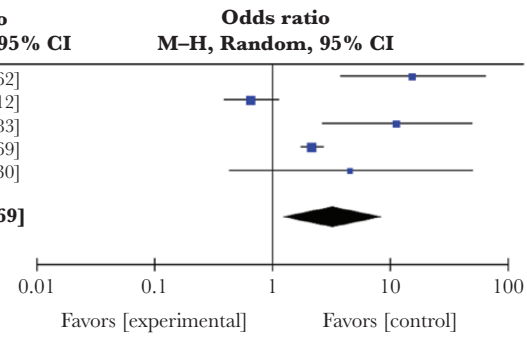


Figure 3. A, Ophthalmology consult. B, Echocardiogram. C, Central line removal. Abbreviation: IDC, infectious disease consult.

they were entered into the cohort. To avoid this type of bias, we considered IDC a time-dependent variable. Notably, Cox hazard models analyzing IDC as a time-dependent variable were performed in only 2 studies, our study and that by Mejia-Chew et al. The hazard ratio for mortality in the Mejia-Chew study became less pronounced, from 0.41 (59% reduction of death) to 0.81 (19% reduction) [15, 35] using this approach, though the Iowa Study did not significantly change. Fourth, it was also not feasible to investigate the rate of adherence to the IDC-recommended interventions in each study. Fifth, we assessed crude, not candidemia-attributable, mortality. Finally, a single study from Mejia-Chew et al. weighted 56% in the forest plot of the main outcome (Figure 2). Therefore, we recalculated ORs removing the study to see a difference (Supplementary Figure 2). The result was very similar after removing the study (OR, 0.46; 95% CI, 0.36–0.60).

In conclusion, our systematic literature review and meta-analysis of patients with candidemia found a strong overall mortality benefit associated with IDC. These results suggest that IDC should be considered in all patients with candidemia.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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editors consider relevant to the content of the manuscript have been disclosed.

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