HHS Public Access

Author manuscript

Lancet Infect Dis. Author manuscript; available in PMC 2020 December 01.

Published in final edited form as:

Lancet Infect Dis. 2019 December ; 19(12): 1336–1344. doi:10.1016/S1473-3099(19)30405-0.

Impact of Infectious Diseases Consultation on Mortality and Treatment of Patients with *Candida* Bloodstream Infections: A Retrospective Cohort Study

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Abstract

Background—*Candida* blood stream infection (BSI) is associated with high mortality. Infectious diseases (ID) consultation improves outcomes in several infections, including *Staphylococcus aureus*, cryptococcosis and resistant organisms. We examine the association between ID consultation for Candida BSI with mortality and differences in management.

Methods—In this retrospective, single-center cohort study, medical charts of all hospitalized patients ≥18 years old with Candida BSI from 2002 to 2015 were reviewed. We collected demographics, comorbidities, predisposing factors, all-cause mortality, antifungal usage, central line removal, ophthalmologic and echocardiographic evaluation to evaluate 90-day all-cause mortality between those with and without an ID consult. For the survival analysis we used Cox proportional hazards model with inverse weighting by propensity score to have an ID consult.

Findings—Analysis included 1,691 patients; 776 (45.9%) in the ID consult group. Most underlying comorbidities were evenly distributed between groups. Ninety-day mortality was 40.8% (690 patients). In the model with inverse weighting by the propensity score, ID consult was associated with a hazard ratio of 0.81 (95% CI: 0.73, 0.91, p<0.001) for mortality. In the consult

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Drafting of the manuscript: Spec, Mejia-Chew, Olsen, O'Halloran.

Statistical analysis: Olsen, Stwalley.

Obtained funding: Spec.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official view of the NIH or Astellas Global Development Pharma, Inc.

group median duration of antifungal therapy was longer (18 vs 14 days, p<0.001) and central line removal (75.6% [587/776] vs 58.8% [538/915], p<0.001), echocardiography use (56.9% [442/776] vs 33.3% [305/915], p<0.001) and ophthalmologic examination (53.1% [412/776] vs 17.5% [160/915], p<0.001) were more frequently done. Fewer patients in the ID consult group were not treated (1.7% [13/776] vs 14% [128/915], p<0.001).

Interpretation—Patients with Candida BSI receiving an ID consult have lower mortality. This may be attributable to a higher receipt of non-pharmacological, evidence-based interventions and lower rate of non-treatment. These data suggest that an ID consult should be an integral part of clinical care of patients with Candida BSI.

Funding—Astellas Global Development Pharma, Inc., Washington University Institute of Clinical and Translational Sciences, the Agency for Healthcare Research and Quality.

Keywords

Candida blood stream infection; candidemia; mortality; Infectious Disease consult; prognosis; therapy

Introduction

In the United States, *Candida* is the most common cause of Health Care-Associated bloodstream infection (BSI) overall, and the most common fungal BSI.[1] Mortality attributable to *Candida* BSI is reported to range between 15–47% [2,3] and delay in initiation of appropriate treatment has been associated with increased mortality.[4] Conversely, adherence to treatment in keeping with the evidence-based guidelines is associated with decreased mortality in patients with candida BSI.[5]

Infectious diseases (ID) consultation has been associated with improved quality of care and treatment outcomes in a variety of infectious diseases including cryptococcal infection and invasive *candidiasis*.[5–7] In an observational study of 119 patients with *Candida* BSI, ID consultation was independently associated with lower mortality at 42 days (18% versus 39%), while a second study of 182 patients with *Candida* BSI demonstrated a lower unadjusted 90-day mortality in those who received ID consultation for BSI.[5,8] Recently, another study with 145 patients showed that patients who received an ID consult were 66% less likely to die within 30 days.[9] However, these studies had small numbers of patient and therefore analysis was limited in its power to properly adjust for possible confounders.

The primary aim of this study was to determine the impact of ID consultation on mortality in patients with candida BSI 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 those who did and did not receive an ID consultation.

Methods

Study design

We performed a retrospective cohort analysis of all patients diagnosed with Candida BSI at Barnes Jewish Hospital, a 1,323 bed tertiary referral center. The Washington University in St. Louis Human Research Protection Office approved the study with a waiver of informed consent.

Cohort Construction

All patients age 18 and older hospitalized between 1/1/2002 and 12/31/2015 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 analyzing recurrences, patients with Candida BSI in the first quarter of 2002 who also had a positive Candida blood culture in the prior 90-days were excluded. Individuals who died within 24 hours of the index blood culture collection date were also excluded, as an ID consult could not reasonably have been obtained. Individuals who were not treated because they underwent palliative care were also excluded.

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, hemoglobin, platelets, alanine aminotransferase, aspartate aminotransferase, amylase, lipase, total and direct bilirubin), neutropenia (absolute neutrophil count $\leq 500/mm^3$), and receipt of total parenteral nutrition (TPN) within 30 days before the index blood culture, inpatient medications ordered within 90 days prior to the index blood culture as well as number and results of subsequent blood cultures and mortality.

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, Clostridium 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 (e.g., results of histopathology and echocardiography), extensive medical record review was performed.

For the analysis we used the most extreme vital signs (highest temperature, respiratory rate, and heart rate; lowest blood pressure) measured within 24 −48 hours prior to or 24 hours post the collection of the index blood culture, and the value most immediate to the index blood culture of the laboratory tests drawn within one week prior or one day after the index blood culture.

Comorbidities present during the admission or in the previous year of the index blood culture were obtained using ICD-9-CM diagnosis codes, including: Elixhauser

comorbidities,[15] receipt of radiation therapy and/or chemotherapy, 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* BSI 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 transesophageal), ophthalmology consult, ID consult and the timing of the ID consultation. For those who did not receive antifungal treatment, we assessed the physician's notes and medication administration logs during the admission. Based on this, three possible categories were established: 1) culture regarded as a contaminant (clinician was aware, but no treatment was given), 2) clinician unawareness (no recorded acknowledgement of cultures in notes) and, 3) leaving the hospital against medical advice before treatment could be initiated. Patients were classified as having received an Infectious Diseases Consultation through a two-step process. First, patients were classified based on an internal database that our department keeps for the purposes of billing. This database has high validity (>99%) as was assessed by previous internal audits. In order to ensure that this database is accurate in our cohort, chart review was performed by the authors for confirmatory purposes. There were no discrepancies encountered. For the analysis, ID consultation was defined as a time-dependent variable to include only those received a consult 24 hours prior and up to seven days after the collection date of the index blood culture.

At the time period of this study there were five ID consult teams, three of them teaching teams that included one ID fellow and one ID pharmacist, in addition to the ID attending. In our institution, all patients regardless of the admitting service have the opportunity of getting an ID consult if requested by the physician caring for the patient.

Outcomes

The primary outcome was 90-day all-cause mortality, as mortality beyond 90 days was considered less likely to be related to *Candida* BSI. Dates of death were extracted from the BJC Medical Informatics database and supplemented when necessary with information from the Social Security Death Index (SSDI). As secondary outcomes we assessed the management of the *Candida* BSI using the following process measures: type and total duration of all antifungals used, central line removal, ophthalmologic and echocardiographic evaluation to rule out endophthalmitis and endocarditis, respectively.

Statistical Analysis

Chi-square or Fisher's exact tests and t-test or Mann-Whitney U test were used for descriptive statistics, as appropriate. To determine the impact of ID consultation on 90-day all-cause mortality, we first developed a nonparsimonious logistic regression model to create the propensity score for receipt of ID consult. In this model, ID consult was the dependent variable, and all potential predictors of ID consult or mortality were included as independent variables.[17] The potential predictors of ID consult included patient demographics, comorbidities, laboratory values in the 24 hours preceding the collection date of the index Candida blood culture, other infections, cancer, and the year of admission. Missing data was

minimized by manual chart review to ensure complete collection of all available information. The one patient missing key laboratory variables was excluded from the final analysis. One participant was excluded from analysis due to 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 minimization of the Akaike Information Criterion.[18] The predicted probabilities (i.e., propensity score) were saved from this model. Balance of covariates was assessed after weighting by the propensity score (PS) using standardized differences, with differences of 0.10 or greater indicating imbalance (Supplement. Table 1) [19]. Modifications to the propensity score model were made until all covariates were balanced (Supplement. Figure 1).

In the second stage a Cox proportional hazards model was used to determine the impact of ID consult on 90-day all-cause mortality, with inverse weighting by the propensity score according to the treatment received (i.e., 1/PS for patients who had an ID consult, and 1/(1-PS) for patients without). ID consult was treated as a time-dependent variable in the model, in order to account for variability in timing of consultation. The population was trimmed prior to performing the second-stage Cox model by removing the top and bottom 1% of the propensity score distribution, since weights at the ends of the distribution are unstable (Supplement. Figure 1).[20] In the primary model the only variable included was ID consult. 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. The proportional hazards assumption was verified for all covariates based on plots of the Schoenfeld residuals. All statistical tests were 2-tailed and significance was set at $\alpha = 0.05$.

Role of the Funding source—This study was funded by Astellas Global Development Pharma, Inc., through an investigator-sponsored grant (MYCA-15L03) to the hosting institution. In addition, research reported in this publication was supported by the Washington University Institute of Clinical and Translational Sciences grant UL1 TR002345 from the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health (NIH), and Grant Number R24 HS19455 through the Agency for Healthcare Research and Quality (AHRQ). The funding sources had no role in the design and conduct of the study; collection, management, and analysis of the data; or preparation, review, and approval of the manuscript.

Results

Cohort

Of 1,794 patients identified with Candida BSI, 103 were excluded (94 due to death within 24 hours of culture results, 7 due to withdrawal of care, and 2 due to previous episodes of Candida BSI prior to January 2002).

Of the 1,691 patients included in the final analysis, mean (±SD) age was 57.7 (16.5) years, 898 (53.1%) were male and 1,066 (63%) were white. There were 776 (45.9%) patients in the ID consult group. The proportion of patients who received an ID consult increased over time (Supplement. Figure 2). Patients in the ID consult group were slightly younger than the non-consult group (56.2 vs 59 years, p=0.007). Distribution of gender and comorbidities was

similar between groups, other than chronic liver disease, which was more common in the non-ID consult group (8.2% [75/915] vs 5.7% [44/776], p=0.04). Predisposing factors and the presence of central lines were evenly distributed between patients with and without an ID consult, except that patients with an ID consult were less frequently coded for hematological malignancy (14% [109/776] vs 20% [183/915], p=0.001) or cancer chemotherapy (4% [31/776] vs 7.1% [65/915], p=0.009). There were more patients admitted to the intensive care unit in the ID consult group (15.9% [124/776] vs 10.1% [93/915], p<0.001). We observed no difference between the two groups in the species of candida isolated (p=0.88) (Table 1).

Management

1,550 (91.7%) patients received antifungal therapy. Initial selection of antifungal treatment was not different between patients with and without an ID consult. Overall, azoles were the most commonly used antifungals in 794/1691 (46.9%), followed by echinocandins in 662/1691 (39.1%) and liposomal amphotericin B in 94/1691 (5.5%) patients. Overall, the median duration of antifungal therapy was longer in patients who received an ID consult (18 days vs 14 days, p<0.001); however, there was no difference between groups on the choice the antifungal agent used (Table 2). One hundred and forty one (8.3%) patients with *Candida* BSI did not receive any treatment. This was less likely in those receiving ID consult (1.7% [13/776] vs 14% [128/915],p<0.001). Of the 141/1691 (8.3%) untreated patients, the reasons not to treat in the ID consult and no consult group were: positive blood culture regarded as a contaminant (0.5% [4/776] vs 9.7% [89/915], p=0.005), culture result unknown to the treating physician (1% [8/776] vs 3.5% [32/915], p=0.007) and leaving the hospital against medical advice before the culture results were available (0.1% [1/776] vs 0.8% [7/915], p=0.57) (Table 2).

Non-pharmacological management also differed between patients who did and did not receive an ID consult (Table 2). Central line removal occurred more frequently in those who received an ID consult compared to those who did not (75.6% [587/776] vs 58.8% [538/915], p<0.001). Both, the median number of blood cultures (9 vs 7, p<0.001) and the median number of positive blood cultures was higher in patients who received an ID consult (2 vs 1, p<0.001). Median time to blood culture clearance was 48 hours and did not differ between groups (p=0.98). Median time to central line removal was 37 hours in the ID consult group compared to 38 hours in the non-consult group (p=0.79).

Use of echocardiography (56.9% [442/776] vs 33.3% [305/915], p<0.001) and ophthalmological evaluation (53.1% [412/776] vs 17.5% [160/915], p<0.001) were more frequently obtained in those who received an ID consult. Diagnosis of endocarditis was more common in the ID consult group (3.9% [30/776] vs 0.5% [5/915]; p<0.001), as was the diagnosis of endophthalmitis (2.9% [23/776] vs 0.5% [4/915]; p<0.001).

Mortality

The 42-day mortality was 173/776 (22.3%) in persons with an ID consult compared to 431/915 (47.1%) in persons without an ID consult (p < 0.001). By 90 days, 690/1691 (40.8%) patients had died. The ID consult group had lower 90-day mortality compared to

patients without an ID consult (28.6% [222/776] vs 51.1% [468/915], p<0.001). Of the 141 untreated patients, 94 (66.7%) had died by day 90.

In the primary inverse propensity-score weighted Cox model, receipt of an ID consult was associated with lower mortality, with a HR of 0.81 (95% CI: 0.73, 0.91, p<0.001) (Fig 1). In the secondary inverse weighted Cox model, that included additional covariates significantly associated with mortality, the protective value of the ID consult remained unchanged (HR 0.82 [95% CI: 0.72, 0.92], p=0.007), translating to a 19% survival benefit to an ID consult. Other risk factors for 90-day mortality in this model included age, renal failure, diabetes, surgical site infections and the year the consult 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 in order 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 (2002–2007) and late (2008–2014). In the models, performed as above for the primary analyses, the association of ID Consult with 90-day mortality remained significant with HRs of HR 0.79 [95%CI 0.67 – 0.93], p = 0.004 and 0.83 [95%CI 0.71–0.97], p = 0.02 for the early and later time periods, respectively. Second, a standard multivariable Cox proportional hazards model (not involving the propensity score) was performed, in which ID consult was treated as a fixed effect and also included as an interaction with year. In that model, the interaction of ID consult by year was nonsignificant for all years, except 2004, a unique year when mortality was particularly low in the ID consult group.

Discussion

In patients with candida BSI, ID consult was associated with an adjusted HR of 0.81 for mortality, translating to a 19% survival benefit. Previous studies have demonstrated 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 ID consult.[6,7] To our knowledge, this is the largest cohort of patients with candida BSI that has examined the association between ID consultation and mortality. In keeping with our findings, prior studies with a smaller numbers of patients with candidemia have also found a beneficial mortality effect associated with the receipt of an ID 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 PS modeling 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.[16,22]

Clinical practice guidelines from the Infectious Disease Society of America (IDSA) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) provide evidence-based recommendations for the management of patients with *Candida* BSI.[23,24] Treatment of candida BSI 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] and 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 have shown to yield better outcomes. [5] A recently developed scoring system, the EQUAL Candida Score, summarizes and weighs the recommendations for the optimal management of Candida BSI, providing a tool that could be used to measure guideline adherence, facilitate clinical decision making and improve quality of care. [29]

Candidemia has been associated with up to 71% mortality, an alarming rate that can be decreased almost in half when appropriate therapy is given.[3] In our study, when an ID consultation was obtained, blood cultures were much less frequently ignored and therefore less patients in this group were not treated (1.7% [13/776] vs 14% [128/915]). The most common causes to not treat patient in the ID consult group were physician unawareness of a positive culture and leaving against medical advice.

Prior studies have demonstrated higher rates of appropriate empirical antimicrobial therapy in patients with other BSI who had an ID consult.[6] Inadequate initial empiric antifungal therapy is associated with increased mortality in patients with Candida BSI.[30] Although, in our study initial selection of antifungals was not dissimilar between groups, patients seen by an ID physician received a significantly longer treatment course (18 vs 14 days). Longer duration of treatment may be attributable to the increased number of candida BSI complications seen in the ID consult group or because documented negative blood culture were 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 BSI.[33] Central line removal is an intervention that has been previously associated with faster blood culture clearance and shown to be a prognostic factor of mortality.[25,31] However, based on the lack of randomized controlled trials to evaluate the effect of central line removal, a recent meta-analysis found no evidence to support catheter removal in patients with *Candida* BSI.[32] In our study removal of the central line was associated with lower 90-day mortality in patients with *Candida* BSI (31.1% vs 76.4%, $p<0.001$); an intervention that was more frequently done when ID physicians were involved in the patient's care.

In our study, patients in the ID consult group were more often assessed for complications of candidemia. Not identifying patients with higher burden of disease could also explain the higher mortality seen in the group who did not received an ID consult. Use of echocardiography and subsequent diagnosis of infective endocarditis were both higher in patients who received an ID consult, similar to the increased use of such diagnostic tool in patients with *S. aureus* bacteremia who were seen by an ID physician.[33] In the ID consult group, the incidence of endocarditis in patients with Candida BSI was 3.9% (30 patients), similar the one seen in a recent retrospective study (4.2%).[34]

The prevalence of hematogenous endophthalmitis can vary between 2.2 to 20.1% in patients with *Candida* BSI.[35] Given that ocular candidiasis may be clinically silent in up to 50% of cases[36] and that many patients with *Candida* BSI are too ill to communicate their symptoms,

current treatment guidelines recommend that all patients with candidemia should have a funduscopic examination.[23] In our study, ophthalmologic examination was more frequently done when patients received and ID consult (53.1% [412/776] vs 17.5% [160/915]), therefore detection of endophthalmitis was also more common in the ID consult group (2.9% [23/776] vs 0.5% [4/915]).

The increased frequency of these interventions, not ignoring positive blood cultures and a longer duration of antifungal therapy, may have been responsible for the decreased mortality seen in the ID consult group. This is in keeping with the mortality benefit of an ID consult in patients with *S. aureus* bacteremia, 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 center, retrospective study subject to potential unmeasured confounding. However, to date, it is the largest cohort of patients with candida BSI and included a very extensive list of established prognostic comorbidities,[15] as well as known specific predisposing factors for development of candida BSI.[37] The beneficial effect of receiving an ID consult appears to be a universal phenomenon across institutions, as seen in much smaller studies.[5,8,9] Notably, this study was conducted in the USA where clinical microbiologists rarely advise physicians on direct patient management. It would be interesting to examine the impact of an infectious disease's physician consult on outcomes in a setting with different clinical practice models. Secondly, even in a large center, the number of patients with some of the significant predisposing factors were small. However, this distribution is likely reflective of the patient case mixes seen in other tertiary referral centers. Finally, selection bias could have occurred as certain patient-populations were underrepresented in each group. However, we adjusted these differences between groups with inverse-weighting by the propensity-score, and used Cox proportional hazards regression analysis, including only ID consult 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 candidal BSI who received an ID consult were significantly less likely to die. The patients in the ID consult group more often had a work-up and treatment consistent with evidence-based practices. The disease was less often left untreated by ID physicians. The protective effect of obtaining an ID consult on mortality in patients with candida BSI suggest that an ID consult should be an integral part of the clinical care of patients with candidemia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Conflict of Interest: Dr. Spec reports grants and personal fees from Astellas Global Development Pharma, Inc., grants from Scynexis, grants from Cidara, grants and personal fees from Mayne Pharma, grants from MiraVista, grants from IMMY, personal fees from Viamet, during the conduct of the study. Dr. Powderly reports grants and personal fees from Merck and Co, personal fees from Gilead Sciences, outside the submitted work. Mr. Stwalley reports personal stock ownership in AbbVie, Inc. and Bristol-Myers Squibb. Dr. Olsen reports grants and personal fees from Pfizer, grants from Merck and grants from Sanofi. The rest of the authors report no conflicts of interest.

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Research in context

Evidence before this study

Candida is a significant cause of morbidity and mortality. Overall, *Candida* now represents the most common cause of Health Care-Associated bloodstream infection (BSI) in the United States, as well as the most common fungal BSI. 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 (ID) consultation”. We limited the search to studies in adults aged 18 years and older, and no language restrictions were applied. This search identified six studies where the impact of an ID consult was evaluated in patients with Candidemia. Currently, the published literature is limited to small cohorts of *Candida* BSI, with limited insights into management differences. Even so, these studies support the inclusion of ID expertise in the diagnosis and treatment of *Candida* BSI. *Candida* BSI attributable mortality is reported to range between 15–47%, but with appropriate therapy, these rates can be reduced by almost half. Infectious diseases (ID) consultations have been found to positively affect mortality outcomes in patients with several BSI, including *Staphylococcus aureus*, *Cryptococcus*, and multi-drug resistant organisms. Increased adherence to disease management drawn from evidence-based recommendations benefits patients with these BSI.

Added value of this study

This is the largest cohort of patients with *Candida* BSI examining the association between ID consultation and mortality, as well the most detailed assessment of BSI management conducted thus far. We established a 20% survival benefit that persists long term associated with ID consult after extensively controlling for patient factors and disease severity using propensity score modeling. 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 PS modeling and to document extensive differences in management. We demonstrated that increased frequency of interventions often recommended by ID, 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 ID consult.

Implications of all the available evidence

Our findings demonstrate that patients with *Candida* BSI who received an ID consultation had significantly decreased 90-day mortality through use of evidence-based interventions. The results of this study, combined with others examining BSI, illustrate that ID consultation significantly lowers the risk of mortality among patients with BSI. This effect is consistently derived from better adherence to evidence-based standards of treatment. An ID consult is appropriate, even preferred, for patients with *Candida* BSI, considering the often-variable presentation and complex management of these patients.

We highlight the benefit of ID consultation for *Candida* BSI, contributing to the literature supporting ID consult for patients with BSI.

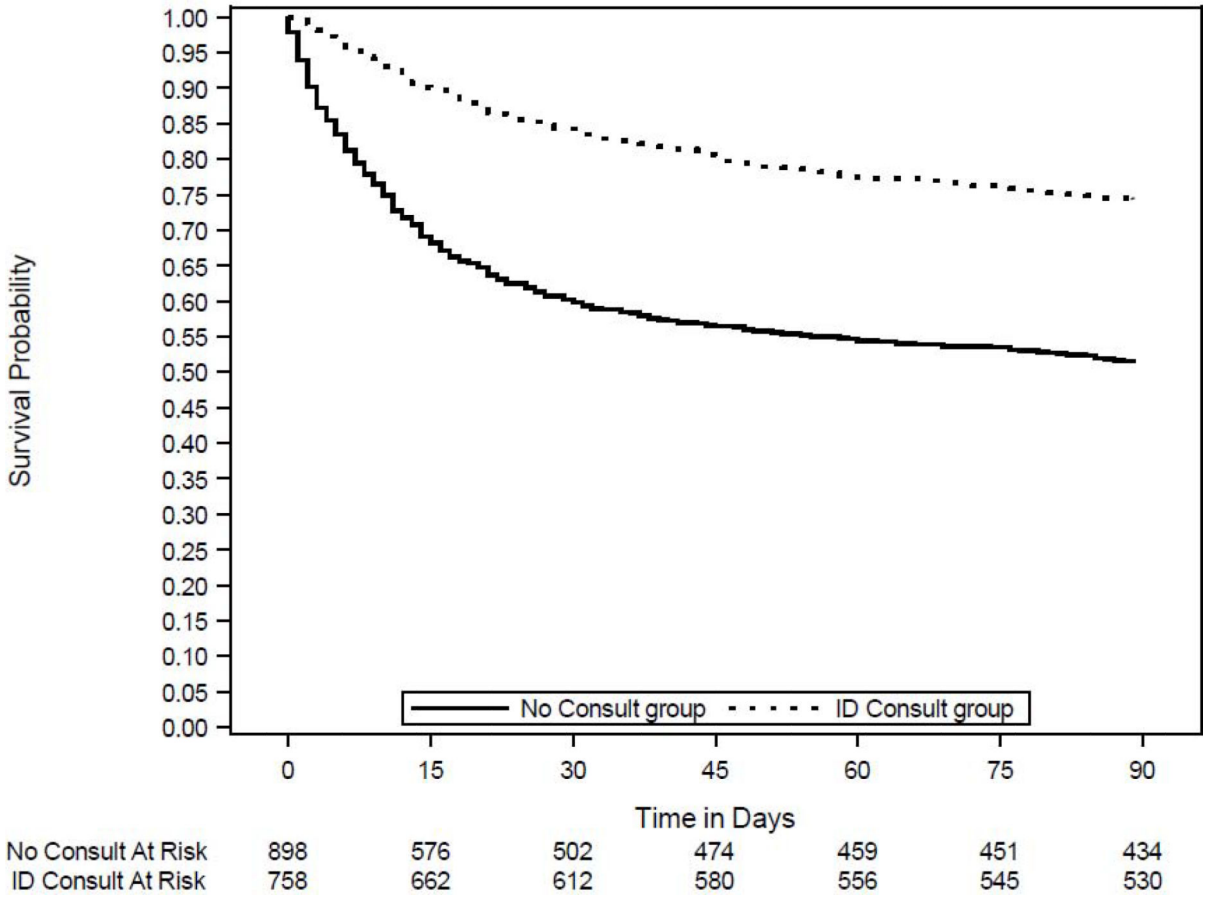

Figure 1.

Survival curve for 90-day all-cause mortality after inverse weighting by the propensity score with Candida bloodstream infection (BSI), by receipt of infectious disease (ID) consultation.

Table 1.

Comparison of Select Characteristics by Receipt of an Infectious Disease Consult

Characteristic	ID consult (n=776)	No ID Consult (n=915)	*P*
Demographics			
Age	56.2 (16.4)	59.0 (16.7)	0.007
Male	411 (53)	487 (53.2)	0.91
Caucasian	509 (65.6)	557 (60.9)	0.04
Comorbidities			
Hypertension	324 (41.8)	378 (41.3)	0.84
Diabetes	185 (23.8)	209 (22.8)	0.62
Coronary artery disease	178 (22.9)	193 (21.1)	0.34
Chronic liver disease	44 (5.7)	75 (8.2)	0.04
Chronic kidney disease	136 (17.5)	131 (14.3)	0.08
Predisposing factor			
Solid tumors	254 (32.7)	328 (35.8)	0.18
Hematological malignancy	109 (14.0)	183 (20.0)	0.001
Bone marrow transplant	2 (0.3)	15 (1.6)	0.007
Solid organ transplant	5 (0.6)	6 (0.7)	0.95
Cancer chemotherapy	31 (4.0)	65 (7.1)	0.009
Radiation therapy	7 (0.9)	12 (1.3)	0.41
Neutropenia	50 (6.4)	79 (8.6)	0.09
TPN within prior 30 days	241 (31.1)	264 (28.9)	0.31
Corticosteroids within prior 90 days	198 (25.5)	258 (28.2)	0.23
Central lines			
Permanent central line	298 (38.4)	329 (36.0)	0.28
Temporary central line	352 (45.4)	449 (49.1)	0.13
Dialysis catheter	73 (9.4)	105 (11.5)	0.17
Microbiology			
Candida albicans	354 (45.6)	442 (48.3)	0.88
Candida glabrata	152 (19.6)	174 (19.0)	
Candida parapsilosis	117 (15.1)	123 (13.4)	
Candida tropicalis	57 (7.3)	63 (6.9)	
Candida krusei	25 (3.2)	27 (3.0)	
Other candidal species	71 (9.1)	86 (9.4)	
Admission to the ICU	124 (15.9%)	93 (10.1%)	<0.001

ID, infectious diseases; TPN, total parenteral nutrition; ICU, intensive care unit; Categorical variables are presented as absolute number (percentage), continuous variables are presented as mean (standard deviation).

Table 2.

Comparison of Treatment Characteristics by Receipt of an Infectious Disease Consult

Characteristic	ID consult (n=776)	No ID Consult (n=915)	*P*
Antifungal therapy (%)			
Echinocandins	328 (42.3)	334 (36.5)	0.11
Azoles	382 (49.2)	412 (45.0)	0.06
Liposomal amphotericin B	53 (6.8)	41 (4.5)	0.27
No treatment	13 (1.7)	128 (14.0)	<0.001
Physician unawareness	8 (1)	32 (3.5)	0.007
Considered a contaminant	4 (0.5)	89 (9.7)	0.005
Left against medical advice	1 (0.1)	7 (0.8)	0.57
Median treatment duration in days (IQR)			
Total duration of therapy *	18 (14, 35)	14 (6, 20)	<0.001
Echinocandins	7 (2, 15)	5 (2, 14)	0.18
Azoles	13 (4, 18)	10 (3, 15)	0.004
Liposomal amphotericin B	4 (1, 8)	3 (1.25, 5.75)	0.47
Microbiological follow-up			
Number of blood cultures performed (median, IQR)	9 (6, 15)	7 (4, 12)	<0.001
Number of positive blood cultures (median, IQR)	2 (1, 3)	1 (1, 2)	<0.001
Median time to blood culture clearance (hrs., IQR)	48 (27.5, 82)	48 (23, 80)	0.98
Interventions			
Echocardiography			
Transthoracic	414 (53.4)	286 (31.3)	<0.001
Transesophageal	127 (16.4)	44 (4.8)	<0.001
Ophthalmology consult	412 (53.1)	160 (17.5)	<0.001
Central line removal	587 (75.6)	538 (58.8)	<0.001

ID, infectious diseases. Categorical variables are presented as absolute number (percentage), continuous variables are presented as median (interquartile range).

* Includes all antifungals agents used.

Table 3.

Factors Associated with 90-day Mortality in Patients with Candida Blood Stream Infection by Receipt of Infectious Disease Consult in the Multivariable Cox Proportional Hazards Model with Inverse Weighting by the Propensity Score

Variable	Hazard Ratio (95% CI)	*P*
Infectious Diseases consult	0.82 (0.72, 0.92)	0.001
Age	1.01 (1.01, 1.02)	<0.001
Year of the candidemia		0.002
2014	0.92 (0.66, 1.29)	
2013	1.50 (1.09, 2.07)	
2012	1.27 (0.93, 1.73)	
2011	1.39 (1.03, 1.87)	
2010	1.17 (0.88, 1.54)	
2009	1.14 (0.85, 1.54)	
2008	1.62 (1.23, 2.12)	
2007	1.36 (1.03, 1.79)	
2006	1.58 (1.21, 2.06)	
2005	1.36 (1.04, 1.77)	
2004	1.07 (0.80, 1.43)	
2003	1.02 (0.77, 1.35)	
Valvular diseases	1.14 (0.99, 1.31)	0.07
Disorder of pulmonary circulation	1.33 (1.15, 1.54)	0.001
Neurological disorders	0.81 (0.71, 0.92)	0..001
Diabetes mellitus	0.71 (0.63, 0.80)	<0.001
Renal failure	0.77 (0.68, 0.88)	0.001
Liver disease	1.22 (1.05, 1.42)	0.01
Solid tumor without metastasis	0.69 (0.57, 0.84)	0.003
Fluid and electrolyte disorders	0.85 (0.74, 0.98)	0.03
Psychoses	0.87 (0.73, 1.03)	0.10
Depression	0.80 (0.69, 0.90)	0.006
Surgical site infection	0.59, (0.51, 0.68)	<0.001
Gastroenteritis	1.22 (1.06, 1.40)	0.007
Upper respiratory tract infection	0.54 (0.37, 0.80)	0.002
Viral infection	1.32 (1.06, 1.64)	0.01
Hemoglobin	0.93 (0.89, 0.97)	0.006

The model was adjusted for white blood cell count and platelet count using cubic splines