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.
of 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 IDC, 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 χ² 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 mortality). We also evaluated the associations between ICD and rate of ophthalmology consultation and echocardiogram order. Heterogeneity between studies was evaluated with I² 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 (62%; 790/1279) 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 I² estimates of 3%, 26%, and 38%, respectively. Heterogeneity in CVC removal was high, with an I² 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) | PValue |
|--------------------------------------------|----------------|--------------|--------|
| Demographics                               |                |              |        |
| Age, mean (SD), y                          | 58.8 (16.6)    | 64.5 (15.5)  | .24    |
| Male sex                                   | 13 (59.1)      | 69 (53.5)    | .65    |
| Injection drug user                        | 1 (4.5)        | 7 (5.4)      | .9     |
| Comorbidities                              |                |              |        |
| Alcohol                                    | 3 (13.6)       | 10 (78)      | .41    |
| Transplant                                 | 1 (4.5)        | 10 (78)      | .9     |
| Morbid obesity                             | 3 (13.6)       | 19 (14.7)    | .9     |
| HIV                                        | 0              | 10 (8.0)     | .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)    | .055   |
| Urinary                                    | 1 (4.5)        | 21 (16.3)    | .017   |
| Unknown                                    | 7 (31.8)       | 6 (4.7)      | .8     |
| Endocarditis                               | 0              | 7 (5.4)      | .01    |
| Bone and joint                             | 0              | 3 (2.3)      | .3     |
| Skin and soft tissue                       | 1 (4.5)        | 1 (0.8)      | .007   |
| IVDU                                       | 0              | 1 (0.8)      | .002   |
| LVAD                                       | 0              | 1 (0.8)      | .002   |
| Clinical management                        |                |              |        |
| Removal of catheter*                       | 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)      | 270 (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.

*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
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].

### 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)          | PValue                 | HR (95% CI)          | PValue                 |
| Age                  | 1.04 (1.02–1.06)     | <.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                  | 1.66 (0.39–7.12)     | .4923                  |
| Alcoholic            | 0.36 (0.12–1.07)     | .0666                  | 0.67 (0.16–2.91)     | .5944                  |
| Transplant           | 0.29 (0.07–1.13)     | .0738                  | 0.88 (0.33–2.35)     | .8040                  |
| Morbid obesity       | 0.37 (0.16–0.87)     | .0226                  | 0.95 (0.53–1.71)     | .8586                  |
| HIV                  | N/A                  |                        | 0.24 (0.03–2.08)     | .1949                  |
| Chronic kidney disease| 0.67 (0.42–1.06)    | <.0001                 | 0.17 (0.03–0.97)     | .0463                  |
| Cirrhosis            | 2.23 (1.59–3.13)     | <.0001                 | 0.29 (0.07–1.13)     | .0738                  |
| Coronary artery disease| 0.79 (0.46–1.36)   | .3988                  | 0.36 (0.12–1.07)     | .0666                  |
| Hypertension         | 1.07 (0.77–1.48)     | .7047                  | 1.07 (0.77–1.48)     | .7047                  |
| Heart failure        | 0.78 (0.41–1.48)     | .4543                  | 0.78 (0.41–1.48)     | .4543                  |
| Type 2 diabetes mellitus| 0.74 (0.49–1.12)     | .1524                  | 0.36 (0.12–1.07)     | .0666                  |
| Malignancy           | 0.40 (0.16–1.00)     | .0489                  | 0.29 (0.07–1.13)     | .0738                  |
| Recent chemotherapy  | 0.67 (0.39–1.33)     | .088                   | 0.67 (0.39–1.33)     | .088                   |
| Recent abdominal surgery| 1.23 (0.87–1.68)    | .2623                  | 1.23 (0.87–1.68)     | .2623                  |
| Total parental nutrition| 0.28 (0.15–0.53)  | <.0001                 | 0.28 (0.15–0.53)     | <.0001                 |
| Central line present >2 d | 0.77 (0.55–1.06) | .1084                  | 0.77 (0.55–1.06)     | .1084                  |
| *C. albicans*        | 1.23 (0.93–1.79)     | .1249                  | 1.23 (0.93–1.79)     | .1249                  |
| *C. glabrata*        | 3.86 (2.64–5.64)     | <.0001                 | 3.86 (2.64–5.64)     | <.0001                 |
| *C. parapsilosis*    | 0.17 (0.07–0.45)     | .0004                  | 0.17 (0.07–0.45)     | .0004                  |
| *C. tropicalis*      | 0.37 (0.10–1.33)     | .1272                  | 0.37 (0.10–1.33)     | .1272                  |
| *C. krusei*          | 0.48 (0.07–3.46)     | .4689                  | 0.48 (0.07–3.46)     | .4689                  |
| Catheter-related infection| 0.76 (0.54–1.07) | .1151                  | 0.76 (0.54–1.07)     | .1151                  |
| Removal of catheter  | 0.76 (0.55–1.05)     | .1002                  | 0.76 (0.55–1.05)     | .1002                  |
| Echocardiogram performed| 0.59 (0.43–0.84)  | .0027                  | 0.59 (0.43–0.84)     | .0027                  |
| Ophthalmologic examination| 1.31 (0.82–2.09) | .2539                  | 1.31 (0.82–2.09)     | .2539                  |
| Evidence of eye disease| 0.64 (0.16–2.57) | .5254                  | 0.64 (0.16–2.57)     | .5254                  |
| IDC                  | 0.25 (0.17–0.36)     | <.0001                 | 0.25 (0.17–0.36)     | <.0001                 |

Abbreviations: HR, hazard ratio; IDC, infectious disease consultation.
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 (20%), 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; 38/89 (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 | 136/181 (73%) | n/a | 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 | 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 | "IDC was associated with obtaining echo P = .005" | 18 |
| Farmakiotis et al. 2014 [16] | Retrospective single-center study, 2005–2013, USA | 146 | Mean, 55 y | 51% | Catheater-associated bloodstream infection | C. albicans 32%, C. glabrata 40%, C. parapsilosis 9%, other 19% | n/a | 56/62 (89%) | n/a | n/a | n/a | 30-d mortality 23/126 (18%) vs 44/157 (28%), 90-d mortality 41/126 (33%) vs 64/157 (41%) | 22 |
| Ishikane et al. 2019 [9] | Retrospective single-center study, 2002–2013, Japan | 275 | Mean, 70 y | 68.6% | HIV 71%, transplant 2.4%, diabetes 28.6%, solid organ cancer 33.3%, hematological malignancy 10.3%, CKD 79%, 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%) | 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 42%, C. glabrata 21%, C. parapsilosis 19%, C. tropicalis 8% | n/a | 56/62 (89%) | n/a | n/a | n/a | 30-d mortality; "patients with IDC who received standard of care had lower mortality 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%, orthosis 6% | C. albicans 42%, C. glabrata 21%, C. krusei 3%, C. parapsilosis 19%, C. tropicalis 8% | n/a | 111/145 (77%) | 72/111 (65%) vs 10/34 (29%) | 84/111 (76%) vs 18/34 (53%) | 30-d mortality 22/111 (20%) vs 17/34 (50%), 60-d mortality 27/111 (24%) vs 20/34 (60%) | 22 |
### Table 3. Continued

| First Author/ Year | Study Design, Period, Region | No. | Age | Male Gender | Patient Population | Candidate 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 | 786/1691 (45.9%) vs 160/915 (17%) | 412/776 (53%) vs 160/915 (17%) | Any echo 442/776 (57%) vs 305/915 (33%) | 587/776 (76%) vs 468/915 (51%) | 6-wk mortality 173/776 (22%) vs 431/915 (47%), 90-d mortality 222/76 (29%) vs 468/915 (51%) | 21 |
| Menichetti et al. 2018 [17] | Retrospective single-center study, 2012–2014, Italy | 276 | Age >65, 61% | 43% | 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 in 2006–2008, 63 in 2016–2018 | 62% in 2006–2008, 62% in 2016–2018 | n/a | C. albicans 63%, C. parapsilosis 16%; 2016–2018: C. albicans 51%, C. glabrata 32% | n/a | 77/245 (31.4%) vs 49/168 (29.3%) | 52/77 (67.5%) vs 40/168 (24.1%) | 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%, immuno-suppression 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 | 6-wk mortality available in 102 patients, 63/63 (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 | 2340 (57.5%) | n/a | n/a | 20/21 (95%) vs 13/16 (81%) | 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%, NDU 2% | 129/151 (85.4%) vs 6/22 (27%) | 114/129 (88%) vs 6/22 (27%) | Any echo 77/129 (60%) vs 8/22 (36%) | 80/84 (95%) | 30-d mortality 23/129 (18%) vs 11/22 (50%), 90-d mortality 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.
candidemia ranged from 28% to 88%. Given the significant sur-
literature review revealed that the rate of IDC for patients with
with candidemia at all institutions. Specifically, our systematic
majority of patients with SAB, this is not the case for patients
appropriate therapy, and also in ICU patients and solid organ trans-
Favorable effects of IDC have also been described in patients
antibiotic duration, and follow-up blood cultures) [28, 29].
standardized evaluation to investigate whether each institu-
whereby a patient is guaranteed to be alive because of the way
bias refers to the time between cohort entry and exposure,
that patients were alive to receive IDC; otherwise they would
measured confounders or by immortal time bias or selection
between those with and without ID consultation could be due
IDC is not available. Third, the mortality difference observed
stewardship team instead of IDC, especially for places where
tribute the most to a decrease in mortality. In addition, further
research is needed to understand which aspects of IDC con-
sensible or ethical to conduct randomized controlled trials. More
these designs are frequently used when it is not logistically fea-
IDC in patients with 

This work has several limitations. First, the retrospective co-
hort study was at a single center; therefore, Candida species dis-
tribution 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 exclu-
sively 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 fea-
sible or ethical to conduct randomized controlled trials. More
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 un-
measured confounders or by immortal time bias or selection
bias. For example, ID may not have been consulted because pa-
tients were too sick or did not survive long enough to receive
IDC. In cases where IDC occurred after candidemia, we know
patients were too sick or did not survive long enough 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
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 appro-
propriate therapy, and also in ICU patients and solid organ trans-
plant 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 sur-
vival 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 im-
plementation of the automatic IDC for candidemia in their in-
stitution 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 institu-
tion is adherent to guidelines is needed to improve the quality
of care.

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

| Study or Subgroup | IDC Events | No IDC Events | Total Events | Total Weight | Odds ratio M–H, Random, 95% CI | Odds ratio M–H, Random, 95% CI |
|------------------|------------|---------------|--------------|--------------|-------------------------------|-------------------------------|
| 1.1.1 28–42 day mortality |           |               |              |              |                               |                               |
| Farmakiotis 2014   | 19         | 56            | 39           | 88           | 6.2%                          | 0.61 [0.31, 1.22] |
| Lee 2019           | 22         | 111           | 17           | 34           | 4.4%                          | 0.25 [0.11, 0.56] |
| Menichetti 2018    | 15         | 76            | 73           | 200          | 7.3%                          | 0.43 [0.23, 0.81] |
| Patel 2005         | 6          | 34            | 27           | 68           | 2.9%                          | 0.33 [0.12, 0.89] |
| Takakura 2006      | 5          | 23            | 9            | 16           | 1.5%                          | 0.22 [0.05, 0.88] |
| Subtotal (95% CI)  | 302        | 406           |              |              | 22.4%                         | 0.39 [0.27, 0.56] |
| Total events       | 67         | 165           |              |              |                               |                               |
| Heterogeneity: Tau² = 0.00, Chi² = 3.72, df = 4 (P = .45); I² = 0% |
| Test for overall effect: Z = 5.07 (P < .00001) |
| 1.1.2 90 day mortality |           |               |              |              |                               |                               |
| Amado 2016         | 38         | 88            | 22           | 36           | 4.7%                          | 0.48 [0.22, 1.07] |
| Chedsachiai 2020   | 21         | 60            | 5            | 8            | 1.3%                          | 0.32 [0.07, 1.49] |
| Lowa study 2019    | 32         | 129           | 11           | 22           | 3.5%                          | 0.33 [0.13, 0.83] |
| Ishikane 2019      | 41         | 126           | 64           | 157          | 12.0%                         | 0.70 [0.43, 1.14] |
| Mejia–Chew 2019   | 222        | 776           | 468          | 915          | 56.2%                         | 0.38 [0.31, 0.47] |
| Subtotal (95% CI)  | 1179       | 1138          |              |              | 77.6%                         | 0.45 [0.33, 0.60] |
| Total events       | 354        | 570           |              |              |                               |                               |
| Heterogeneity: Tau² = 0.03; Chi² = 5.49, df = 4 (P = .24); I² = 27% |
| Test for overall effect: Z = 5.43 (P < .00001) |
| Test for subgroup differences: Chi² = 0.30, df = 1 (P = .58), I² = 0% |
| Total (95% CI)     | 1481       | 1544          | 100.0%       |              | 0.41 [0.35, 0.49] |
| Total events       | 421        | 735           |              |              |                               |                               |
| Heterogeneity: Tau² = 0.00; Chi² = 9.30, df = 9 (P = .41); I² = 3% |
| Test for overall effect: Z = 9.92 (P < .00001) |
| Test for subgroup differences: Chi² = 0.30, df = 1 (P = .58), I² = 0% |
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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**Figure 3.** A, Ophthalmology consult. B, Echocardiogram. C, Central line removal. Abbreviation: IDC, infectious disease consult.
editors consider relevant to the content of the manuscript have been disclosed.

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