Infection and Drug Resistance

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ORIGINAL RESEARCH

Epidemiology, practice patterns, and prognostic factors for candidemia; and characteristics of fourteen patients with breakthrough *Candida* bloodstream infections: a single tertiary hospital experience in Japan

This article was published in the following Dove Press journal:
Infection and Drug Resistance

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Background: Candidemia is associated with high mortality, and its prognostic factors need to be examined in more detail in order to improve its management. A case of breakthrough (BT) candidemia is defined as the development of candidemia during antifungal therapy. The microbiological characteristics of and appropriate clinical practices for BT candidemia remain unclear.

Objectives: The primary objective of the present study was to identify the prognostic factors of candidemia, while the secondary objective was to elucidate the microbiological characteristics of patients with BT candidemia.

Materials and methods: A total of 121 patients diagnosed with candidemia between January 2007 and December 2016 were enrolled in this study. The primary outcome was the 30-day mortality rate.

Results: The overall incidence of candidemia was 0.056 cases/1000 inpatients. Among the 126 *Candida* isolated, *C. albicans* accounted for 36%, *C. parapsilosis* 26%, *C. glabrata* 12%, *C. guilliermondii* 14%, *C. tropicalis* 3%, *C. pelliculos* 1%, and other unidentifiable *Candida* species 8%. The 30-day mortality rate was 33%. In a multivariate Cox hazard analysis, *C. albicans*, the absence of antifungal therapy, age, lung disease, and mechanical ventilation were associated with a high mortality rate, whereas *C. parapsilosis*, the removal of a central venous catheter, and surgical wards were associated with a lower mortality rate. Fourteen patients had BT candidemia. A significant difference was observed in the proportion of *C. guilliermondii* and other *Candida* species exhibiting resistance to fluconazole and voriconazole, between patients with and without BT candidemia. Resistance to fluconazole was prominent in patients that developed candidemia with a history of azole antifungal agents.

Conclusion: The prompt initiation of antifungal therapy and removal of central venous catheter were essential for better outcomes. A class switch to other antifungal agents needs to be considered in empirical antifungal therapy for BT candidemia with a history of exposure to azole antifungal agents.

Keywords: antifungal stewardship, breakthrough candidemia, candidemia, Japan

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Introduction

A case of candidemia is defined as the isolation of *Candida* species from blood cultures, and exhibits a high mortality rate.[1,2] Various *Candida* species have been isolated from clinical specimens. The susceptibility patterns of *Candida* species to antifungal agents differ among each species. *Candida albicans* (*C. albicans*) is generally

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http://dx.doi.org/10.2147/IDR.S156633

the most frequently isolated species among patients with candidemia. The proportion of non-*C. albicans* exhibits geographical differences.[3] *C. glabrata* is generally more common in Western countries, whereas *C. parapsilosis* is frequently isolated in Latin America.[3] *C. tropicalis* is more common in Asia.[4] Various surveillances have reported the emergence of *Candida* species that exhibit resistance to widely used antifungal agents such as fluconazole (FLCZ) and micafungin (MCFG), and, thus, are associated with a high mortality rate.[5,6] Therefore, continual surveillance is required to monitor the emergence of these resistant *Candida* species in each country.

The concept of antimicrobial stewardship programs (ASPs) has been proposed in order to prevent the development of multidrug-resistant bacteria. However, few studies have conducted antifungal stewardship programs (AFSPs) in patients with candidemia. Clinical practice guidelines for the management of candidiasis have been published by the Infectious Diseases Society of America (IDSA).[7] The compliance of Japan with the IDSA recommended clinical practice guidelines has not yet been examined in detail. Investigations on the prognostic factors of candidemia based on each institution's practice data are essential in order to implement AFSPs and improve the management of this infection.[8]

The prophylactic use of antifungal agents has been prevalent because they reduce the risk of invasive fungal infections, particularly in patients with hematological malignancies.[9] A case of breakthrough (BT) candidemia is defined as the development of candidemia during the administration of systemic antifungal agents, and is associated with a high mortality rate.[10,11] Established treatment strategies for BT candidemia are lacking, due to its low incidence. Studies focusing on the clinical and microbiological characteristics of BT candidemia are essential to better understand the management of this infection.

The primary objective of the present study was to identify prognostic factors based on species distribution and clinical practice patterns among patients with candidemia. The secondary objective was to investigate the clinical and microbiological characteristics of patients with BT candidemia.

Materials and methods

Study design and population

One hundred and twenty-one patients diagnosed with candidemia in Aomori Prefectural Central Hospital between January 2007 and December 2016 were enrolled in this study. The number of total *Candida* isolates was 126, because five patients were diagnosed with a mixed infection of two *Candida* species. Aomori Prefectural Central Hospital is a general hospital with 684 beds and is located in Aomori City, Japan. We defined a case of candidemia as a patient with symptoms of infection (e.g., fever up to 37°C) and with at least one positive blood culture for *Candida* species.[12] The study protocol was approved by the Ethics Committee of Hirosaki University Graduate School of Medicine, and the Ethics Committee of Aomori Prefectural Central Hospital. Patient consent was not required, due to the retrospective nature of this study without clinical intervention. We examined patient medical records while assuring anonymity.

Outcome evaluation and infectious disease consultation

The primary outcome of this study was the 30-day mortality rate after the diagnosis of candidemia, according to previous studies.[13] We evaluated the appropriateness of treatment of candidemia among 114 patients who received systemic antifungal agents. Days from the submission of blood cultures to the initiation of antifungal therapy, the dosage of initial antifungal agents, follow-up blood cultures to confirm the clearance of *Candida* species, the appropriate duration of antifungal therapy, appropriate therapy based on susceptibility tests, central venous catheter (CVC) removal, and ophthalmological consultations to rule out endophthalmitis were evaluated for the management of candidemia.

Infectious disease (ID) consultations by an antifungal stewardship team were implemented from October 2015 among patients with the isolation of *Candida* species from blood cultures. This team consists of physicians and pharmacists. We provided the following items to physicians as bundles: (1) initiation of an adequate dosage of antifungal therapy based on the IDSA guidelines, (2) removal of CVC, (3) follow-up blood cultures to confirm the clearance of *Candida* species, (4) ophthalmological consultations to rule out endophthalmitis, and (5) an adequate duration of antifungal therapy.

Fifteen patients who received these bundles were defined as the ID consultation group. We compared the achievement rates of each item between patients with and without ID consultations.

Definitions and clinical data

We evaluated age, sex, complications, the main disease, and previous use of antimicrobial agents, as well as antifungal agents. We confirmed whether CVCs in patients were removed after the diagnosis of candidemia. We calculated the acute physiology and chronic health evaluation II score (APACHE II score) of 69 patients (57%). The calculation of

each patient's APACHE II score was performed according to previous studies.[14] *Candida* endophthalmitis was diagnosed by an ophthalmologist, based on the finding of fungal endophthalmitis.

Administration of cyclosporine, tacrolimus, or systemic steroids was defined as immunosuppressive therapy.[12] Administration of anticancer agents was defined as anticancer therapy.[12] Patients who had a neutrophil count <500 cell/μL were regarded as having neutropenia. Patients who required hemodialysis or those with serum creatinine ≥3.0 mg/dL were regarded as having renal failure. Patients who had more than five-times the upper limit for aspartate transaminase, alanine transaminase, or gamma glutamyl transpeptidase were regarded as having liver failure. Patients who had underlying diseases, such as asthma, pneumonia, lung abscess, interstitial pneumonia, empyema, and lung cancer were regarded as having lung disorders.

We evaluated the history of the use of antimicrobial agents within 30 days prior to the onset of candidemia. The definition of each antimicrobial agent was as follows. Anti-methicillin-resistant *Staphylococcus aureus* (MRSA) agents were defined as vancomycin, teicoplanin, linezolid, and daptomycin. Broad spectrum antimicrobial agents were defined as carbapenem, fourth generation cephem, and anti-*Pseudomonas aeruginosa* penicillin containing a beta lactamase inhibitor. Anti-*Clostridium difficile* (CD) agents were defined as oral vancomycin and metronidazole. Anti-anaerobic agents were defined as carbapenem, a beta lactamase inhibitor containing penicillin, cefmetazole, clindamycin, and metronidazole.

A case of BT candidemia was defined as a patient who received systemic antifungal therapy more than 7 days prior to the onset of candidemia.[15]

A case of an adequate duration of antifungal therapy was defined as a patient who received antifungal therapy for more than 14 days after the confirmation of the clearance of *Candida* species from blood cultures.[7] The appropriate dosage of antifungal therapy was evaluated based on the IDSA guidelines.[7] When the detected *Candida* species was treated with an antifungal agent to which the fungus is susceptible, based on the Clinical and Laboratory Standards Institute (CLSI) criteria, or the fungus was the wild type based on the epidemiological cut-off values (ECVs), the therapy administered to the patient was regarded as appropriate.[16] Inappropriate therapy was defined as a patient who received systemic antifungal agents that exhibited non-susceptible or non-wild-type.

Patients who underwent surgery within 90 days prior to the submission of blood cultures were defined as patients with a history of surgery. *Candida* colonization was defined as patients with the isolation of *Candida* species from non-sterile clinical tissues such as sputum or stools.

Mycological data collection

Mycological data were collected from the records of each patient's blood cultures. Blood cultures were performed by the BacT/ALERT 3D blood culture system (SYSMEX; bioMérieux, Lyon, France). Blood culture bottles with suspected yeast-like fungi by microscopy were subcultured on CHROM agar *Candida* culture medium (Kanto Chemical, Tokyo, Japan) and incubated at 30°C for 48 h. The identification of each *Candida* species was performed using the ID32C system (SYSMEX; bioMérieux), between January 2007 and August 2014. The identification kit was changed to VITEK 2 YST ID Card (SYSMEX; bioMérieux) from September 2014. In our institution, two different methods (CHROM agar *Candida* culture medium and ID32C or VITEK 2 YST ID Card) were used to increase the accuracy of identification of *Candida* species. Antifungal susceptibility tests were performed using the yeast-like fungal drug susceptibility kit ASTY (Kyokuto Pharmaceutical Industrial, Tokyo, Japan). The antifungal susceptibility of each agent was assessed based on the minimum inhibitory concentration (MIC) after an incubation at 35°C for 48 h. Blood cultures with no growth of *Candida* species after 7 days incubation were defined as negative. The incubation period was extended to 14 days for patients admitted to hematological wards due to a physician's request. CLSI M27-S4, species-specific antifungal agent drug susceptibility break points, were used to determine susceptibility.[17] ECVs were applied to assess susceptibility in *Candida* species that have no species-specific break point according to a previous study.[18] We defined ten unidentifiable *Candida* species as other *Candida* species. CLSI M27-A3 was applied to other *Candida* species in order to evaluate susceptibility.[19] The CLSI M27-A3 of each antifungal agent was as follows: susceptibility was defined as MIC≤8 μg/mL, susceptible dose-dependent was defined as MIC=16–32 μg/mL, and resistant was defined as MIC≥64 μg/mL for fluconazole. Susceptibility was defined as MIC≤1 μg/mL and resistant as MIC≥4 μg/mL for voriconazole (VRCZ). Susceptibility was defined as MIC≤2 μg/mL and resistant as MIC≥4 μg/mL for MCFG.

Statistical analysis

Results are expressed as means±standard deviation or n (%). Continuous data were analyzed using the Student's t-test, and categorical data were analyzed using the χ^2 test. Fisher's exact test was used when a value smaller than 10 was included in the expected values of cells of the 2×2 contingency table,

and the χ^2 test was used otherwise. The 30-day mortality rate was examined by Kaplan–Meier plots and the Log-rank test. Significant items in the univariate comparison analysis were selected for inclusion in a multivariate Cox hazard analysis. $P<0.05$ was considered to be significant. All statistical analyses were performed using Excel-Toukei 2012 (Social Survey Research Information Co., Ltd., Tokyo, Japan).

Results

Epidemiology and species distribution among patients with candidemia

A total of 121 patients were included in the present study. The overall incidence of candidemia was 0.056 cases/1000 inpatients. The 126 *Candida* isolates from blood cultures consisted of *C. albicans* (n=46, 36%), *C. parapsilosis* (n=33, 26%), *C. glabrata* (n=15, 12%), *Candida guilliermondii* (*C. guilliermondii*) (n=17, 14%), *C. tropicalis* (n=4, 3%), *C. pelliculos* (n=1, 1%), and other *Candida* species (n=10, 8%) (Figure 1A).

The distribution of isolated *Candida* species according to clinical wards is shown in Figure 1B. One pediatric patient was excluded due to the lack of a case number. The proportion of isolates of *C. albicans* was high in surgical wards, as well as internal medicine wards. *C. glabrata* was high in intensive care wards, whereas *C. guilliermondii* was high in hematological wards. The proportion of *C. parapsilosis* was approximately 20–30% in every ward.

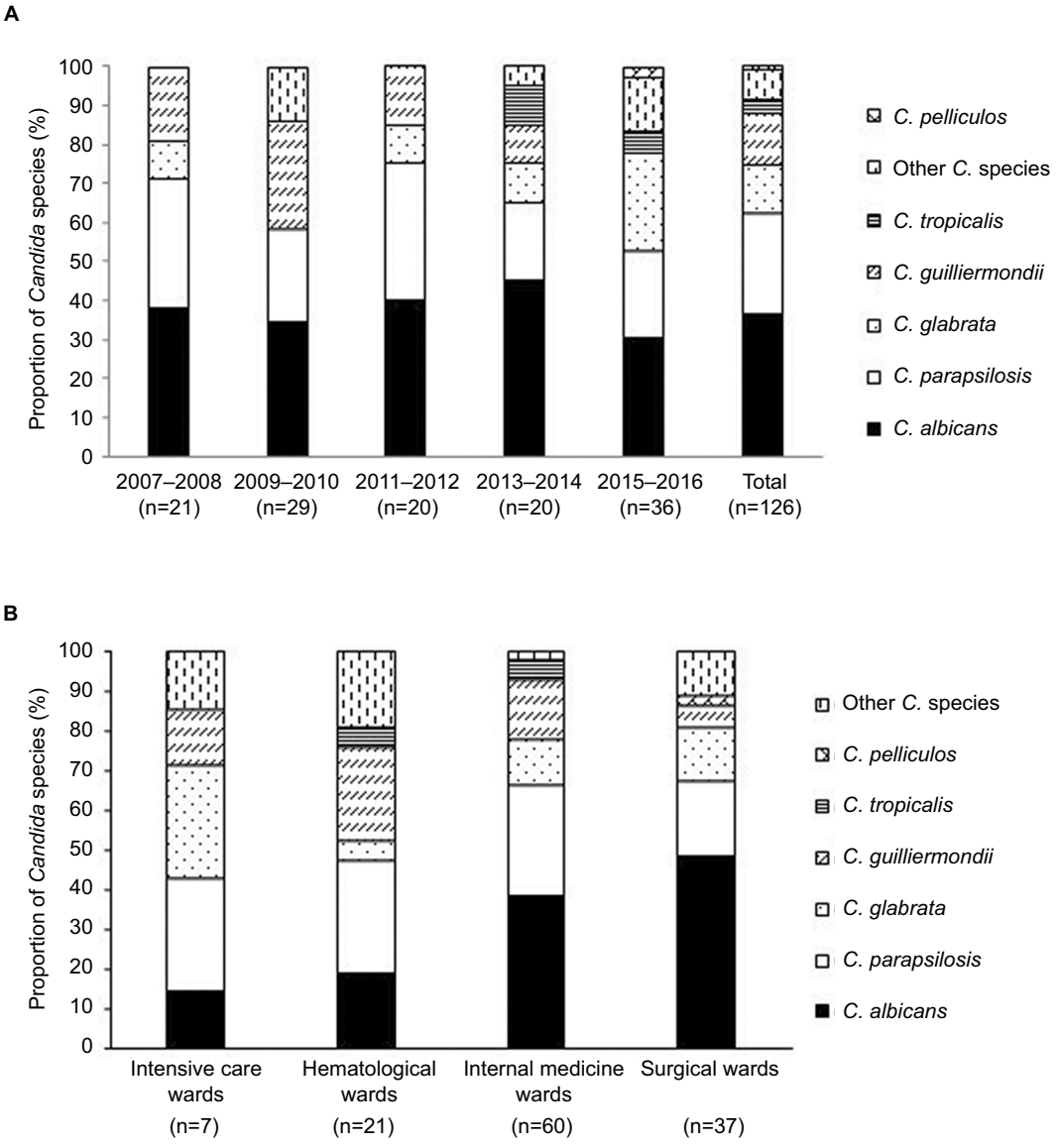

Figure 1 Distribution of *Candida* species isolated from blood cultures, according to periods (**A**) and wards (**B**).
Note: One pediatric ward patient was excluded from **B**.

Susceptibility patterns of each *Candida* species to antifungal agents

The susceptibility patterns of the isolated *Candida* species from blood cultures as shown in Table 1 after as follows: 78.5% (99/126) of the isolates were susceptible to FLCZ, 94.3% (117/124) were susceptible to MCFG, 91.4% (107/117) were susceptible to VRCZ, and 100% (125/125) were susceptible to amphotericin B (AMB) according to the CLSI breakpoints as well as ECVs. *C. albicans* showed high susceptibilities to each antifungal agent. In addition, 9% (3/33) of *C.parapsilosis* were resistant to FLCZ, 15.3% (2/13) of *C.glabrata* were resistant to VRCZ, and 17.6% (3/17) of *C. guilliermondii* were resistant to FLCZ, and 13.3% (2/15) were resistant to VRCZ. No resistant strains to MCFG and AMB were observed in *C. guilliermondii*. Two out of the four *C. tropicalis* strains were resistant to FLCZ, although the number isolated was small.

Adherence to the IDSA recommended treatment strategy guidelines among patients with candidemia

Systemic antifungal therapy was administered to 114 patients with candidemia (Figure 2). The mean number of days from the submission of blood cultures to the initiation of antifungal therapy was 1.76±1.73 days (median=2 days, range=0–9 days). Half of the patients (50%) received an appropriate

Table 1 Antifungal susceptibilities of isolated *Candida* species in the present study

Antifungal agents	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	S or WT (%)	I or S-DD (%)	R or non-WT (%)
C. albicans					
FLCZ (n=46)	0.25	0.5	46 (100)	0	0
MCFG (n=46)	0.03	0.125	45 (97.8)	0	1 (2.1)
VRCZ (n=45)	<0.015	0.015	45 (100)	0	0
AMB (n=46)	0.5	1	46 (100)	ND	0
C. parapsilosis					
FLCZ (n=33)	1	2	29 (87.8)	1 (3)	3 (9)
MCFG (n=33)	1	2	30 (90.9)	2 (6)	1 (3)
VRCZ (n=29)	0.015	0.06	27 (93.1)	1 (3.4)	1 (3.4)
AMB (n=33)	0.5	1	33 (100)	ND	0
C. glabrata					
FLCZ (n=15)	8	32	ND	15 (100)	0
MCFG (n=14)	<0.03	0.06	13 (92.8)	0	1 (7.1)
VRCZ (n=13)	0.25	1	11 (84.6)	0	2 (15.3)
AMB (n=15)	0.5	1	15 (100)	ND	0
C. guilliermondii					
FLCZ (n=17)	8	16	14 (82.3)	0	3 (17.6)
MCFG (n=17)	0.5	1	16 (94.1)	1 (5.8)	0
VRCZ (n=15)	0.25	0.5	13 (86.6)	0	2 (13.3)
AMB (n=17)	0.5	0.5	17 (100)	ND	0
C. tropicalis					
FLCZ (n=4)	4	8	1 (25)	1 (25)	2 (50)
MCFG (n=4)	0.06	0.125	4 (100)	0	0
VRCZ (n=4)	0.06	0.5	2 (50)	2 (50)	0
AMB (n=4)	0.5	0.5	4 (100)	ND	0
Other *C.* species					
FLCZ (n=10)	0.5	64<	8 (80)	ND	2 (20)
MCFG (n=10)	0.125	16<	9 (90)	ND	1 (10)
VRCZ (n=10)	<0.015	8	8 (80)	ND	2 (20)
AMB (n=10)	0.5	1	ND	ND	ND
C. pelliculos					
FLCZ (n=1)	4	1 (100)	0	0	
MCFG (n=1)	0.03	ND	ND	ND	
VRCZ (n=1)	0.125	1 (100)	0	0	
AMB (n=1)	0.25	ND	ND	ND	

Note: Clinical and Laboratory Standards Institute (CLSI) M27-S4 break points or epidemiological cut-off values were applied to each *Candida* species except for other unidentifiable *C.* species. CLSI M27-A3 break points were applied to other *C.* species due to the lack of species-specific susceptibility break points.

Abbreviations: MIC, minimum inhibitory concentration; S, susceptible; I, intermediate; S-DD, susceptible dose-dependent; R, resistant; WT, wild-type; FLCZ, fluconazole; MCFG, micafungin; VRCZ, voriconazole; AMB, amphotericin B; ND, not determined.

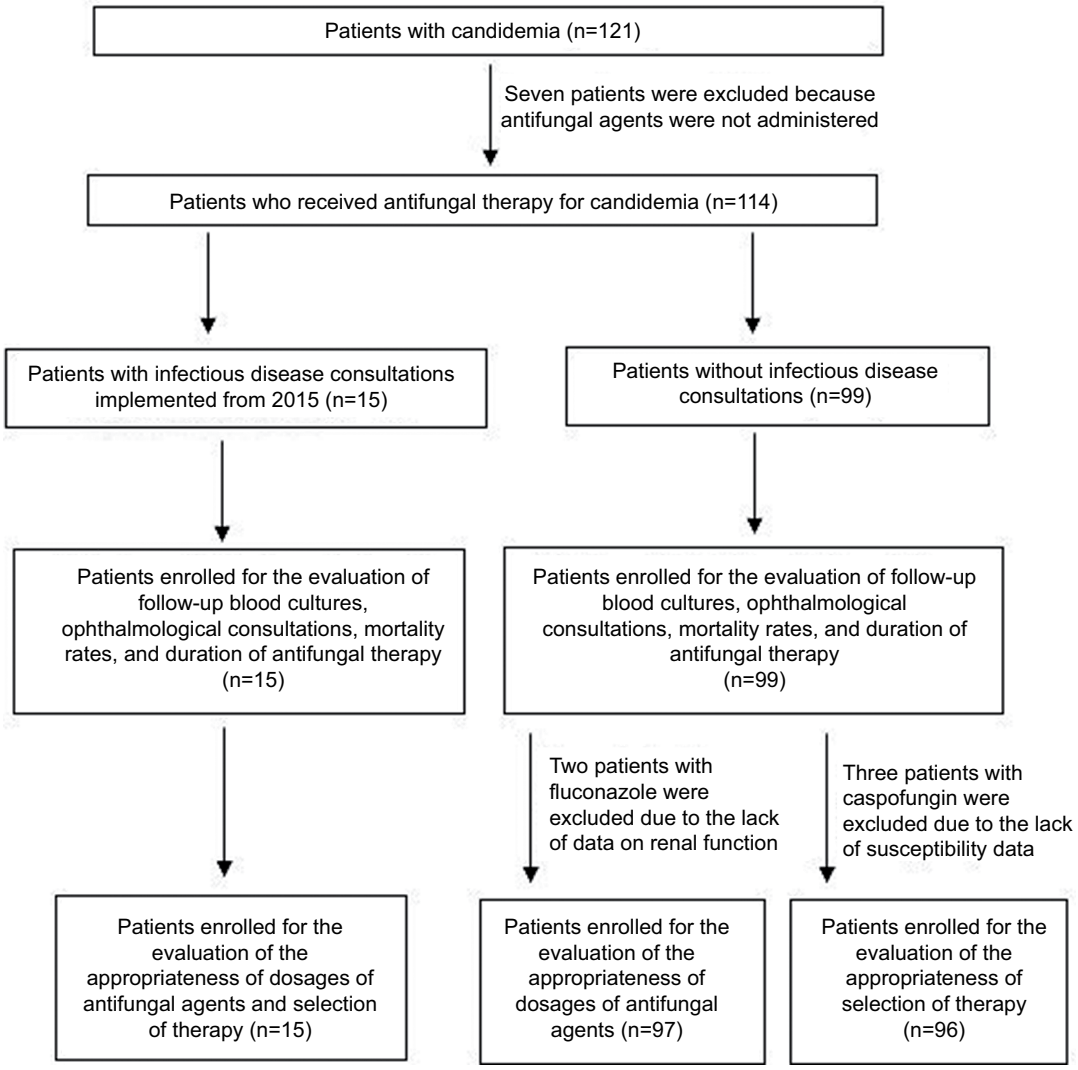

Figure 2 Procedure for the evaluation of compliance with IDSA-recommended elements for candidemia between patients with and without infectious disease consultations.
Abbreviation: IDSA, Infectious Diseases Society of America.

dosage of antifungal therapy. The rate of appropriate therapy based on the antifungal susceptibility test was 88.5%, follow-up blood cultures to confirm the clearance of *Candida* species 62.2%, ophthalmological consultations 46.4%, and the removal of CVC 67.5%. Only 21% of patients received an appropriate duration of antifungal therapy.

Comparisons in each area of candidemia therapy between patients with and without ID consultations are summarized in Table 2. Significant differences were observed in the dosage of initial antifungal therapy (ID consultations 86.6% vs without ID consultations 44.4%), follow-up blood cultures to confirm the clearance of *Candida* species (ID consultations 100% vs without ID consultations 56.5%), ophthalmological consultations to rule out endophthalmitis (ID consultations 80% vs without ID consultations 41.4%), and an appropriate duration of antifungal therapy (ID consultations 60% vs without ID consultations 15.1%). No significant difference was observed in the 30-day mortality rate between patients with and without ID consultations (ID consultations 20%, without ID consultations 30.3%) (Figure 3A, P=0.38).

Factors associated with the death of candidemia

Comparisons of various parameters between survivors and non-survivors are summarized in Table 3. The 30-day mortality rate was 33% (40/121). In the univariate analysis, significant differences were observed in age, serum albumin, mechanical ventilation, lung disease, intensive care wards, surgical wards, CVC removal, absence of antifungal therapy, *C. albicans*, and *C. parapsilosis* between surviving and non-surviving patients. The multivariate Cox hazard analysis

Table 2 Compliance with IDSA-recommended elements between patients with and without infectious disease consultations

	Patients who received antifungal agents	Patients with infectious disease consultations	Patients without infectious disease consultations	*P*-value
Number of cases	114	15	99	
Days from blood culture tests to initiation of antifungal agents				
0 days	31 (27.1)	3 (20)	28 (28.2)	0.75
1 day	23 (20.1)	2 (13.3)	21 (21.2)	0.73
2 days	36 (31.5)	4 (26.6)	32 (32.3)	0.77
3 days	12 (10.5)	2 (13.3)	10 (10.1)	0.65
More than 4 days	12 (10.5)	4 (26.6)	8 (8)	0.051
Appropriateness of dosage of the initial antifungal agent				
Appropriate dosage of the initial antifungal agent	57 (50)	13 (86.6)	44 (44.4)	<0.01
Inappropriate dosage	54 (47.3)	2 (13.3)	52 (52.5)	<0.01
Patients excluded due to the lack of data	3 (2.6)	0	3 (3)	NA
Appropriateness of therapy				
Appropriate therapy based on the susceptibility test	101 (88.5)	15 (100)	86 (86.8)	0.35
Inappropriate therapy based on the susceptibility test	11 (9.6)	0	11 (11.1)	0.35
Patients excluded due to the lack of data	2 (1.7)	0	2 (2.0)	NA
Follow-up blood cultures and ophthalmological consultations				
Patients with follow-up blood cultures to confirm the clearance of *Candida* species	71 (62.2)	15 (100)	56 (56.5)	<0.01
Patients with ophthalmological consultations to rule out endophthalmitis	53 (46.4)	12 (80)	41 (41.4)	0.01
Central venous catheter management				
Patients with CVC	102 (89.4)	12 (80)	90 (90.9)	0.19
Patients with the removal of CVC	77 (67.5)	10 (66.6)	67 (67.6)	0.72
Duration of therapy and mortality rate				
Appropriate duration of antifungal therapy	24 (21)	9 (60)	15 (15.1)	<0.01
Death within 30 days of the diagnosis of candidemia	33 (28.9)	3 (20)	30 (30.3)	0.38

Notes: Data are expressed as the number (%) of patients. The appropriateness of the dosage and duration of antifungal therapy was evaluated by the IDSA candidiasis guidelines.

Abbreviations: IDSA, Infectious Diseases Society of America; NA, not applicable; CVC, central venous catheter.

identified factors that had significant relationships with death: *C. albicans* (hazard ratio (HR)=3.62, 95% confidence interval (CI)=1.61–8.12, $P<0.01$), absence of antifungal therapy (HR=20.16, 95% CI=4.9–81.8, $P<0.01$), advanced age (HR=1.03, 95% CI=1.0–1.05, $P=0.019$), lung disease (HR=2.15, 95% CI=1.02–4.5, $P=0.042$), and mechanical ventilation (HR=4.12, 95% CI=1.3–12.6, $P=0.013$) were significant factors for a high mortality rate, whereas *C. parapsilosis* (HR=0.2, 95% CI=0.039–0.97, $P=0.047$), the removal of CVC (HR=0.21, 95% CI=0.094–0.47, $P<0.01$), and surgical wards (HR=0.3, 95% CI=0.11–0.86, $P=0.025$) were associated with a lower mortality rate (Table 4).

APACHE II scores were calculated in 69 patients. The mean value of this score was 17.7±6.9 (median=16, range=6–42). Non-survivors had a significantly higher APACHE II score (mean=23.0±7.0) than survivors (mean=15.0±5.2) ($P<0.01$, Student's *t*-test). We divided patients for whom APACHE II scores were calculated into two groups based on the median value (Figure 3B). Patients with higher APACHE II scores (≥17) had a significantly higher mortality rate than patients with lower APACHE II scores (≤16) according to the Log-rank test ($P<0.01$).

Clinical and microbiological characteristics among patients with BT candidemia

BT candidemia occurred in 14 patients (11.5%). Comparisons of various parameters between patients with and without BT candidemia are summarized in Table 5. Prior to the onset of BT candidemia, eight patients were exposed to azole antifungal agents (FLCZ, n=6; VRCZ, n=1; itraconazole (ITCZ), n=1), whereas six were exposed to non-azole antifungal agents (MCFG, n=4, liposomal amphotericin B (L-AMB), n=2). Seven patients were administered antifungal agents as prophylaxis (FLCZ, n=5; MCFG, n=2), and seven were administered them as therapeutic agents (FLCZ, n=1; ITCZ, n=1; VRCZ, n=1; MCFG, n=2; L-AMB, n=2). Based on microbiological characteristics, significant differences were observed in *C. guilliermondii*, resistant to FLCZ and VRCZ, between patients with and without BT candidemia.

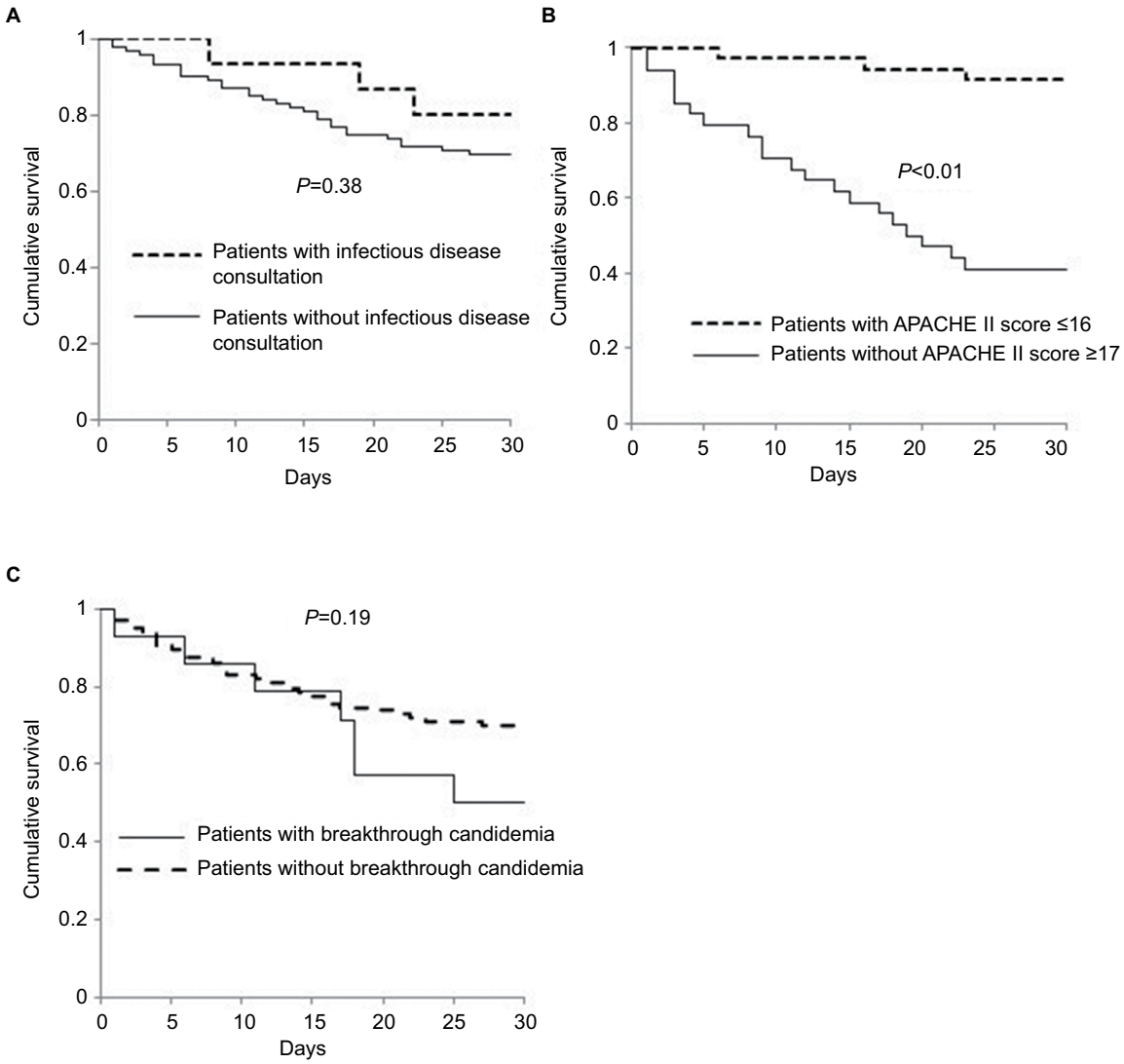

Figure 3 Kaplan–Meier plots of 30-day survival rates; infectious disease consultations (**A**), APACHE II scores (**B**), and breakthrough candidemia (**C**).
Note: *P*-values were obtained by the Log-rank test. The cut-off value for APACHE II scores was assessed by the median value of all patients for whom this score was calculated (**B**).
Abbreviation: APACHE II, acute physiology and chronic health evaluation II.

The MCFG resistance rate in patients with BT candidemia was 6.6%, which was similar to that in patients without BT candidemia (2.7%). No strain had resistance to AMB. BT candidemia mostly occurred in patients admitted to hematological wards. The proportion of patients with BT candidemia with a neutrophil count >1000 cells/μL was significantly lower than that in patients without BT candidemia. On the other hand, the proportion of neutropenia was significantly higher in patients with, than in those without, BT candidemia. In the therapeutic background, the rates of anticancer agents, immunosuppressive therapy, and hematopoietic stem cell transplantation were significantly higher in patients with, than in those without, BT candidemia. In the history of antibiotic therapy, the rates of anti-MRSA antibiotics and anti-CD antibiotics were significantly higher in patients with, than in those without, BT candidemia. The 30-day mortality rates of each group were as follows: patients with BT candidemia, 50%, and those without BT candidemia, 30.8%. No significant differences were observed in 30-day mortality rates (Figure 3C, P=0.19). The proportion of *Candida* species that showed resistance to FLCZ was 50% in patients with a history of the use of azole antifungal agents, which was higher than that in patients exposed to non-azole antifungal agents (0%); however, no significant difference was observed among the groups (P=0.076, Fisher's exact test). No *Candida* species showed resistance to MCFG or AMB in the six patients exposed to non-azole antifungal agents.

Table 3 Comparison of various parameters among survivors and non-survivors

	Non-survivors	Survivors	*P*-value
Number of cases	40	81	
Clinical demographics			
Age	69.6±13.6	59.6±19.3	<0.01
Serum albumin (mg/dL)	2.1±0.6	2.6±0.6	<0.01
Sex (male)	32 (80)	55 (67.9)	0.16
Presence of CVC	34 (85)	73 (90.1)	0.54
Immunosuppressive therapy	12 (30)	22 (27.1)	0.74
Anticancer therapy	11 (27.5)	24 (29.6)	0.8
Total parenteral nutrition	31 (77.5)	62 (76.5)	1
Mechanical ventilation	10 (25)	6 (7.4)	0.01
Renal failure	7 (17.5)	5 (6.1)	0.06
Liver failure	11 (27.5)	18 (22.2)	0.65
Solid tumor	12 (30)	36 (44.4)	0.12
Hematological tumor	8 (20)	8 (9.8)	0.15
Lung disease	17 (42.5)	14 (17.2)	<0.01
Diabetes mellitus	8 (20)	14 (17.2)	0.8
Hematopoietic stem cell transplantation	5 (12.5)	5 (6.1)	0.29
Neutropenia	5 (12.5)	3 (3.7)	0.11
Intensive care wards	5 (12.5)	2 (2.4)	0.038
Internal medicine wards	20 (50)	37 (45.6)	0.65
Surgical wards	6 (15)	31 (38.2)	0.011
Hematological wards	9 (22.5)	10 (12.3)	0.18
History of surgery	7 (17.5)	25 (30.8)	0.11
Therapeutic implementation for candidemia			
Presence of CVC	34 (85)	73 (90.1)	0.54
Removal of CVC	15 (37.5)	64 (79.0)	<0.01
Initiation of antifungal therapy within 3 days of blood cultures	30 (75)	72 (88.8)	0.063
Initiation of antifungal therapy within more than 4 days of blood cultures	3 (7.5)	9 (11.1)	0.74
Appropriate dosage of initial antifungal agents	15 (37.5)	42 (51.8)	0.86
FLCZ	9 (22.5)	26 (32)	0.52
MCFG	19 (47.5)	43 (53)	0.83
L-AMB	2 (5)	6 (7.4)	1
VRCZ	0	3 (3.7)	0.55
ITCZ	2 (5)	1 (1.2)	0.21
CPFG	2 (5)	1 (1.2)	0.21
Absence of antifungal therapy	6 (15)	1 (1.2)	<0.01
Patients with infectious disease consultations	3 (7.5)	12 (14.8)	0.38
Microbiological characteristics of *Candida* species			
C. albicans	22 (55)	22 (27.1)	<0.01
C. parapsilosis	2 (5)	29 (35.8)	<0.01
C. glabrata	4 (10)	9 (11.1)	1
C. guilliermondii	2 (5)	13 (16)	0.14
C. tropicalis	3 (7.5)	1 (1.2)	0.10
Other *C.* species	4 (10)	4 (4.9)	0.43
Mixed infection by *Candida* species	2 (5)	3 (3.7)	0.66
Resistance to FLCZ	4 (10)	6 (7.4)	0.72
Resistance to MCFG	1 (2.5)	3 (3.7)	1
Resistance to VRCZ	2 (5)	5 (6.1)	1

Note: Data are expressed as the number (%) of patients or mean±standard deviation.
Abbreviations: CVC, central venous catheter; FLCZ, fluconazole; MCFG, micafungin; L-AMB, liposomal amphotericin B; VRCZ, voriconazole; ITCZ, itraconazole; CPFG, caspofungin.

Discussion

Candidemia is one of the most serious nosocomial infections, due to its high mortality rate. Its incidence has been increasing because of the development of immunosuppressive therapy and aging of the population.[2] Therefore, identifying the prognostic factors of candidemia, based on each institution's epidemiological trends and practice patterns, is essential for improving the management of this infection.

Table 4 Risk factors for death within 30 days of being diagnosed with candidemia according to Cox's regression analysis

	Hazard ratio	95% CI	*P*-value
Candida albicans	3.62	1.610–8.120	<0.01
Candida parapsilosis	0.20	0.039–0.970	0.047
Absence of antifungal therapy	20.16	4.900–81.80	<0.01
Age	1.03	1.000–1.050	0.019
Removal of CVC	0.21	0.094–0.470	<0.01
Surgical wards	0.30	0.110–0.860	0.025
Lung disease	2.15	1.020–4.500	0.042
Intensive care wards	0.33	0.077–1.420	0.13
Mechanical ventilation	4.12	1.300–12.60	0.013
Serum albumin	0.63	0.330–1.100	0.14

Note: Each factor was selected by a univariate analysis between survivors and non-survivors.
Abbreviations: CVC, central venous catheter; CI, confidence interval.

Epidemiology of candidemia

In the present study, the overall incidence of candidemia was 0.056 cases/1000 hospital admissions, which was lower than that of previous studies in Japan (1.74/1000 hospital admissions).[20] Previous studies reported the incidence of candidemia in the US (0.16–0.33/1000 hospital admissions) and in European countries (0.92–1.5/1000 hospital admissions).[21–23] The incidence noted in the present study was similar to that in Finland (0.026–0.03/1000 hospital admissions).[24]

Impact of ID consultations on treatment and prognostic factors associated with candidemia

Takesue et al[25] reported that compliance with bundles based on IDSA candidiasis guidelines correlated with the outcomes of candidemia. Based on this finding, we performed ID consultations using bundles that appeared to influence mortality. Significant differences were observed in the dosage of initial antifungal therapy, follow-up blood cultures for the confirmation of the clearance of *Candida* species, ophthalmological consultations to rule out endophthalmitis, and an adequate duration of antifungal therapy between patients with and without ID consultations. Inappropriate antifungal therapy, such as an inadequate dosage, and an inadequate duration of therapy were found to be responsible for poor outcomes.[25,26] Therefore, our ID consultation contributes to the better management of candidemia, even though no significant difference was observed in the mortality rate. The number of patients who received ID consultation was only 15, because our AFSPs were implemented from October 2015. Further observation may be necessary to evaluate the impact of our ID consultation on the mortality rate.

We identified some factors associated with death using a multivariate analysis. In terms of therapeutic practices, the absence of antifungal therapy and removal of CVC were identified as significant factors for death. The removal of CVC contributes to favorable outcomes, because most cases of candidemia are attributable to CVC.[13,27] The early initiation of antifungal therapy is required to improve outcomes.[16,23] Our results were similar to these findings, indicating that the early removal of CVC and administration of antifungal agents are essential for better outcomes in candidemia.

C. parapsilosis is isolated from the skin tissue of healthy volunteers.[28] This species is known to cause catheter-related bloodstream infections.[28,29] Candidemia caused by *C. parapsilosis* has a lower mortality rate than that by *C. albicans*.[30] The removal of CVC has been associated with a lower mortality rate among patients with *C. parapsilosis* bloodstream infections.[30] In addition to the potentially low mortality rate of candidemia caused by *C. parapsilosis*, the elimination of the focus of infection was easily achieved by removing CVC. Therefore, *C. parapsilosis* correlated with a lower mortality rate because of these clinical and microbiological characteristics.

In the present study, surgical wards were confirmed to correlate with a lower mortality rate. Patients with higher APACHE II scores (≥17) had a significantly higher mortality rate than those with lower APACHE II scores (≤16). APACHE II scores are a known indicator of the general condition of a patient. High APACHE II scores have been associated with a higher mortality rate.[13,14] Among 69 patients for whom APACHE II scores were calculated, the proportion of patients with higher APACHE II scores was 35.5% in surgical wards, which was significantly lower than that among patients admitted to other wards (60.5%). Therefore, confounding factors such as general condition may influence the lower mortality rate among patients in surgical wards.

Clinical and microbiological characteristics among patients with BT candidemia

In this study, 14 patients (11.5%) were defined as BT candidemia. The incidence of BT candidemia was similar to that in previous studies.[31] Profound neutropenia, as well as immunosuppressive therapy, have been reported as risk factors of this infection.[10,11] In the present study, most patients with BT candidemia received immunosuppressive therapy, anticancer agents, and hematopoietic stem cell transplantation. In addition to these classical factors, a significant difference was observed in the history of anti-MRSA agents and anti-CD agents. The gastrointestinal tract has been reported as an important entry source of *Candida*

Table 5 Clinical and microbiological characteristics of patients with breakthrough and non-breakthrough candidemia

	Breakthrough candidemia	Non-breakthrough candidemia	*P*-value
Number of cases	14	107	
Candida species			
Number of *Candida* species isolated from blood cultures	15	111	
C. albicans	3 (20)	43 (38.7)	0.25
C. parapsilosis	2 (13.3)	31 (27.9)	0.35
C. glabrata	0	15 (13.5)	0.21
C. guilliermondii	5 (33.3)	12 (10.8)	0.031
C. tropicalis	0	4 (3.6)	1.0
C. pelliculos	0	1 (0.9)	1.0
Other *C.* species	5 (33.3)	5 (4.5)	<0.01
Resistance to antifungal agents			
FLCZ resistance	4 (26.6)	6 (5.4)	0.018
MCFG resistance	1 (6.6)	3 (2.7)	0.4
VRCZ resistance	3 (20)	4 (3.6)	0.036
Clinical wards			
Internal medicine wards	0	57 (53.2)	<0.01
Surgical medicine wards	2 (14.2)	35 (32.7)	0.22
Hematological medicine wards	12 (85.7)	7 (6.5)	<0.01
Intensive care wards	0	7 (6.5)	1.0
Pediatric medicine wards	0	1 (0.9)	1.0
Neutrophil count			
Neutrophil count more than 1000 (cell/μL)	4 (28.5)	101 (94.3)	<0.01
Neutrophil count less than 500 (cell/μL)	7 (50)	1 (0.9)	<0.01
Neutrophil count less than 100 (cell/μL)	5 (35.7)	1 (0.9)	<0.01
Patients with a lack of data	1 (7.1)	5 (4.6)	NA
Underlying disease			
Lung disease	0	31 (28.9)	0.02
Diabetes mellitus	2 (14.2)	20 (18.6)	1.0
Solid tumor	1 (7.1)	47 (43.9)	<0.01
Hematological tumor	10 (71.4)	5 (4.6)	<0.01
Clinical background and mortality			
Death within 30 days of candidemia	7 (50)	33 (30.8)	0.19
Immunosuppressive therapy	8 (57.1)	26 (24.2)	0.022
Anticancer agents	9 (64.2)	26 (24.2)	<0.01
Low albumin (<2.5 mg/dL)	6 (42.8)	59 (55.1)	0.4
Hematopoietic stem cell transplantation	7 (50)	3 (2.8)	<0.01
Mechanical ventilation	2 (14.2)	14 (13)	1.0
History of surgery	2 (14.2)	30 (28)	0.35
Presence of a central venous catheter	13 (92.8)	93 (86.9)	1.0
History of *Candida* colonization	4 (28.5)	23 (21.4)	0.51
Total parenteral nutrition	13 (92.8)	79 (73.8)	0.18
History of antibiotic therapy			
Anti-MRSA antibiotics	12 (85.7)	24 (22.4)	<0.01
Broad spectrum antibiotics	12 (85.7)	65 (60.7)	0.08
Anti-CD antibiotics	6 (42.8)	12 (11.2)	<0.01
Anti-anaerobic antibiotics	10 (71.4)	66 (61.6)	0.56

Note: Data are expressed as the number (%) of patients or *Candida* species.
Abbreviations: FLCZ, fluconazole; MCFG, micafungin; VRCZ, voriconazole; MRSA, methicillin-resistant *Staphylococcus aureus*; CD, *Clostridium Difficile*; NA, not applicable.

species, particularly in patients with neutropenia.[32] A history of heavy antibiotic exposure was identified as a risk factor for BT candidemia.[10,33] Therefore, the excessive use of antibiotics disturbed the distribution of the bacterial flora in the gastrointestinal tract, which may promote the growth of *Candida* species and development of BT candidemia among patients with neutropenia.

The proportion of species that showed resistance to azole antifungal agents was significantly higher among patients with than among those without BT candidemia.

Resistance to azole antifungal agents was prominent in BT candidemia cases that developed under exposure to azole antifungal agents. This result was consistent with previous findings.[31] Among the four FLCZ-resistant strains isolated from BT candidemia, three (one of *C. guilliermondii* and two of other *Candida* species) exhibited cross resistance to VRCZ. According to the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) candidiasis guidelines, a switch to another class of antifungal therapy is recommended among patients with a history of FLCZ administration.[34] Among BT candidemia, *C. guilliermondii* was the most frequently isolated in the present study. A significant difference was observed in the incidence of *C. guilliermondii* between patients with and without BT candidemia. This species was frequently isolated among patients with hematological malignancy; however, the microbiological characteristics of *C. guilliermondii*-associated candidemia have not yet been examined in detail.[35] A high resistant rate to azole antifungal agents has been reported for *C. guilliermondii*.[36] In the present study, approximately 20% of *C. guilliermondii* showed resistance to FLCZ, while MCFG and AMB showed high susceptibility rates. Therefore, the present results support the importance of a class switch to other antifungal agents in the treatment of BT candidemia in patients with a history of exposure to azole antifungal agents.

Limitations

The limitations of the present study were as follows. We were unable to include APACHE II scores to evaluate prognostic factors in the multivariate analysis, because APACHE II scores were not calculated for approximately 40% of patients. Difficulties were associated with evaluating this score in many cases, due to the lack of clinical data, which may be because of the retrospective study design. A prospective study will be required to resolve this issue. Furthermore, the number of cases that developed BT candidemia was so small that it was not possible to perform a multivariate analysis to examine risk factors for the onset of BT candidemia. This study was a retrospective analysis of a single hospital, which resulted in difficulties in performing meaningful statistical analyses on BT candidemia. Multicenter research may be needed in order to address this issue, because the incidence of BT candidemia was extremely low.

Conclusion

Our ID consultations using bundles contributed to the better management of candidemia therapy. In terms of clinical practice, no administration of antifungal agents was a significant risk factor for a high mortality rate, whereas CVC removal was associated with a lower mortality rate. Patients with higher APACHE II scores had a higher mortality rate, which indicates that physicians need to consider the prompt initiation of treatment for patients with a poor general condition. *Candida* species that exhibited azole resistance were more abundant in patients with, than in those without, BT candidemia. This result was marked in cases exposed to azole antifungal agents. A class switch to other antifungal agents needs to be considered in the empirical antifungal treatment of BT candidemia with a history of exposure to azole antifungal agents.

Acknowledgments

We thank Ryuichi Teshiromori (Medical Technologist, Department of Laboratory Medicine, Aomori Prefectural Central Hospital), and Eriko Shibata (Medical Technologist, Department of Laboratory Medicine, Aomori Prefectural Central Hospital) for their help in this study.

Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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