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Original Article

The interplay of infectious diseases consultation and antimicrobial stewardship in candidemia outcomes: A retrospective cohort study from 2016 to 2019

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Abstract

Objective: To evaluate the need for mandatory infectious diseases consultation (IDC) for candidemia in the setting of antimicrobial stewardship guidance.

Design: Retrospective cohort study from January 2016 to December 2019.

Setting: Academic quaternary-care referral center.

Patients: All episodes of candidemia in adults (n = 92), excluding concurrent bacterial infection or death or hospice care within 48 hours.

Methods: Primary outcome was all-cause 30-day mortality. Secondary outcomes included guideline-adherence and treatment choice. Guideline-adherence was assessed with the EQUAL *Candida* score.

Results: Of 186 episodes of candidemia, 92 episodes in 88 patients were included. Central venous catheters (CVCs) were present in 66 episodes (71.7%) and were the most common infection source (N = 38, 41.3%). The most frequently isolated species was *Candida glabrata* (40 of 94, 42.6%). IDC was performed in 84 (91.3%) of 92 candidemia episodes. Mortality rates were 20.8% (16 of 77) in the IDC group versus 25% (2 of 8) in the no-IDC group ($P = .67$). Other comparisons were numerically different but not significant: repeat blood culture (98.8% vs 87.5%; $P = .17$), echocardiography (70.2% vs 50%; $P = .26$), CVC removal (91.7% vs 83.3%; $P = .45$), and initial echinocandin treatment (67.9% vs 50%; $P = .44$). IDC resulted in more ophthalmology examinations (67.9% vs 12.5%; $P = .0035$). All patients received antifungal therapy. Antimicrobial stewardship recommendations were performed in 19 episodes (20.7%). The median EQUAL *Candida* score with CVC was higher with IDC (16 vs 11; $P = .001$) but not in episodes without CVC (12 vs 11.5; $P = .81$).

Conclusions: In the setting of an active antimicrobial stewardship program and high consultation rates, mandatory IDC may not be warranted for candidemia.

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Candidemia is the second most common cause of healthcare-associated bloodstream infections in the United States, with an in-hospital mortality rate of ~25%.[1,2] A meta-analysis evaluating infectious diseases consultation (IDC) in candidemia found lower mortality and increased ophthalmology consultation, echocardiography use, and central venous catheter (CVC) removal with IDC.[3] Adherence to Infectious Diseases Society of America (IDSA) candidemia guidelines is associated with lower mortality.[4] The European Confederation of Clinical Mycology QUALity of Clinical Candidemia Management (EQUAL) score measures adherence to European and IDSA guidelines via a weighted quantitative score (Supplementary Table 1 online).[5–8] Lower EQUAL scores are associated with higher 30-day mortality, although some have not demonstrated mortality differences.[9–13] A Spanish study associated higher EQUAL scores with IDC, and some propose adding IDC to the EQUAL score as a quality measure.[6,13] The EQUAL score has not been evaluated in a US cohort.

Antimicrobial stewardship program (ASP) interventions in candidemia are associated with improved adherence to guidelines and care bundles without a mortality difference.[14–17] Some institutions have mandated IDC for candidemia.[18] To determine whether mandatory IDC for candidemia would be beneficial at our institution with established ASP blood-culture review and guidance, we examined the influence of IDC on mortality and measures of guideline adherence, including the EQUAL score.

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Methods

We performed a retrospective cohort study at a 718-bed academic hospital and its accompanying 91-bed community hospital. Patients with at least 1 blood culture positive for *Candida* spp between January 1, 2016, and December 31, 2019, were reviewed. Exclusion criteria included age <19 years, concurrent bacteremia in initial blood cultures, death or hospice care within 48 hours of positive blood-culture notification, patient-directed discharge within 7 days of positive blood-culture notification, and recurrent episodes of candidemia in which the initial episode predated January 2016. Time zero for an episode of candidemia was defined as the time of clinician notification of positive blood cultures for yeast. Microbiologic methods and EQUAL score calculation methodology are detailed in the Supplementary Methods (online).

Our ASP consisted of infectious diseases (ID) pharmacists and physicians who reviewed all positive blood-culture results and provided prospective audit and feedback during weekday standard business hours. Institutional guidelines for invasive candidiasis are available on our ASP website.[19]

Researchers J.R. and E.S. performed manual data extraction from a list of all blood cultures with *Candida*. We collected demographics, microbiology, CVC removal (including exchanges), infection source (defined by treating clinicians), ophthalmologic examination, and echocardiogram performance within 1 week, antifungals, IDC, and ASP interventions. Charlson comorbidity index (CCI) was calculated.[20] Treatment duration was calculated using the planned duration, including at discharge. If death or an indefinite duration occurred, then these episodes were excluded from duration of therapy.

Primary outcome was all-cause 30-day mortality. Secondary outcomes included length of stay, 60-day recurrence, and components of the EQUAL score. Outcomes were stratified by IDC. A post hoc analysis included stratification of results by IDC within 48 hours of positive blood-culture notification.

Descriptive statistics were used for patient characteristics. The Fisher exact test and the Mann-Whitney test were used for associations of categorical and continuous data between IDC groups, respectively. All analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC). $P < .05$ was considered statistically significant. The University of Nebraska Medical Center Institutional Review Board (IRB) designated this work as a quality improvement effort, exempt from IRB review.

Results

We reviewed 186 episodes of candidemia. Reasons for exclusions were age <19 years (n = 21), death or hospice care within 48 hours (n = 33), concurrent bacteremia (n = 38), and patient-directed discharge (n = 2). We included 88 patients with 92 episodes of candidemia. IDC occurred in 84 (91.3%) of 92 episodes. Patient characteristics, microbiology, CVC type, and infection source were stratified by IDC (Table 1). The most frequently isolated species was *C. glabrata* (40 of 94, 42.6%). Among 92 episodes, 66 patients (71.7%) had CVCs. The most common sources of *Candida* were CVCs (41.3%) and intra-abdominal catheters (25%). Endophthalmitis was identified in 2 cases, and endocarditis was identified in 6 cases; all received an IDC.

The 30-day all-cause mortality rates in the IDC group versus the no-IDC group were 20.5% (16 of 77) versus 25% (2 of 8; $P = .67$), respectively. Also, 3 patients (all with IDC) were excluded from mortality calculations because incomplete medical record data posthospitalization precluded 30-day survival confirmation. Outcomes stratified by IDC are detailed in Table 2. IDC resulted in more ophthalmology examinations (67.9% vs 12.5%; $P < .0035$). All candidemia episodes received antifungal therapy. Mean time to empiric therapy was 38.9 hours overall. In the IDC group, mean time to empiric therapy was 37 hours, and in the no-IDC group, the mean time was 58.1 hours ($P = .007$). The median planned treatment duration was higher in those with an IDC than in those with no IDC (17 days vs 15 days; $P = .15$). Also, 18 episodes had no assigned treatment duration due to indefinite duration or death. Among episodes with repeat blood cultures, treatment duration after blood-culture clearance was ≥14 days in 61 (92.4%) of 66 with IDC compared to 3 (50%) of 6 without IDC ($P = .016$). For episodes in patients with a CVC, the median EQUAL score was 16 in the IDC group versus 11 in the no-IDC group ($P = .001$). In episodes in patients without a CVC, the median EQUAL score was 12 with an IDC and 11.5 without IDC ($P = .81$). Table 3 demonstrates individual components of the EQUAL score stratified by IDC.

The ASP made recommendations in 19 (20.7%) of 92 episodes. The ASP recommended both IDC and antifungal therapy change recommendations in 6 (6.5%) of 92 cases, IDC alone in 2 (2.2%) of 92 cases, and antifungal therapy change alone in 11 (12.0%) of 92 cases. All recommendations for IDC were accepted. ASP did not document recommendation for IDC in the 8 patients without an IDC. The ASP recommended antifungal therapy changes in 15 episodes (17.9%) in the IDC group versus 2 episodes (25%) in the no-IDC group ($P = .64$).

A post hoc analysis of outcomes based on whether IDC occurred within 48 hours of positive blood-culture notification demonstrated that ophthalmology examination and the EQUAL score with CVC present were no longer significantly different. Other outcomes remained similar (Supplemental Table 2).

Discussion

We evaluated the effect of IDC on candidemia outcomes in the setting of an active ASP and included the first analysis of the EQUAL score in a US cohort. IDC occurred in >90% of episodes. Mortality within 30 days was lower among patients receiving IDC compared to those without an IDC, but this difference was not statistically significant. We detected higher EQUAL scores in candidemia episodes with a CVC and IDC.

ASPs play an important role in candidemia management, as demonstrated by ASP-implemented candidemia bundles,[14–17] but improved adherence has not translated to decreased mortality.[15–17] Our ASP contributed to nearly 10% of the IDCs performed and recommended therapeutic changes in 25% of episodes without an IDC, which may have offset a mortality benefit by providing optimal antifungal therapy. ASPs using audit and feedback serve a vital role in oversight by coordinating with IDCs. We demonstrated that a 48-hour delay in IDC did not result in worse outcomes, which supports the pragmatic weekday monitoring of blood cultures.

In contrast to prior studies,[3,18,21–23] we did not detect a significant difference in mortality with IDC. Our 30-day mortality rate of 20.8% in the IDC group was akin to those in other studies (17.8%–20%).[3,18,22] However, these studies had a markedly higher 30-day mortality rates (28%–50%) without IDC.[3,18,22] We found similar rates of echocardiogram use, ophthalmologic examination, repeated blood culture, and CVC removal to prior studies with both the IDC and no-IDC groups.[18,21]

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Table 1. Patient Characteristics Stratified by IDC (n=88 Patients)

Characteristic	IDC (n=80)	No IDC (n=8)	*P* Value
Age, median y (IQR)	53.9 (38.6–69.9)	54.8 (41.6–69.2)	.72
Sex, male, no./total (%)	48/80 (60)	5/8 (62.5)	1.00
TPN use within 7 d, no./total (%)	30/80 (37.5)	4/8 (50)	.71
Intravenous drug use, no./total (%)	2/80 (2.4)	1/8 (12.5)	.24
ICU required within 48 h, no./total (%)	43/80 (51.2)	4/8 (50)	1.00
Charlson comorbidity index, median (IQR)	4.0 (2.0–6.0)	3.5 (2–5.5)	.66
Liver disease, no./total (%)	17/80 (21.3)	3/8 (37.5)	.37
Diabetes mellitus, no./total (%)	26/80 (32.5)	2/8 (25)	1.00
CKD/ESRD, no./total (%)	8/80 (10)	0/8 (0)	1.00
Solid tumor malignancy, no./total (%)	17/80 (21.3)	1/8 (12.5)	1.00
Leukemia/lymphoma, no./total (%)	5/80 (6.3)	0/8 (0)	1.00
Solid organ transplant, no./total (%)	19/80 (23.75)	3/8 (37.5)	.41
CVC present, no./total (%)	60/84 (71.4)	6/8 (75)	1.00
CVC type, no./total (%)			
PICC	23/60 (38.3)	3/8 (50)	.67
Temporary CVC	19/60 (31.7)	2/8 (33.3)	1.00
Tunneled CVC	16/60 (26.7)	0/8 (0)	.32
Port	8/60 (13.3)	2/8 (33.3)	.22
Other	1/60 (1.7)	0/8 (0)	1.00
Microbiology, no./total (%)[a]			
Candida glabrata	37/86 (43)	3/8 (37.5)	1.00
C. albicans/dublienensis	31/86 (36.1)	4/8 (50)	.46
C. parapsilosis	7/86 (8.1)	1/8 (12.5)	.53
C. tropicalis	6/86 (7.0)	0/8 (0)	1.00
C. krusei	2/86 (2.3)	0/8 (0)	1.00
C. famata	2/86 (2.3)	0/8 (0)	1.00
C. guilliermondii	1/86 (1.2)	0/8 (0)	1.00
Source of infection, no./total (%)[b]			
CVC	35/84 (41.7)	3/8 (37.5)	1.00
Intra-abdominal infection	21/84 (25)	2/8 (25)	1.00
Genitourinary infection	13/84 (15.5)	0/8 (0)	.60
Other[c]	8/84 (9.5)	1/8 (12.5)	.58
Indeterminate or unspecified	14/84 (16.7)	2/8 (25)	.62

Note. IDC, infectious diseases consultation; IQR, interquartile range; TPN, total parenteral nutrition; ICU, intensive care unit; CKD, chronic kidney disease; ESRD, end-stage renal disease; CVC, central venous catheter; PICC, peripherally inserted central catheter.
[a]Multiple *Candida* spp isolated from 2 patients in the IDC group.
[b]Multiple categories of sources were identified for 7 patients in the IDC group, so percentages do not add up to 100%.
[c]Includes endocarditis/presumed endovascular infection, osteomyelitis, pulmonary source, and injection related.

Several possible explanations exist for why our results differ. The primary reason is likely the high baseline rate of IDC >90%; a meta-analysis reported an IDC rate of only 50%.[3] Strong relationships between ID consultants and primary teams, especially with immunocompromised services, also facilitated high IDC rates. Second, our small sample size limited our ability to detect a significant difference in mortality. Third, our ASP team may have mitigated the effect of missing IDCs, as discussed above. The use of rapid diagnostic testing in conjunction with easily accessible institutional guidelines may have contributed also. Fourth, there were no untreated episodes of candidemia, which have been associated with a mortality of nearly 70%.[24] A prior study reported that 14% of patients without an IDC were untreated.[21] This difference may be due to a more modern cohort in which clinicians are more likely to treat candidemia. Lastly, we detected high rates of CVC removal regardless of IDC compared to prior studies, and CVC removal has been associated with improved mortality.[3,18,21,25]

To our knowledge, no prior studies have evaluated the EQUAL score in a US cohort. We found a significantly higher EQUAL score in the group with CVC who received an IDC. Although higher scores imply increased adherence to guideline recommendations, several issues are inherent with this measurement. Namely, higher

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Table 2. Outcomes by Episodes of Candidemia

Outcomes	IDC (n=84)	No IDC (n=8)	*P* Value
30-d all-cause mortality, no./total (%)[a]	16/77 (20.8)	2/8 (25)	.67
Length of admission, median d (IQR)	17 (9–52)	23.5 (16–43.5)	.771
60-d recurrence, no./total (%)	1/84 (1.2)	0/8 (0)	1.00
CVC removal, No./total (%)	55/60 (91.7)	5/6 (83.3)	.45
CVC removal <24 h	30/55 (54.6)	2/5 (40)	.83
CVC removal 24–72 h	11/55 (20)	1/5 (20)	
CVC removal >72 h	14/55 (25.5)	2/5 (40)	
Repeat blood cultures, no./total (%)	83/84 (98.8)	7/8 (87.5)	.17
Ophthalmology examination, no./total (%)	57/84 (67.9)	1/8 (12.5)	.0035
Echocardiography, no./total (%)	59/84 (70.2)	4/8 (50)	.26
Time to blood-culture clearance, median h (IQR)	88.9 (59.8–138.6) (n=82)	100.1 (81.0–133.6) (n=6)	.54
Total duration of treatment, median d (IQR)	17 (15–27) (n=67)	15 (14–16) (n=7)	.15
Duration of treatment ≥14 d after blood-culture clearance, no./total (%)	61/66 (92.4)	3/6 (50)	.016
Initial antifungal echinocandin, no./total (%)	57/84 (67.9)	4/8 (50)	.44
Initial antifungal fluconazole, no./total (%)	27/84 (32.1)	4/8 (50)	
Initial antifungal susceptible, no./total (%)[b]	78/83 (94)	6/8 (75)	.11
Fluconazole stepdown performed, no./total (%)[c]	36/57 (63.2)	1/4 (25)	.29
ASP recommended IDC, no./total (%)	8/84 (9.5)	0/8 (0)	1.00
ASP recommended therapy change, no./total (%)	15/84 (17.9)	2/8 (25)	.64

Note. IDC, infectious diseases consultation; IQR, interquartile range; CVC, central venous catheter; ASP, antimicrobial stewardship program.
[a]n=85 due to 3 excluded patients who survived hospitalization but could not confirm 30-d survival, all in IDC group.
[b]One patient received empiric voriconazole, for which minimum inhibitory concentrations are provided, but susceptibility interpretation is not provided in our laboratory.
[c]Only calculated if patient received empiric micafungin.

Table 3. EQUAL Score Components Stratified by IDC

Category	IDC (n=84), No./Total (%)[a]	No IDC (n=8), No./Total (%)[a]	*P* Value
Initial blood culture (40 mL)	0 (0)	0 (0)	. . .
Species identification	84 (100)	8 (100)	. . .
Susceptibility testing	84 (100)	8 (100)	. . .
Echocardiography	59 (70.2)	4 (50)	.26
Ophthalmology examination	57 (67.9)	1 (12.5)	.004
Initial echinocandin	57 (67.9)	4 (50)	.44
Fluconazole stepdown	36 (42.9)	1 (12.5)	.14
14 d of treatment	78 (92.9)	4 (50)	.004
No CVC	24 (28.6)	2 (25)	1.00
CVC removal in <24 h	30/60 (50)	2/6 (33.3)	.67
CVC removal within 24–48 h	11/60 (18.3)	1/6 (16.7)	1.00
Follow-up blood culture	83 (98.8)	7 (87.5)	.17
Total EQUAL Scores			
CVC Present EQUAL *Candida* score, median points (IQR)	16 (14–17.5) (n=60)	11 (10–12) (n=6)	.001
No CVC EQUAL *Candida* score, median points (IQR)	12 (10–14.5) (n=24)	11.5 (11–12) (n=2)	.81

Note. EQUAL, European Confederation of Clinical Mycology QUALity of Clinical Candidemia Management; IDC, infectious diseases consultation; CVC, central venous catheter; IQR, interquartile range.
[a]Units unless otherwise specified.

rates of ophthalmologic examination and echocardiography drove the higher score in the IDC group. The utility of routine ophthalmologic examination is under scrutiny because the American Academy of Ophthalmology no longer recommends routine screening in candidemia.[26] Only 67.9% of episodes with an IDC received an ophthalmologic exam: a discordance between

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practicing ID physicians and the guidelines. Echocardiography use is also controversial because it is recommended by European guidelines but not by the Infectious Diseases Society of America (IDSA), which may limit the generalizability of the EQUAL score in the United States.[7,8] Future revisions of the EQUAL score should reconsider the inclusion of echocardiography and ophthalmologic examination. Ultimately, both IDC and no-IDC groups in our study had an average EQUAL score >10, which has been used as a mortality cutoff, although other studies have used scores of 15 and 17 as their cutoffs.[9,10,13]

The strengths of our study included our evaluation of the EQUAL *Candida* score in relation to IDC in a US cohort, which may have applicability to US academic medical centers. Our population was highly immunosuppressed with well-balanced comorbidities between groups. Our study adds to data suggesting that ASPs play a complementary role to IDC in candidemia management. Although ASPs can improve care, they cannot replace IDC; the benefit of direct patient evaluation and longitudinal management by ID experts has been demonstrated in similar conditions such as *Staphylococcus aureus* bacteremia.[27]

This study had several limitations. It was conducted retrospectively at a single center and sample sizes were small, which limited our power to detect differences in mortality. The predominance of IDC further limited the size of the no-IDC group, precluding adjustment for baseline and time-varying differences. We did not assess antifungal dosing, for example, high-dose fluconazole for susceptible dose-dependent *C. glabrata*. Therapies assessed as targeting susceptible organisms may have been less effective. ASP interventions were assessed using charted documentation only, which may have underestimated the true effect of our ASP.

Given our institution's high rates of IDC, ASP involvement, and absence of untreated candidemia, we did not find mandatory IDC to be necessary. The advantages of avoiding mandatory consultation may include increased provider autonomy and prioritization of ASP interventions. Additionally, we did not find an advantage to earlier IDC in our cohort. We ascribe this finding to an active ASP with institutional guidelines, rapid diagnostic testing, high baseline rates of institutional IDC, frequent CVC removal, and lack of untreated candidemia. We did find higher rates of guideline-concordant care in the IDC group, as reflected in a higher EQUAL score in patients with a CVC. However, the clinical utility of this score warrants further study.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2022.209

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