Effect of infectious disease consultation on mortality and treatment of patients with candida bloodstream infections: a retrospective, cohort study

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Summary

Background Candida bloodstream infection is associated with high mortality. Infectious disease consultation improves outcomes in several infections, including *Staphylococcus aureus* and cryptococcosis, as well as multidrug-resistant organisms. We aimed to examine the association between infectious disease consultation and differences in management with mortality in candida bloodstream infections.

Methods In this retrospective, single-centre cohort study, we reviewed the medical charts of all patients admitted to Barnes-Jewish Hospital (St Louis, MO, USA), a tertiary referral centre, aged 18 years or older with candida bloodstream infection from 2002 to 2015. We collected data for demographics, comorbidities, predisposing factors, all-cause mortality, antifungal use, central-line removal, and ophthalmological and echocardiographic evaluation to assess 90-day all-cause mortality between individuals with and without an infectious disease consultation. For the survival analysis we used Cox proportional hazards model with inverse weighting by propensity score to assess the effects of infectious disease consultation on mortality and differences in management.

Findings Between Jan 1, 2002, and Dec 31, 2015, of 1794 patients assessed for eligibility, we analysed 1691 patients with candida bloodstream infection; 776 (45·9%) who had an infectious disease consultation and 915 (54·1%) who did not have an infectious disease consultation. All 1691 patients were included in the analysis. None were missing data. Most underlying comorbidities were evenly distributed between groups. 90-day mortality was lower in the infectious disease consultation group than in patients who did not receive an infectious disease consultation (29% [222/776] *vs* 51% [468/915]; p<0·0001). In the model with inverse weighting by the propensity score, infectious disease consultation was associated with a hazard ratio of 0·81 (95% CI 0·73–0·91; p<0·0001) for mortality. In the consultation group, median duration of antifungal therapy was longer (18 [IQR 14–35] *vs* 14 [6–20] days; p<0·0001) and central-line removal (587 [76%] of 776 *vs* 538 [59%] of 915; p<0·0001), echocardiography use (442 [57%] of 776 *vs* 305 [33%] of 915; p<0·0001), and ophthalmological examination (412 [53%] of 776 *vs* 160 [17%] of 915; p<0·0001) were more frequently done. Fewer patients in the infectious disease consultation group were not treated (13 [2%] of 776 *vs* 128 [14%] of 915; p<0·0001).

Interpretation Patients with candida bloodstream infection receiving an infectious disease consultation have lower mortality. This finding might be attributable to these individuals receiving a higher number of non-pharmacological, evidence-based interventions and lower amounts of non-treatment. These data suggest that an infectious disease consultation should be an integral part of clinical care of patients with candida bloodstream infection.

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Introduction

In the USA, candida is the second most common cause of health-care associated bloodstream infection overall, and the most common fungal bloodstream infection.[1] Mortality attributable to candida bloodstream infection ranges between 15% and 47%,[2,3] and delay in initiation of appropriate treatment has been associated with increased mortality.[4] Conversely, adherence to treatment in keeping with evidence-based guidelines is associated with decreased mortality in patients with candida bloodstream infection.[5]

An infectious disease consultation involves gathering accurate information about patients, through history and physical examination. Particular attention is given to risk factors related to infection with the aim of providing better patient care through appropriate antimicrobial management and implementation of infection control measures. Infectious disease consultation has been associated with improved quality of care and treatment outcomes in various infectious diseases including cryptococcal infection and invasive candidiasis.[5–7] In an observational study of 119 patients with candida

Research in context

Evidence before this study

Candida is a substantial cause of morbidity and mortality. Overall, candida now represents the second most common cause of health-care-associated bloodstream infection in the USA, as well as the most common fungal bloodstream infection. In a preliminary systematic review, we searched MEDLINE and Embase from Jan 1, 1967, to May 8, 2019, using the search terms "candidemia" or "candida blood stream infection" and "infectious diseases consultation". We limited the search to studies in adults aged 18 years and older, with no language restrictions. This search identified six studies in which the effect of an infectious disease consultation was evaluated in patients with candidaemia. Currently, the published literature is limited to small cohorts of candida bloodstream infection, with limited insights into management differences. Even so, these studies support the inclusion of infectious disease expertise in the diagnosis and treatment of candida bloodstream infection. Candida bloodstream infection attributable mortality is reported to range between 15–47%, but with appropriate therapy, these rates can be reduced by almost half. Infectious disease consultations have been found to positively affect mortality outcomes in patients with several bloodstream infections, including *Staphylococcus aureus*, cryptococcus, and multidrug-resistant organisms. Increased adherence to disease management drawn from evidence-based recommendations benefits patients with these bloodstream infections.

Added value of this study

To our knowledge, this is the largest cohort of patients with candida bloodstream infection examining the association between infectious disease consultation and mortality, as well as the most detailed assessment of bloodstream infection management done thus far. We established a 19% survival benefit that persists long-term, which is associated with infectious disease consultation after extensively controlling for patient factors and disease severity using propensity score modelling. Previous cohort studies were too small to allow a robust statistical approach to control for potential confounders. This is the first study to include an extensive number of known risk factors to account for confounding by indication with propensity score modelling and to document extensive differences in management. We showed that increased frequency of interventions often recommended by infectious disease specialists, including central-line removal, echocardiography for detection of endocarditis, more consistent recognition of positive blood cultures, and prolonged duration of antifungal therapy explain the decrease in mortality associated with infectious disease consultation.

Implications of all the available evidence

Our findings show that patients with candida bloodstream infection who received an infectious disease consultation had significantly decreased 90-day mortality through use of evidence-based interventions. The results of this study, combined with others examining bloodstream infection, illustrate that infectious disease consultation significantly lowers the risk of mortality among patients with bloodstream infection. This effect is consistently derived from better adherence to evidence-based standards of treatment. An infectious disease consultation is appropriate, even preferred, for patients with candida bloodstream infection, considering the often variable presentation and complex management of these patients. We highlight the benefit of this consultation for candida bloodstream infection, contributing to the literature supporting its use for patients with bloodstream infection.

bloodstream infection, infectious disease consultation was independently associated with lower mortality at 42 days (18% *vs* 39%), while a second study of 182 patients with candida bloodstream infection showed a lower unadjusted 90-day mortality in individuals who received infectious disease consultation.[5,8] In 2018, another study with 145 patients showed that patients who received an infectious disease consultation were 66% less likely to die within 30 days.[9] However, these studies had small numbers of patients and therefore analysis was limited in its power to properly adjust for possible confounders.

The primary aim of this study was to determine the effect of infectious disease consultation on mortality in patients with candida bloodstream infection using very conservative propensity score analysis to limit potential confounding by indication. We also sought to ascertain what specific aspects of management, if any, were associated with differences in mortality between individuals who did and did not receive an infectious disease consultation.

Methods

Study design and participants

We did a retrospective cohort analysis of all patients diagnosed with candida bloodstream infection at Barnes-Jewish Hospital (St Louis, MO, USA), a tertiary referral centre.

All patients aged 18 years and older admitted to hospital between Jan 1, 2002, and Dec 31, 2015, with at least one blood culture positive for *Candida* spp were included in this study. The first blood culture positive for *Candida* spp in the time frame of the study was defined as the index blood culture. To avoid analysing recurrences, patients with candida bloodstream infection in the first 3 months of 2002 who also had a positive candida blood culture in the previous 90 days were excluded. Individuals who died within 24 h of the index blood culture collection date were also excluded, as an infectious disease consultation could not reasonably have been obtained. Individuals who were not treated because they underwent palliative care were also excluded.

The Washington University in St Louis Human Research Protection Office approved the study with a waiver of informed consent.

Procedures

We used the BJC Healthcare Medical Informatics database to collect demographic data, medical history including oncological and transplant history, vital signs, laboratory values (white blood cells, absolute neutrophil, absolute lymphocytes, haemoglobin, platelets, alanine aminotransferase, aspartate aminotransferase, amylase, lipase, and total and direct bilirubin), neutropenia (absolute neutrophil count ≤500 cells per µL), and receipt of total parenteral nutrition within 30 days before the index blood culture, inpatient medications ordered within 90 days before the index blood culture, and number and results of subsequent blood cultures and mortality. Dates of death were also extracted from the BJC Healthcare Medical Informatics database and supplemented when necessary with information from the Social Security Death Index.

The BJC Healthcare Medical Informatics database was originally developed for surveillance of hospital-acquired infections,[10] but later used for numerous studies by Washington University investigators, including development of pharmacy alerts,[11] automated surveillance of central-line associated bloodstream infections,[12] risk factors and outcomes of multidrug-resistant organisms, surgical-site infections, *Clostridioides difficile* infections, and many others.[13,14] The database contains discrete data obtained directly from the electronic applications used to display clinical data to health-care workers, including administrative, laboratory, vital signs, and pharmacy data. For variables that are not captured in the informatics database (eg, results of histopathology and echocardiography), extensive medical record review was done.

For the analysis, we used the most extreme vital signs (ie, highest temperature, respiratory rate, and heart rate, and lowest blood pressure) measured within 24–48 h before or 24 h after the collection of the index blood culture, and the value most immediate to the index blood culture of the laboratory tests drawn within 1 week before or 1 day after the index blood culture.

Comorbidities present during the admission or in the previous year of the index blood culture were obtained with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes, including: Elixhauser comorbidities,[15] receipt of radiation therapy or chemotherapy (or both), history of solid organ and bone-marrow transplant, burns, infections, coronary artery disease, and malignancy. A full description of all ICD-9-CM diagnosis codes included has previously been published.[16]

To assess the management of the candida bloodstream infection, we used chart review to identify antifungal agents, length of antifungal therapy (including switches, and starting from the day the index blood culture was drawn), central venous catheter removal, echocardiography (transthoracic or transoesophageal), ophthalmology consultation, infectious disease consultation, and the timing of the infectious disease consultation. For individuals who did not receive antifungal treatment, we assessed the physician's notes and medication administration logs during the admission. On the basis of the notes and logs, three possible categories were established: culture regarded as a contaminant (clinician was aware, but no treatment was given), clinician unaware (no recorded acknowledgment of cultures in notes), and leaving the hospital against medical advice before treatment could be initiated. Patients were classified as having received an infectious disease consultation through a two-step process. First, patients were classified on the basis of an internal database that our department keeps for the purposes of billing. This database has high validity (>99%), based on previous internal audits. To ensure that this database is accurate for our cohort, chart review was done by the authors (CM, JO, RK, CL, ASS, AS) for confirmatory purposes. No discrepancies were encountered. For the analysis, infectious disease consultation was defined as a time-dependent variable to include only individuals who received a consultation 24 h before and up to 7 days after the collection date of the index blood culture.

During this study, there were five infectious disease consultation teams at the Barnes-Jewish Hospital, three of them teaching teams that included one infectious disease fellow and one infectious disease pharmacist, in addition to the infectious disease attending physician. At the Barnes-Jewish Hospital, all patients, regardless of the admitting service, have the opportunity for an infectious disease consultation if requested by the physician caring for the patient.

Statistical analysis

The primary outcome was 90-day all-cause mortality, as mortality beyond 90 days was considered less likely to be related to candida bloodstream infection. As secondary outcomes, we assessed the management of the candida bloodstream infection using the following process measures: type and total duration of all antifungals used, central-line removal, ophthalmological evaluation to rule out endophthalmitis, and echocardiographic evaluation to rule out endocarditis.

χ^2 or Fisher's exact tests and the *t* test or Mann-Whitney U test were used for descriptive statistics, as appropriate. To determine the effect of infectious disease consultation on 90-day all-cause mortality, we first developed a non-parsimonious logistic regression model to create the propensity score for receipt of infectious disease consultation. In this model, infectious disease consultation was the dependent variable, and all potential predictors of infectious disease consultation or mortality were included as independent variables.[17] The potential predictors of infectious disease consultation comprised patient demographics, comorbidities, laboratory values in the 24 h preceding the collection date of the index candida

	Infectious disease consultation (n=776)	No infectious disease consultation (n=915)	p value
Age, years	56·2 (16·4)	59·0 (16·7)	0·0071
Sex			
Women	365 (47%)	428 (37%)	
Men	411 (53%)	487 (53%)	0·91
Ethnicity			
White	509 (66%)	557 (61%)	0·042
Black	261 (33%)	345 (38%)	
Other	6 (1%)	13 (1%)	
Comorbidities			
Hypertension	324 (42%)	378 (41%)	0·84
Diabetes	185 (24%)	209 (23%)	0·62
Coronary artery disease	178 (23%)	193 (21%)	0·34
Chronic liver disease	44 (6%)	75 (8%)	0·038
Chronic kidney disease	136 (18%)	131 (14%)	0·084
Predisposing factors			
Solid tumours	254 (33%)	328 (36%)	0·18
Haematological malignancy	109 (14%)	183 (20%)	0·0001
Bone marrow transplant	2 (<1%)	15 (2%)	0·0069
Solid organ transplant	5 (1%)	6 (1%)	0·95
Cancer chemotherapy	31 (4%)	65 (7%)	0·0087
Radiation therapy	7 (1%)	12 (1%)	0·41
Neutropenia	50 (6%)	79 (9%)	0·094
Total parenteral nutrition within previous 30 days*	241 (31%)	264 (29%)	0·31
Corticosteroids within previous 90 days*	198 (26%)	258 (28%)	0·23
Central lines			
Permanent central line	298 (38%)	329 (36%)	0·28
Temporary central line	352 (45%)	449 (49%)	0·13
Dialysis catheter	73 (9%)	105 (12%)	0·17
Microbiology			
Candida albicans	354 (46%)	442 (48%)	0·88
Candida glabrata	152 (20%)	174 (19%)	..
Candida parapsilosis	117 (15%)	123 (13%)	..
Candida tropicalis	57 (7%)	63 (7%)	..
Candida krusei	25 (3%)	27 (3%)	..
Other *Candida* species	71 (9%)	86 (9%)	..
Admission to the intensive care unit	124 (16%)	93 (10%)	<0·0001

Data are mean (SD) or n (%). *Of the index blood culture.

Table 1: **Baseline characteristics**

blood culture, other infections, cancer, and the year of admission. Missing data were minimised by manual chart review to ensure complete collection of all available information One participant was excluded from analysis because of missing key variables. The use of restricted cubic splines was assessed for all continuous variables, with the choice of a simple continuous variable or spline and number of knots based on minimisation of the Akaike Information Criterion.[18] The predicted probabilities (ie, propensity score) were saved from this model. Balance of covariates was assessed after weighting by the propensity score using standardised differences, with differences of 0·10 or more indicating imbalance (appendix p 1).[19] Modifications to the propensity score model were made until all covariates were balanced (appendix p 4).

See Online for appendix

In the second stage, a Cox proportional hazards model was used to establish the effect of infectious disease consultation on 90-day all-cause mortality, with inverse weighting by the propensity score according to the treatment received (ie, 1/propensity score for patients who had an infectious disease consultation, and 1/[1–propensity score] for patients without). Infectious disease consultation was treated as a time-dependent variable in the model, to account for variability in timing of consultation. The population was trimmed before doing the second-stage Cox model by removing the top and bottom 1% of the propensity score distribution, because weights at the ends of the distribution are unstable (appendix p 4).[20] In the primary model, the only variable included was infectious disease consultation. Survival by time was plotted from the results of the primary Cox model. In a separate adjusted model, we included additional covariates significantly associated with mortality. Due to small number of cases in the partial year of data (2015), cases from that year were grouped with the previous (2014) year. The proportional hazards assumption was verified for all covariates based on plots of the Schoenfeld residuals. All statistical tests were two-tailed and significance was set at $\alpha=0\cdot05$.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 1, 2002, and Dec 31, 2015, of 1794 patients identified with candida bloodstream infection, 103 were excluded (94 because of death within 24 h of culture results, six because of withdrawal of care, two because of previous episode of candida bloodstream infection before January, 2002, and one because of missing data and withdrawal of care).

Of the 1691 patients included in the final analysis, the mean age was 57·7 years (SD 16·5), 898 (53·1%) were men and 793 (46·9%) were women, and 1066 (63·0%) were white and 606 (35·9%) were black (table 1). 776 (45·9%) patients had an infectious disease consultation and 915 (54·1%) did not have an infectious disease consultation. The proportion of patients who received an infectious disease consultation increased over time (appendix p 5). Patients in the infectious disease consultation group were slightly younger than those

	Infectious disease consultation (n=776)	No infectious disease consultation (n=915)	p value
Antifungal therapy			
Echinocandins	328 (42%)	334 (37%)	0·11
Azoles	382 (49%)	412 (45%)	0·057
Liposomal amphotericin B	53 (7%)	41 (4%)	0·27
No treatment	13 (2%)	128 (14%)	<0·0001
Physician unawareness	8 (1%)	32 (4%)	0·0065
Considered a contaminant	4 (1%)	89 (10%)	0·0052
Left against medical advice	1 (<1%)	7 (1%)	0·57
Treatment duration, days			
Total duration of therapy*	18 (14–35)	14 (6–20)	<0·0001
Echinocandins	7 (2–15)	5 (2–14)	0·18
Azoles	13 (4–18)	10 (3–15)	0·0039
Liposomal amphotericin B	4 (1·00–8·00)	3 (1·25–5·75)	0·47
Microbiological follow-up			
Number of blood cultures performed	9 (6–15)	7 (4–12)	<0·0001
Number of positive blood cultures	2 (1–3)	1 (1–2)	<0·0001
Time to blood culture clearance, h	48 (27·5–82·0)	48 (23·0–80·0)	0·98
Echocardiography			
Overall	442 (57%)	305 (33%)	<0·0001
Transthoracic	414 (53%)	286 (31%)	<0·0001
Transoesophageal	127 (16%)	44 (5%)	<0·0001
Ophthalmology consultation	412 (53%)	160 (17%)	<0·0001
Central-line removal	587 (76%)	538 (59%)	<0·0001

Data are n (%) or median (IQR). *Includes all antifungal agents used.

Table 2: **Comparison of treatment characteristics**

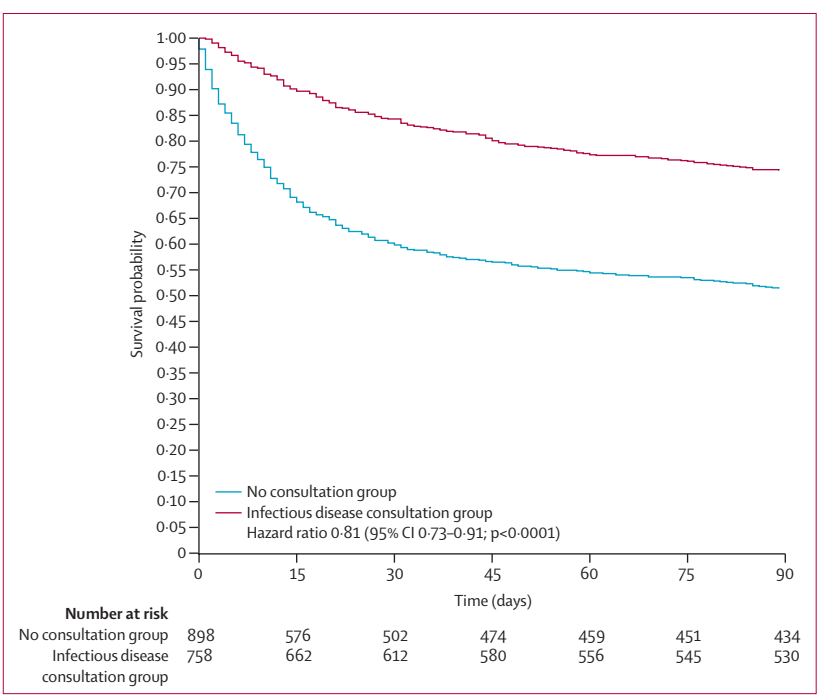

Figure: **Survival curve for 90-day all-cause mortality after inverse weighting by propensity score**

in the non-consultation group (56·2 *vs* 59·0 years; p=0·0071). Distribution of sex and comorbidities was similar between groups, other than chronic liver disease, which was more common in participants without an infectious disease consultation (75 [8%] of 915 *vs* 44 [6%] of 776; p=0·042). Predisposing factors and the presence of central lines were evenly distributed between patients with and without an infectious disease consultation, except that patients with an infectious disease consultation were less frequently coded for haematological malignancy (109 [14%] of 776 *vs* 183 [20%] of 915; p=0·0001) or cancer chemotherapy (31 [4%] of 776 *vs* 65 [7%] of 915; p=0·0094). There were more patients admitted to the intensive care unit in the infectious disease consultation group (124 [16%] of 776 *vs* 93 [10%] of 915; p<0·0001). We observed no difference between the two groups in the species of *Candida* isolated (p=0·88; table 1).

1550 (91·6%) of 1691 patients received antifungal therapy. Initial selection of antifungal treatment was not different between patients with and without an infectious disease consultation. Overall, azoles were the most commonly used antifungals in 794 (46·9%) of 1691 patients, followed by echinocandins in 662 (39·1%), and liposomal amphotericin B in 94 (5·6%). Overall, the median duration of antifungal therapy was longer in patients who received an infectious disease consultation (18 *vs* 14 days; p<0·0001; table 2). 141 (8·3%) patients with candida bloodstream infection did not receive any treatment. This finding was less common in individuals who had an infectious disease consultation (13 [2%] of 776 *vs* 128 [14%] of 915; p<0·0001). Of the untreated patients, the reasons not to treat in the infectious disease consultation and no consultation group were: positive blood culture regarded as a contaminant (four [1%] of 776 *vs* 89 [10%] of 915; p=0·0052), culture result unknown to the treating physician (eight [1%] of 776 *vs* 32 [4%] of 915; p=0·0065); and leaving the hospital against medical advice before the culture results were available (one [<1%] of 776 *vs* seven [1%] of 915; p=0·57; table 2).

Non-pharmacological management also differed between patients who did and did not receive an infectious disease consultation (table 2). Central-line removal occurred more frequently in individuals who received an infectious disease consultation than individuals who did not (587 [76%] of 776 *vs* 538 [59%] of 915; p<0·0001). Both the median number of blood cultures (nine *vs* seven; p<0·0001) and the median number of positive blood cultures (two *vs* one; p<0·0001) was higher in patients who received an infectious disease consultation than in individuals who did not. Median time to blood culture clearance was 48 h and did not differ between groups (p=0·98). Median time to central-line removal was 37 h in the infectious disease consultation group compared with 38 h in the non-consultation group (p=0·79).

Use of echocardiography (56·9% [442/776] *vs* 33·3% [305/915]; p<0·0001) and ophthalmological evaluation

were more frequently obtained in individuals who received an infectious disease consultation. Diagnosis of endocarditis was more common in the infectious disease consultation group (30 [4%] of 776 *vs* five [1%] of 915; p<0·0001), as was the diagnosis of endophthalmitis (23 [3%] of 776 *vs* four [1%] of 915; p<0·0001).

The 42-day mortality was 22% (173 of 776) in people with an infectious disease consultation compared with 47% (431 of 915) in people without an infectious disease consultation (p<0·0001). By 90 days, 690 (40·8%) of 1691 patients had died. The infectious disease consultation group had lower 90-day mortality than patients without an infectious disease consultation (222 [29%] of 776 *vs* 468 [51%] of 915; p<0·0001). Of the 141 untreated patients, 94 (67%) had died by day 90.

In the primary inverse propensity-score weighted Cox model, infectious disease consultation was associated with lower mortality than no infectious disease consultation, with a hazard ratio (HR) of 0·81 (95% CI 0·73–0·91; p<0·0001; figure), translating to a 19% survival benefit for infectious disease consultation. In the secondary inverse weighted Cox model, which included additional covariates significantly associated with mortality, the protective value of the infectious disease consultation remained unchanged (HR 0·82, 0·72–0·92; p=0·0061), Other risk factors for 90-day mortality in this model included age, renal failure, diabetes, surgical-site infections, and the year the consultation was received (table 3). Comorbidities including pulmonary circulation disorders and liver disease were significantly associated with increased risk of 90-day mortality (table 3).

Although year of diagnosis was used as a covariate in our models to account for change over time, we further explored the effect of year with two additional analyses. First, we created separate propensity score models using the data in two time periods, early (2002–07) and late (2008–15). In the models, done as above for the primary analyses, the association of infectious disease consultation with 90-day mortality remained significant with HRs of 0·79 (95% CI 0·67–0·93; p=0·0044) for the early time periods of 2002–07 and 0·83 (0·71–0·97; p=0·021) for the later time periods of 2008–15. Second, a standard multivariable Cox proportional hazards model (not involving the propensity score) was done, in which infectious disease consultation was treated as a fixed effect and also included as an interaction with year. In that model, the interaction of infectious disease consultation by year was non-significant for all years, except 2004, a unique year when mortality was particularly low in the infectious disease consultation group.

	Hazard ratio (95% CI)	p value
Infectious disease consultation	0·82 (0·72–0·92)	0·0061
Age	1·01 (1·01–1·02)	<0·0001
Year of candidaemia	..	0·0022
2003	1·02 (0·77–1·35)	..
2004	1·07 (0·80–1·43)	..
2005	1·36 (1·04–1·77)	..
2006	1·58 (1·21–2·06)	..
2007	1·36 (1·03–1·79)	..
2008	1·62 (1·23–2·12)	..
2009	1·14 (0·85–1·54)	..
2010	1·17 (0·88–1·54)	..
2011	1·39 (1·03–1·87)	..
2012	1·27 (0·93–1·73)	..
2013	1·50 (1·09–2·07)	..
2014	0·92 (0·66–1·29)	..
Valvular diseases	1·14 (0·99–1·31)	0·068
Disorder of pulmonary circulation	1·33 (1·15–1·54)	0·0067
Neurological disorders	0·81 (0·71–0·92)	0·0093
Diabetes	0·71 (0·63–0·80)	<0·0001
Renal failure	0·77 (0·68–0·88)	0·0005
Liver disease	1·22 (1·05–1·42)	0·013
Solid tumour without metastasis	0·69 (0·57–0·84)	0·0003
Fluid and electrolyte disorders	0·85 (0·74–0·98)	0·034
Psychoses	0·87 (0·73–1·03)	0·10
Depression	0·80 (0·69–0·90)	0·0065
Surgical-site infection	0·59 (0·51–0·68)	0·0004
Gastroenteritis	1·22 (1·06–1·40)	0·0074
Upper respiratory tract infection	0·54 (0·37–0·80)	0·0021
Viral infection	1·32 (1·06–1·64)	0·011
Haemoglobin	0·93 (0·89–0·97)	0·0061

Multivariable Cox proportional hazards model with inverse weighting by propensity score. The model was adjusted for white blood cell count and platelet count using cubic splines.

Table 3: **Factors associated with 90-day mortality in patients with candida bloodstream infection**

Discussion

In patients with candida bloodstream infection, infectious disease consultation was associated with an adjusted HR of 0·81 for mortality, translating to a 19% survival benefit. Previous studies have shown that patients with serious and complex infections that have diverse presentations and outcomes have decreased mortality or improvements in other quality-of-care metrics when managed with the assistance of an infectious disease consultation.[6,7] To our knowledge, this is the largest cohort of patients with candida bloodstream infection in which the association between infectious disease consultation and mortality has been examined. In keeping with our findings, previous studies with a smaller number of patients with candidaemia have also found improved survival associated with having an infectious disease consultation.[5,8,9,21] However, this is the first study that included an extensive number of known risk factors to account for confounding by indication through the use of propensity score modelling and to extensively document the differences in management. Furthermore, this particular cohort was constructed specifically to study outcomes in patients with *Candida*

spp infections and has been previously used to address other research questions related to candida.[16,22]

Clinical practice guidelines from the Infectious Disease Society of America and the European Society of Clinical Microbiology and Infectious Diseases provide evidence-based recommendations for the management of patients with candida bloodstream infection.[23,24] Treatment of candida bloodstream infection can be complex given the need for timely interventions that improve patient outcomes, such as indwelling device and catheter removal,[25] prompt initiation of antifungal treatment[26] of adequate duration,[23] need for medical and surgical specialty interventions,[27] as well as consideration of *Candida* spp and host specific factors.[28] Appropriate management of these factors seem to yield better outcomes.[5] A scoring system developed in 2018, the EQUAL Candida Score, summarises and weighs the recommendations for the optimal management of candida bloodstream infection, providing a tool that could be used to measure guideline adherence, facilitate clinical decision making, and improve quality of care.[29]

Candidaemia is associated with up to 71% mortality, an alarming rate that can be decreased by almost half when appropriate therapy is given.[3] In our study, when an infectious disease consultation was done, blood cultures were much less frequently ignored and therefore fewer patients in this group went untreated. The most common causes of not treating patients in the infectious disease consultation group were physician unawareness of a positive culture and the patient leaving against medical advice.

Previous studies have shown higher rates of appropriate empirical antimicrobial therapy in patients with bloodstream infections caused by other types of microorganisms who had an infectious disease consultation.[6] Inadequate initial empirical antifungal therapy is associated with increased mortality in patients with candida bloodstream infection.[30] Although in our study initial selection of antifungals was not dissimilar between groups, patients seen by an infectious disease physician received a significantly longer treatment course (18 *vs* 14 days). Longer duration of treatment could be attributed to the increased number of candida bloodstream infection complications seen in the infectious disease consultation group or because documented negative blood culture was established as the first day of the prescribed treatment course received, as recommended per current treatment guidelines.[23]

Central lines are a well known predisposing factor for candida bloodstream infection.[31] Central-line removal is an intervention that is associated with faster blood culture clearance and shown to be a prognostic factor of mortality.[25,31] However, based on the absence of randomised controlled trials to evaluate the effect of central-line removal, a 2016 meta-analysis found no evidence to support catheter removal in patients with candida bloodstream infection.[32] In our study, removal of the central line was associated with lower 90-day mortality in patients with candida bloodstream infection; an intervention that was more frequently done when infectious disease physicians were involved in the patient's care.

In our study, patients in the infectious disease consultation group were more often assessed for complications of candidaemia. Not identifying patients with a higher burden of disease could also explain the higher mortality seen in the group who did not have an infectious disease consultation. Use of echocardiography and subsequent diagnosis of infective endocarditis were both more common in patients who received an infectious disease consultation, similar to the increased use of such diagnostic tools in patients with *Staphylococcus aureus* bacteraemia who were seen by an infectious disease physician.[33] In the infectious disease consultation group, the incidence of endocarditis in patients with candida bloodstream infection was 3·9% (30 patients), similar to that seen in a 2015 retrospective study (4·2%).[34]

The prevalence of haematogenous endophthalmitis can vary between 2·2% to 20·1% in patients with candida bloodstream infection.[35] Given that ocular candidiasis can be clinically silent in up to 50% of cases,[36] and that many patients with candida bloodstream infection are too ill to communicate their symptoms, current treatment guidelines recommend that all patients with candidaemia should have a funduscopic examination.[23] In our study, ophthalmological examination was more frequently done when patients had an infectious disease consultation and therefore detection of endophthalmitis was also more common in this group.

The increased frequency of these interventions, not ignoring positive blood cultures and a longer duration of antifungal therapy, might have been responsible for the decreased mortality seen in the infectious disease consultation group. This finding is in keeping with the mortality benefit of a consultation in patients with *S aureus* bacteraemia, in which it has been shown that the effect is derived from better adherence to these quality-of-care standards.[33]

However, our study has several limitations. First, it is a single centre, retrospective study subject to potential unmeasured confounding. However, to date, it is the largest cohort of patients with candida bloodstream infection and included a very extensive list of established prognostic comorbidities,[15] as well as known specific predisposing factors for development of candida bloodstream infection.[37] The beneficial effect of receiving an infectious disease consultation appears to be a universal phenomenon across institutions, as seen in much smaller studies.[5,8,9] Notably, this study was done in the USA where clinical microbiologists rarely advise physicians on direct patient management. It would be interesting to examine the effect of an infectious disease physician consultation on outcomes in a setting with different clinical practice

models. Second, even in a large centre, the number of patients with some of the important predisposing factors were small. However, this distribution is likely to be reflective of the patient case mixes seen in other tertiary referral centres. Finally, selection bias could have occurred as some patient populations were under-represented in each group. However, we adjusted these differences between groups with inverse weighting by propensity score and used Cox proportional hazards regression analysis. In the primary analysis, we included only infectious disease consultation in the model, and in secondary analysis, other variables independently associated with 90-day mortality.

In conclusion, in our study, using a conservative analysis method, patients with candida bloodstream infection who received an infectious disease consultation were significantly less likely to die than patients without an infectious disease consultation. The patients in the infectious disease consultation group more often had investigations and treatment consistent with evidence-based practices. The disease was less often left untreated by infectious disease physicians. The protective effect of obtaining an infectious disease consultation on mortality in patients with candida bloodstream infection suggests that this consultation should be an integral part of the clinical care of patients with candidaemia.

Contributors

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. AS, CM-C, MAO, KH, and JO'H were responsible for study concept and design. CM-C, JO'H, MAO, DS, ASS, RK, CL, KH, GP, and AS were responsible for acquisition, analysis, or interpretation of data. AS, CM-C, MAO, and JO'H were responsible for drafting of the manuscript. MAO and DS were responsible for statistical analysis. AS obtained funding.

Declaration of interests

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