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MAJOR ARTICLE

Impact of Infectious Diseases Consultation in Patients With Candidemia at a Multisite Health Care System With Established Antimicrobial Stewardship and Telemedicine Services

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Background. Infectious diseases consultation improves outcomes in patients with candidemia, although some facilities lack access to consultation. This multisite health care system study compared in-hospital mortality in patients with candidemia across 3 groups—those who received on-site consultation, telemedicine consultation, or no consultation. All patients were reviewed by an antimicrobial stewardship pharmacist.

Methods. A retrospective observational cohort study was performed of adult hospitalized patients with candidemia from January 2018 to October 2021. The primary outcome was in-hospital mortality. Secondary outcomes included receipt and duration of antifungals, removal of central venous lines if present, ophthalmologic examination, echocardiography, and determination of infection source.

Results. A total of 265 patients were evaluated: 187 in the on-site consultation group, 49 in the telemedicine consultation group, and 29 in the nonconsultation group. Although in-hospital mortality did not differ significantly between the on-site and nonconsultation groups, it was significantly lower in the telemedicine group when compared with the nonconsultation group (10.2% vs 34.5%, $P = .009$). Patients who received on-site or telemedicine consultation had significantly more antifungal therapy initiated, appropriate therapy duration, central lines removed, and echocardiography performed, as well as fewer unknown candidemia sources, vs those in the nonconsultation group.

Conclusions. This is the first study of a multisite health care system providing telemedicine services to evaluate the impact of infectious diseases consultation on candidemia mortality. These findings suggest that when on-site consultation is unavailable, infectious diseases telemedicine consultation and antimicrobial stewardship can improve outcomes and should be considered for all patients with candidemia at resource-limited sites.

Keywords. antimicrobial stewardship; candidemia; infectious diseases consultation; mortality; telemedicine.

Candida species are the fourth-leading cause of nosocomial bloodstream infection in the United States and are associated with high rates of morbidity and mortality and increased lengths of hospital stay [1, 2]. The Centers for Disease Control and Prevention's surveillance data indicate that the in-hospital all-cause mortality among patients with candidemia is approximately 25% [3]. Previous literature demonstrates that consultation with infectious diseases specialists decreases mortality, results in more appropriate antifungal prescribing, allows for earlier identification and control of infectious sources, and enables timelier removal of central lines in patients with candidemia as compared with no infectious diseases consultation (IDC) [4–7]. Despite these advantages, some institutions lack the resources to support consistent IDC services. To bridge this gap in access to specialty care, the delivery of IDC through a telemedicine (TM) platform may be a viable option for resource-limited hospitals, avoiding the need to transfer patients and minimizing delays in care [8, 9]. Clinical practice guidelines from the Infectious Diseases Society of America (IDSA) provide evidence-based recommendations for the treatment of patients with invasive candidiasis [10]. The following approach is recommended for all patients with invasive candidiasis: initiation of an appropriate antifungal agent, repeat

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blood cultures until resolution of candidemia, a minimum 2 weeks of definitive antifungal therapy after documented clearance of candidemia, removal of central venous catheters (CVCs) if presumed to be the source of candidemia, and dilated ophthalmologic examination within the first week of diagnosis of candidemia. Antimicrobial stewardship is an essential component in the treatment of patients with infectious diseases and is recognized by the IDSA, the Society for Healthcare Epidemiology of America, the Pediatric Infectious Diseases Society, and the Centers for Disease Control and Prevention for its role in improving patient outcomes through optimization of antimicrobial selection, dosing, duration, and route of administration [11]. Antimicrobial stewardship interventions in patients with candidemia have also been associated with improved guideline-concordant care [12–14]. The IDSA recently endorsed the use of TM services as a means to expand access to specialty care and improve patient outcomes [9]. The purpose of this study is to compare in-hospital mortality and clinical outcomes of patients with candidemia who received IDC, delivered on-site or via TM, against those with candidemia who did not receive IDC in conjunction with preexisting antimicrobial stewardship services.

METHODS

Study Design

This retrospective observational cohort study included patients with candidemia admitted to 1 of 15 acute care or acute rehabilitation hospitals at Atrium Health in the metro area of Charlotte, North Carolina, between 1 January 2018 and 28 October 2021. Adult patients with candidemia were considered for inclusion. Patients >89 years of age, those who transitioned to palliative care or died within 48 hours of index culture, and those with nonviable *Candida* organisms were excluded. An organism was considered "nonviable" by the microbiology laboratory when it was detected by BioFire FilmArray polymerase chain reaction but failed to grow sufficiently in culture. The primary outcome was to compare the in-hospital mortality of patients with candidemia who received IDC (delivered on-site or via TM) against those with candidemia who did not receive IDC (non-IDC). Secondary outcomes were as follows: receipt of appropriate antifungal therapy having in vitro activity against the identified *Candida* species, time to initiation of antifungal therapy, antifungal duration of therapy, obtainment of repeat blood cultures, time to culture clearance, incidence of persistent candidemia ≥5 days, removal of CVCs, obtainment of ophthalmologic examination and echocardiography, identification of suspected infectious source, and hospital length of stay. An additional predetermined subgroup analysis was performed to assess in-hospital mortality and clinical outcomes for patients who received IDC via TM vs non-IDC. Immunosuppression was defined as receipt of solid organ transplant, presence of neutropenia (absolute neutrophil count $<0.5 \times 10^3/\mu L$), autoimmune disorder with immunosuppressive medication, hematopoietic stem cell transplant within 100 days, primary immunodeficiency, or other condition requiring immunosuppression. The Charlson Comorbidity Index and Pitt bacteremia score were used to assess differences in comorbidities or severity of illness among groups. Fluconazole susceptibilities were defined in accordance with the Clinical and Laboratory Standards Institute's breakpoints categorizing ≤32 mcg/mL as susceptible dose dependent for *C glabrata* and ≤2 mcg/mL as susceptible for *C albicans*, *C parapsilosis*, and *C tropicalis* [15].

All 11 acute care and 4 acute rehabilitation hospitals within Atrium Health were able to deliver IDC on-site or by using TM services (Supplementary Table 1). A team of 26 ID physicians worked within the included hospitals, for which protocols and formularies are standardized on a systemwide level, with a goal to provide unified care at any facility. The team of ID physicians is organized into 2 divisions consisting of 21 physicians in the south/central division and 5 in the northeast. All ID physicians performing TM services share responsibilities and rotate on a weekly basis among sites primarily within their division, routinely providing TM and on-site consultations as scheduled. TM was offered routinely at 5 remote acute care and rehabilitation hospitals by live audio-video consultation with the assistance of an on-site nurse at least 3 times weekly. Of note, during the study period, 1 acute care and 1 rehabilitation hospital had on-site ID and TM consultations, but all patients received care via a single modality without crossover. On non-TM consult days, ID physicians were accessible through an on-call platform and communicated directly with the primary team. All patients systemwide with candidemia were reviewed daily by 1 of 17 ID pharmacists as part of Atrium Health's antimicrobial stewardship program (ASP), including holidays and weekends from 7 AM to 4:30 PM. Antimicrobial stewardship pharmacists were alerted to a positive blood culture via real-time notification from the microbiology laboratory and/or a clinical decision support system (TheraDoc; Premiere). Review occurred in collaboration with a designated ID physician during daily ASP rounds, and any recommendations were communicated to the primary team (including but not limited to initiation or modification of antifungal therapy, obtainment of repeat blood cultures, or formal ID consultation). If patient transfer between hospitals within Atrium Health occurred, the hospital completing treatment for candidemia was the assigned hospital for the admission. Patient transfers primarily occurred within the first 24 to 72 hours, and length of stay was calculated from the date of admission at the initial acute care hospital to the date of discharge from the hospital at which treatment was completed.

Patient Consent Statement

The study was approved by the Institutional Review Board at Wake Forest University Health Sciences and with a waiver

for informed consent (IRB00082216 No. 11-21-14E). Due to the study design, the requirement for signed patient consent was waived.

Statistical Analysis

Patients were grouped by receipt of IDC. Descriptive statistics were used to compare baseline characteristics among groups. Categorical variables were compared with a chi-square or Fisher exact test. Normally distributed continuous variables were compared with a *t* test, and those not normally distributed were compared by a Mann-Whitney or Wilcoxon test. All tests were 2-sided, and $P < .05$ was considered statistically significant. A sample size of at least 243 patients allocated in an 8:1 ratio (216 in the IDC group and 27 in the non-IDC group) was predicted to provide 80% power to detect a difference of 25% between groups for in-hospital mortality. Statistical analyses were performed with SPSS version 27 (IBM Corp).

Microbiology

The index culture was defined as the first blood culture positive for *Candida* species during hospital admission at an Atrium Health facility. Microbiology services were available at each hospital, and susceptibility testing was performed at a centralized location within Atrium Health. Bloodstream isolates were identified at the species level with BioFire FilmArray (bioMérieux USA) for the following *Candida* species: *C albicans*, *C glabrata*, *C krusei*, *C parapsilosis*, and *C tropicalis*. Other *Candida* species were identified by matrix-assisted laser desorption ionization–time of flight (Bruker). Susceptibility testing was performed with the Sensititre YeastOne susceptibility panel (Thermo Fisher Scientific), and results were routinely available within 48 to 72 hours of identification.

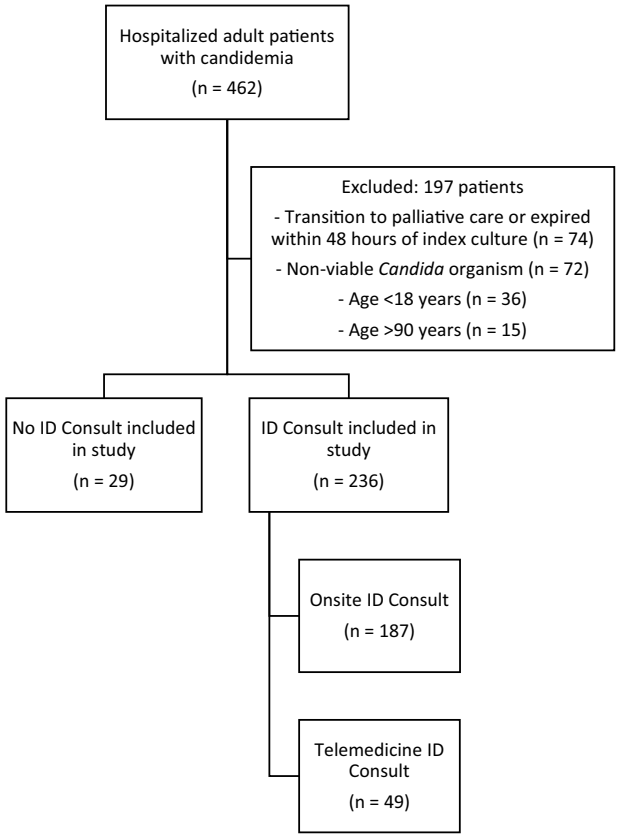

Figure 1. CONSORT diagram for study design. ID, infectious diseases.

RESULTS

All adult patients with candidemia during the study period were screened for inclusion, and 197 met at least 1 exclusion criterion (Figure 1). The final analysis included 265 patients: 236 (89%) in the IDC group and 29 (11%) in the non-IDC group. Of the patients who received IDC, 187 received on-site IDC and 49 received IDC via TM. Baseline characteristics, comorbidities, and predisposing factors were similar among groups with the notable exception of immunosuppression (Table 1). All patients who were immunosuppressed were represented in the on-site IDC group. The most common *Candida* species in both groups were *C albicans* and *C glabrata*, with *C glabrata* being more common in the non-IDC group (29.7% vs 48.3%; $P = .042$). Incidence of fluconazole resistance was more common in patients who received IDC (8.9% vs 0%; $P < .01$), with the majority of these patients receiving on-site IDC. Though the most common source of candidemia was CVC related across all groups, there were significantly fewer patients without an identified source of candidemia in the group that received IDC (40.3% vs 82.8%; $P < .001$).

In-hospital mortality was lower in the IDC group vs non-IDC (20.8% vs 34.5%; $P = .094$) and in the on-site IDC group vs non-IDC (23.5% vs 34.5%; $P = .205$), though this did not reach statistical significance (Table 2). However, a significant reduction in in-hospital mortality was observed in the TM IDC group vs the non-IDC group (10.2% vs 34.5%; $P = .009$). Clinical management and outcomes did not differ significantly between on-site IDC and TM IDC, except in-hospital mortality and hospital length of stay were greater in the on-site IDC group vs the TM IDC group.

Antifungal therapy was initiated more often in patients who received TM IDC vs non-IDC (98% vs 69%; $P < .001$), although time to initiation of antifungal therapy was not significantly different (Table 2). Mean duration of antifungal therapy was significantly longer in the TM IDC group vs the non-IDC group (17.1 vs 8.4 days; $P < .001$). Patients in the TM IDC group were more likely to have documented clearance of fungemia (96% vs 55%; $P < .001$), removal of CVC when present (78% vs 47%; $P = .060$), and echocardiography performed (65% vs 3%; $P < .001$) than those in the non-IDC group. There was no difference in hospital length of stay, intensive care unit length of stay,

Table 1. Demographics and Candidemia-Related Characteristics

Characteristic	No. (%), Mean ± SD, or Median [IQR]				*P* Value	
	IDC (n = 236)	On-site IDC (n = 187)	TM IDC (n = 49)	Non-IDC (n = 29)	IDC vs Non-IDC	On-site vs TM IDC
Age, y	57.3 ± 16.5	57.6 ± 16.4	56.3 ± 17.1	61.1 ± 15.6	.231	.647
Male sex	137 (58.1)	110 (58.8)	27 (55.1)	10 (34.5)	.016	.638
Race					.862	.130
African American	59 (25.0)	52 (27.8)	7 (14.3)	8 (27.6)	.862	.130
Asian	4 (1.7)	4 (2.1)	0 (0)	0 (0)	.762	.052
White	161 (68.2)	121 (64.7)	40 (81.6)	19 (65.5)	>.99	.575
Other	12 (5.1)	10 (5.3)	2 (4.1)	2 (6.9)	.719	.026
Total body weight, kg	82.6 ± 25.6	82.5 ± 24.0	79.5 ± 31.0	81.9 ± 34.8	.919	.535
Pitt bacteremia score	3.2 ± 2.6	3.3 ± 2.6	2.7 ± 2.3	3.0 ± 2.6	.818	.170
Charlson Comorbidity Index	2.4 [0-13]	2.4 [1-4]	2.3 [1-3]	2.3 [1-3]	.913	.728
Comorbidity						
End-stage renal disease	18 (7.6)	14 (7.5)	4 (8.2)	2 (6.9)	>.99	.772
Moderate-severe liver disease	5 (2.1)	3 (1.6)	2 (4.1)	0 (0)	>.99	.278
Leukemia	12 (5.1)	11 (5.9)	1 (2.0)	0 (0)	.373	.468
Lymphoma	3 (1.3)	3 (1.6)	0 (0)	0 (0)	>.99	>.99
Metastatic solid tumor	15 (6.4)	11 (5.9)	4 (8.2)	2 (6.9)	>.99	.521
HIV	2 (0.8)	2 (1.1)	0 (0)	0 (0)	>.99	>.99
Predisposing factor						
Immunosuppression	31 (11.7)	31 (16.6)	0 (0)	0 (0)	.032	<.001
Active malignancy in prior 90 d	40 (16.9)	35 (18.7)	5 (10.2)	4 (13.8)	.796	.157
Chronic steroid therapy in prior 30 d	6 (2.5)	5 (2.7)	1 (2.0)	1 (3.4)	.560	>.99
Recent abdominal surgery in prior 30 d	36 (15.3)	31 (28.5)	5 (10.2)	5 (17.2)	.780	.269
Receipt of TPN in prior 30 d	44 (18.6)	37 (19.8)	7 (14.3)	6 (20.7)	.790	.199
Microbiology						
Candida species						
C albicans	91 (38.6)	76 (40.6)	15 (30.6)	7 (24.1)	.129	.199
C glabrata	70 (29.7)	51 (27.3)	19 (38.8)	14 (48.3)	.042	.117
C parapsilosis	37 (15.7)	32 (17.1)	5 (10.2)	4 (13.8)	>.99	.236
C tropicalis	27 (11.4)	18 (9.6)	9 (18.4)	3 (10.3)	>.99	.087
C krusei	6 (2.5)	6 (3.2)	0 (0)	0 (0)	>.99	.349
Other	17 (7.2)	13 (7.0)	4 (8.2)	3 (10.3)	.468	.759
Polymicrobial index culture	108 (45.8)	86 (46.0)	22 (44.9)	12 (41.4)	.654	.891
Fluconazole resistance	21 (8.9)	18 (9.6)	3 (6.1)	0 (0)	<.01	.580
Receipt of antifungal in prior 30 d	52 (22)	45 (24.1)	7 (14.3)	3 (10.3)	.223	.158
Primary source	156 (66.1)	121 (64.7)	35 (71.4)	5 (17.2)	<.001	.376
Catheter related	80 (33.9)	69 (36.9)	11 (22.4)	1 (3.4)	<.001	<.001
Intra-abdominal	36 (15.3)	30 (16.0)	6 (12.2)	4 (13.8)	>.99	.787
Bone and joint	2 (0.8)	1 (0.5)	1 (2.0)	0 (0)	>.99	.491
Skin and soft tissue	4 (1.7)	1 (0.5)	3 (6.1)	0 (0)	>.99	.013
Endocarditis	3 (1.3)	2 (1.1)	1 (2.0)	0 (0)	>.99	.705
Urinary	23 (9.7)	15 (8.0)	8 (16.3)	0 (0)	.088	.039
Device related	1 (0.4)	0 (0)	1 (2.0)	0 (0)	>.99	.109
Other	7 (3.0)	3 (1.6)	4 (8.2)	0 (0)	>.99	.025
Unknown/undetermined	95 (40.3)	77 (41.2)	18 (36.7)	24 (82.8)	<.001	<.001

Abbreviations: IDC, infectious diseases consultation; TM, telemedicine; TPN, total parenteral nutrition.

leaving against medical advice, or 30-day candidemia-related readmission for patients who received TM IDC vs non-IDC.

DISCUSSION

This is the first study to demonstrate that delivery of IDC via TM significantly decreases the in-hospital mortality of patients with candidemia and in one aspect complements the existing body of literature that IDC decreases mortality [4–6, 16]. However, in contrast to previous studies, the difference in in-hospital mortality between patients who received on-site IDC, or IDC vs non-IDC did not reach statistical significance and warrants further explanation [4–6, 16]. Notably, there was no difference in time to initiation of antifungal therapy,

Table 2. Clinical Management and Outcomes

	No. (%) or Mean ± SD				*P* Value			
	IDC (n = 236)	On-site IDC (n = 187)	TM IDC (n = 49)	Non-IDC (n = 29)	IDC vs Non-IDC	TM IDC vs Non-IDC	On-site IDC vs Non-IDC	On-site IDC vs TM IDC
Antifungal therapy initiated after index culture	231 (97.9)	183 (97.9)	48 (98.0)	20 (69.0)	<.001	<.001	<.001	.996
No treatment	5 (2.1)	4 (2.1)	1 (2.0)	9 (31.0)	.147	.690	.640	>.99
Physician unawareness	1 (0.4)	1 (0.5)	0 (0)	3 (10.3)	.004	.048	.008	>.99
Considered a contaminant	3 (1.3)	3 (1.6)	0 (0)	1 (3.4)	.374	.377	.353	>.99
Other	1 (0.4)	0 (0)	1 (2.0)	5 (17.2)	<.001	.025	<.001	.208
Time to initiation of antifungal therapy, h	48.1 ± 26.8	46.9 ± 26.8	52.6 ± 26.7	50.2 ± 24.6	.720	.722	.601	.193
Duration of therapy, d	17.5 ± 11.6	17.6 ± 12.5	17.1 ± 7.8	8.4 ± 6.2	<.001	<.001	.001	.738
Obtainment of repeat blood cultures	224 (94.9)	177 (93.7)	47 (95.9)	16 (55.2)	<.001	<.001	<.001	.855
Time to blood culture clearance, h	95.6 ± 63.7	98.7 ± 67.2	84.1 ± 47.6	87.9 ± 64.4	.671	.838	.564	.095
Persistent candidemia	17 (7.6)	16 (9.1)	1 (2.1)	0 (0)	.609	>.99	.619	.132
Removal of catheter when present	116/142 (81.7)	102/124 (82.3)	14/18 (77.8)	8/17 (47.1)	.001	.060	.001	.744
Echocardiogram performed	143 (60.5)	111 (59.4)	32 (65.3)	1 (3.4)	<.001	<.001	<.001	.158
Ophthalmologic examination	62 (26.3)	54 (28.9)	8 (16.3)	2 (6.9)	.021	.307	.011	.076
In-hospital mortality	49 (20.8)	44 (23.5)	5 (10.2)	10 (34.5)	.094	.009	.205	.041
Length of stay, d								
Hospital	25.0 ± 25.6	27.6 ± 27.5	15.1 ± 12.2	25.2 ± 54.3	.974	.211	.709	.002
Intensive care unit	12.5 ± 12.7	12.5 ± 12.7	12.7 ± 13.8	13.6 ± 12.1	.735	.841	.727	.942
Left against medical advice	3 (1.3)	2 (1.1)	1 (2.0)	3 (10.3)	.019	.142	.018	.504
30-d candidemia-related readmission	1 (0.4)	1 (0.5)	0 (0)	0 (0)	>.99	>.99	>.99	>.99

Abbreviations: IDC, infectious diseases consultation; TM, telemedicine.

time to obtainment of repeat blood cultures, and time to culture clearance among groups. A key factor that may have contributed to these results is the routine antimicrobial stewardship review of all patients with candidemia, regardless of IDC. A recent study performed at the University of Nebraska Medical Center similarly demonstrated numerically, though not significantly, different outcomes, including mortality, obtainment of repeat blood cultures, and treatment initiation. Authors indicated that an active ASP, which reviewed all positive blood cultures and provided prospective audit and feedback during standard business hours, may have offset a mortality benefit from IDC by providing optimal antifungal therapy [17].

At Atrium Health, standardized ASP services are provided for all patients systemwide. Specifically, all positive blood cultures from all hospitals, regardless of IDC status or consultation modality, are reviewed daily by the ASP pharmacist, and recommendations are communicated to the primary team. Although ID consultation is highly encouraged and routinely recommended by ASP in patients with candidemia, it was not mandatory. In all cases, the ASP pharmacist served as an extension of the Division of Infectious Diseases in non-IDC cases and provided recommendations consistent with best practice guidelines. The observed difference in in-hospital mortality between on-site IDC and TM IDC may in part be explained by the inherent differences in patient population between these sites—for example, no patients were immunocompromised in the TM IDC group (0% vs 17% in the on-site IDC group; $P < .001$). It is worth noting that there was a baseline difference in the distribution of infecting *Candida* species between groups, with 29.7% *C glabrata* in the IDC group and 48.3% in the non-IDC group. Although interesting, this does not entirely explain the outcomes, as there was no mortality reduction between the on-site IDC group (27% *C glabrata*) and non-IDC group (Table 1). One potential contributing factor to the difference in mortality in TM IDC vs non-IDC is that there may be unquantifiable differences in the inherent house staff practices as well as relationships and willingness to accept ASP recommendations at the facilities routinely providing only TM.

This study has several unique strengths. First, it was conducted in a large health care system with standardized protocols, formularies, service lines, and technologies, including the routine use of rapid diagnostics for organism identification, which may have contributed to more timely administration of appropriate antifungal therapy. The strengths and limitations of these advanced technologies need to be acknowledged. During this period, there was an increased risk of false-positive

Candida results when we used the FilmArray Blood Culture Identification Panel from BioFire (RFIT-ASY-0126 and RFIT-ASY-0127) with blood culture bottles from Thermo Fisher (VersaTREK REDOX), bioMérieux (BACT/ALERT), and BD (BACTEC). Therefore, only cultures with sufficient growth were included to avoid results that represented DNA from nonviable organisms. Furthermore, this study utilized only the first blood culture positive for *Candida* species during hospital admission at an Atrium Health facility; therefore, results may not be generalized to nonsystem-based patients.

Application of best practice recommendations for the management of candidemia has been shown to significantly affect mortality in hospitalized patients with candidemia [10, 18, 19]. Our study demonstrates that inpatient TM ID consultation provides a platform to successfully evaluate infection source and implement treatment guidelines. TM IDC facilitated initiation of appropriate antifungal therapy (98% vs 69%; $P < .001$), removal of the CVC (78% vs 47%; $P = .060$), obtainment of repeat blood cultures (96% vs 55%; $P < .001$), and appropriate duration of antifungal therapy (17.1 vs 8.4 days; $P < .001$) when combined with robust antimicrobial stewardship. Increased adherence to guideline-concordant care via TM ID consultation has already been described in patients with *Staphylococcus aureus* bacteremia [8]. The use of TM to deliver IDC has been endorsed by the IDSA, with the aim to increase access to ID specialty care and improve patient outcomes [9]. To our knowledge, this is the only study to include facilities that utilize TM as a mode of IDC delivery in examining the impact of IDC and mortality in patients with candidemia. TM IDC can facilitate improved outcomes for patients with candidemia at sites that lack consistent, routine access to specialty care with IDC.

Future research may be warranted given limitations of the current study, including the retrospective observational design and lack of randomization, which introduced a potential for time and selection bias. However, an attempt to minimize this bias was made by excluding those with imminent death or transition to palliative care within 48 hours from the time of index culture. Additionally, external validity may be less for institutions without a comprehensive ASP. The observed impact of IDC or TM IDC may have been enhanced by rapid review of positive blood cultures by the ASP pharmacist. Conversely, extensive ASP review may have altered the care provided to patients without an IDC, and institutions without ASP may find the impact of IDC or TM IDC to be even more substantial.

CONCLUSION

An overall decrease in in-hospital mortality for patients with candidemia who received an IDC vs no IDC was detected; however, a significant reduction was seen for only a subset of patients who received IDC via TM vs no IDC. Although not intended to overshadow in-person care, these findings provide evidence to support the effective use of TM as a method to deliver IDC in the management of candidemia in conjunction with an established ASP. In resource-limited institutions where on-site IDC is not possible, TM should be strongly considered for 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.

Notes

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