Published in final edited form as:

J Infect. 2012 January ; 64(1): . doi:10.1016/j.jinf.2011.11.002.

Rare opportunistic (non-*Candida*, non-*Cryptococcus*) Yeast Bloodstream Infections in Patients with Cancer

Maria N. Chitasombat¹, Diamantis P. Kofteridis¹, Ying Jiang¹, Jeffrey Tarrand², Russell E. Lewis^{1,3}, and Dimitrios P. Kontoyiannis^{1,3}

¹Department of Infectious Diseases, Infection Control and Employee Health, Houston, Texas

²Department of Laboratory Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas

³Department of College of Pharmacy, University of Houston, Houston, Texas

Abstract

Background—Rare opportunistic (non-*Candida*, non-*Cryptococcus*) yeast bloodstream infections (ROYBSIs) are rare, even in cancer patients.

Methods—We retrospectively reviewed all episodes of ROYBSIs occurring from 1998 to 2010 in our cancer center.

Results—Of 2984 blood cultures positive for *Candida* and non-*Candida* yeasts, 94 (3.1%) were positive for non-*Candida* yeasts, representing 41 ROYBSIs (incidence, 2.1 cases/100,000 patient-days). Catheter-associated fungemia occurred in 21 (51%) patients. Breakthrough ROYBSIs occurred in 20 (49%) patients. The yeast species distribution was *Rhodotorula* in 21 (51%) patients, *Trichosporon* in 8 (20%) patients, *Saccharomyces cerevisiae* in 8 (20%) patients, *Geotrichum* in 2 (5%) patients, *Pichia anomala*, and *Malassezia furfur* in 1 patient each. All tested *Trichosporon*, *Geotrichum*, and *Pichia* isolates were azole-susceptible, whereas the *Rhodotorula* isolates were mostly azole-resistant. We noted echinocandin nonsusceptibility (minimal inhibitory concentration ≥ 2 mg/L) in all but the *S. cerevisiae* isolates. Most of the isolates (28/33 [85%]) were susceptible to amphotericin B. The mortality rate in all patients at 30 days after ROYBSIs diagnosis was 34%. Multivariate survival analysis revealed increased risk of death in patients with *S. cerevisiae* infections (hazard ratio, 3.7), *Geotrichum* infections (hazard ratio, 111.3), or disseminated infections (hazard ratio, 33.4) and reduced risk in patients who had catheter removal (hazard ratio, 0.1).

Conclusions—ROYBSIs are uncommon in patients with cancer, and catheters are common sources of them. Half of the ROYBSIs occurred as breakthrough infections, and in vitro species-specific resistance to echinocandins and azoles was common. Disseminated infections resulted in the high mortality rate.

© 2011 The British Infection Society. Published by Elsevier Ltd. All rights reserved.

Reprints or correspondence: Dr. Dimitrios P. Kontoyiannis, Department of Infectious Diseases, Infection Control and Employee Health, Unit 1460, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030. Telephone: (713) 792-6237; Fax: (713) 745-6839 (dkontoyi@mdanderson.org).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Potential conflicts of interest. M.N.C, D.K., J.T., and Y.J: no conflicts.

Keywords

Non-*Candida* yeast; Cancer; Immunosuppression

Non-*Candida* and non-*Cryptococcus* yeasts, although uncommon, could cause severe infections in patients with cancer [1]. Treatment of these infections is challenging owing to their rarity and common in vitro resistance to standard antifungals [2]. Furthermore, the full spectrum of infections caused by these yeasts in immunocompromised patients with cancer is incompletely characterized, as the literature mostly consists of case reports and small case series [3-7]. In addition, the significance of recovering non-*Candida* yeasts from blood culture specimens remains unknown, given that these fungi can colonize in the skin and contaminate blood cultures [8, 9]. Not surprisingly, consistent definitions of rare opportunistic yeast bloodstream infections (ROYBSIs) are lacking, and European Organization for Research and Treatment of Cancer/Mycoses Study Group consensus guidelines do not address the significance of recovery of uncommon yeasts from blood cultures [10]. To that end, we reviewed our experience in treating ROYBSIs at The University of Texas MD Anderson Cancer Center. The present study, to our knowledge, is the largest single-center contemporary series of consecutive ROYBSIs in patients with cancer to date.

PATIENTS AND METHODS

Isolates

The MD Anderson clinical microbiology laboratory database was searched for blood cultures positive for non-*Candida* and non-*Cryptococcus* yeasts from January 1998 to October 2010. The isolates' susceptibility to antifungal agents was tested using broth microdilution according to the Clinical Laboratory Standards Institute (CLSI) reference procedure outlined in document M27-A3 [11]. Because established breakpoints defining antifungal susceptibility of non-*Candida* yeasts are lacking, the MICs of amphotericin B, fluconazole, itraconazole, voriconazole, posaconazole, and caspofungin in a subset of infection-causing bloodstream yeast isolates were determined using broth microdilution according to the CLSI criteria [11]. Breakpoints for susceptibility were adopted according to CLSI criteria, and an echinocandin minimal inhibitory concentration (MIC) ≥ 2 mg/L was used to identify yeasts not susceptible to caspofungin [12].

Laboratory analysis

Yeasts were isolated and identified using standard methods [13]. Specifically, yeasts were identified using a Vitek Yeast Biochemical Card (bioMérieux Vitek Inc., Hazelwood, MO) and/or an API 20C Aux (bioMérieux, Marcy-l'Étoile, France). Although morphologic characteristics of non-*Candida* and non-*Cryptococcus* yeasts and assimilation of carbon sources in biochemical panels may facilitate species-level identification of non-*Candida* yeasts, this is not always possible [13]. Over the database-search period, all *Trichosporon* isolates were grouped as *Trichosporon* species based on urease production and the presence of arthroconidia. Supplemental morphologic studies of all unusual yeasts were performed using Cornmeal Tween 80 agar and the slide culture technique [14]. Blood culture were drawn and analyzed with quantitative method assessed by colony counts, greater than 50 colony-forming units (CFUs) in blood cultures drawn from central line would be suggestive of catheter related bloodstream infection [15].

Clinical data

We collected from the patients' medical records, data regarding demographic characteristics, underlying malignancies, prior immunosuppressive agent use, hematologic stem cell transplantation, neutropenia, catheter use, intensive care unit admission, laboratory test results, concomitant infections, antifungal prophylaxis/treatment, catheter management, and outcome.

Definitions

Because standard definitions for diagnosis of ROYBSIs are lacking [10], the infections were defined based on previously published criteria [16]. Proven fungemia was defined as the presence of a non-*Candida* yeast in blood with histopathologic evidence of budding yeast and/or hyphae in tissue specimens from sites other than blood or persistently positive blood cultures over time in a patient with signs and symptoms of infection. Probable fungemia was defined as the presence of non-*Candida* and non-*Cryptococcus* yeasts in blood and a clinical picture compatible with fungemia in a typical clinical setting and without other microbes. Indeterminate fungemia was defined as a case meeting the probable fungemia criteria but with blood cultures concomitantly yielding other pathogens [17]. Transient fungemia was defined as presence of a yeast in blood cultures only for single day. Catheter-related fungemia was defined according to previously published guidelines [15]. At our institution, such diagnosis relies heavily on the use of quantitative blood culture methods. De novo fungemia was defined as an infection in a patient not receiving systemic antifungal therapy. Breakthrough fungemia was defined as an infection in a patient receiving systemic antifungal therapy for at least 7 consecutive days before the index blood culture. Neutropenia was defined as an absolute neutrophil count (ANC) of less than 500 cells/mm³. Neutrophil recovery was defined as restoration of the ANC to greater than 500/mm³ for 3 consecutive days after ROYBSIs diagnosis. Antifungal therapy was considered appropriate if the yeast isolate was susceptible to the drug in vitro. Response to antifungal treatment was modeled using previously proposed criteria for candidemia [18]. Crude mortality within 30 days after ROYBSIs diagnosis was assessed. Yeast-related death was defined as 1) histopathologic involvement of a major organ by the yeast at autopsy and antemortem evidence of severe dysfunction of the affected organ, 2) the presence of an ROYBSIs at or shortly before (within 48 hours) death in the absence of an autopsy, 3) death while receiving antifungals in patients having signs or symptoms of ROYBSIs, or 4) death while exhibiting signs or symptoms of infection 7-14 days after discontinuation of antifungal therapy for the initial ROYBSIs episode without another obvious cause. Patients who died of causes other than ROYBSIs during therapy were considered to have a cure if their signs and symptoms of infection resolved and fungemia cleared before death or they had no evidence of infection at autopsy [19].

Statistical analysis

Categorical variables among patient groups were compared using the χ^2 test or Fisher exact test where appropriate, and continuous variables were compared using the Student *t*-test. Factor associated with breakthrough infections, disseminated infection, mortality at 30 days were analyzed. Variables associated with differences in survival with two-sided *P* values less than .15 were further analyzed using a multivariate survival model with the Cox regression method in a stepwise fashion. Except as described above, two-sided *P* values less than .05 were considered statistically significant. The analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

Microbiology

There were 51,714 positive blood cultures from total of 463,304 blood cultures processed during the study period. Fungi were isolated from 3382 blood culture specimens (6.5%); of those, 2984 isolates (5.8%) were positive for yeasts. Non-*Candida* and non-*Cryptococcus* yeasts were isolated from 94 blood culture specimens (from 41 patients), representing 0.02% of all blood cultures, 0.18% of all positive blood cultures, 2.8 % of all positive fungal blood cultures and 3.1% of all positive blood culture for yeasts. The overall incidence of ROYBSIs in the study period was 2.1 cases per 100,000 patient-days. The incidence of non-*Candida* and non-*Cryptococcus* yeasts increased slightly over time, going from 1.8 cases per 100,000 patient-days in 1998-2004 to 2.35 cases per 100,000 patient-days in 2005-2010 ($P = .47$). Of the 41 ROYBSIs, 13 (32%) were proven, 20 (49%) were probable, and 8 (20%) were indeterminate (Table 1). We found non-*Candida* and non-*Cryptococcus* yeasts-positive blood cultures from peripheral sites, central lines, or both in 24 of 35 (69%), 26 of 32 (81%), and 8 of 26 (31%) cases, respectively. Twenty-seven (66%) patients had transient fungemia and 14 (34%) had persistent fungemia. Two (9%) of 23 patients whose catheters were removed had yeast-positive catheter tip cultures. Nine of 21 catheter-related bloodstream infections (CRBSIs) were associated with high-grade fungemia, with colony counts greater than 50 colony-forming units (CFUs) in blood cultures obtained via central lines. These infections were caused by *Rhodotorula* in seven cases, *Geotrichum* species, and *M. furfur* in one case each. In all non-catheter-related infections, the colony count in yeast-positive blood cultures from central lines was less than 10 CFUs. Bloodstream infections with *Trichosporon* spp. and *S. cerevisiae* yielded low fungemia levels, with no more than 10 CFUs in all cases. Concomitant bloodstream infections occurred in 21 (51%) patients; 7 (33%) of them had another fungal infection, including those with *Candida*, *Fusarium*, or *Aureobasidium* species. Three (7%) patients had invasive pulmonary aspergillosis, and three others had respiratory viruses.

Patient characteristics

The patients' demographic, clinical, and microbiologic characteristics are shown in Table 2. Of these, 12 (29%) patients were hematopoietic stem cell transplant recipients (allogeneic in 10 patients). The median duration from hematopoietic stem cell transplantation to onset of fungemia was 15 days (range, 6-330 days). Also, most of the patients received cytotoxic chemotherapy ($n = 32$ [78%]) or systemic corticosteroids ($n = 23$ [56%]) within 30 days after diagnosis. A central venous catheter was present in 39 (95%) patients. Twenty-one (51%) patients had CRBSIs. *Rhodotorula* spp. were significantly associated with CRBSI in 16 of 21 (76%) patients ($P = .002$). However, none of the patients with *Rhodotorula* infections had dissemination compared to other ROYBSI ($P = .009$). *Trichosporon* bloodstream infections occurred in 8 of 27 (30%) patients with hematologic malignancies compared to other ROYBSI ($P = .035$), and in 7 of 20 (35%) patients with neutropenia compared to other ROYBSI ($P = .02$), and in association with non-catheter-related infections in 7 of 20 (35%) patients ($P = .02$) and dissemination in 4 of 6 (67%) patients ($P = .009$), compared to other ROYBSI.

Breakthrough infections

Breakthrough infections occurred in 20 (49%) patients while receiving prophylactic or empiric antifungal therapy (Table 2). All of them had underlying hematologic malignancies; 11 of them were hematopoietic stem cell transplant recipients. Most of the patients with breakthrough infection had severe neutropenia (13 [65%] compared to 5 [24%] patients without breakthrough infections; $P = .012$). In addition, most of them received prior corticosteroids (15 [75%] compared to 8 [38%] patients without breakthrough infections; P

= .028). The yeast species distribution was *Rhodotorula* in 8 (40%) patients, *Trichosporon* in 6 (30%) patients, *S. cerevisiae* in 3 (15%) patients, *Geotrichum* in 2 (10%) patients, and *P. anomala* in 1 (5%) patient. Eleven of 19 (58%) available isolates causing breakthrough infections were not susceptible to antifungals that patients were receiving for prophylactic or empiric therapy. A catheter was deemed the infection source in 9 (45%) of such patients. Of note, 4 (20%) patients had disseminated infections (*Trichosporon* in 3 patients, *S. cerevisiae* in 1 patient).

In vitro susceptibility to antifungal drugs

Thirty-three isolates were available for in vitro susceptibility testing (Table 3). All *Trichosporon*, *Geotrichum*, and *P. anomala* isolates were susceptible to azoles. We noted amphotericin nonsusceptibility (MIC >1 mg/L) in 5 (15%) of 33 isolates, including 2 *Trichosporon* isolates, 2 *Rhodotorula* isolates, and 1 *Geotrichum* isolate. None of the *Trichosporon*, *Geotrichum*, or *Rhodotorula* isolates were susceptible to echinocandins, whereas all of the *S. cerevisiae* isolates were susceptible to them.

Treatment

Catheters were removed from 26 of 39 (67%) patients, (median time of catheter removal from the day of positive blood culture for yeast was 4 days [range, 0-10 days]). Thirty-five (85%) patients received antifungals (Table 4). Twenty-four (69%) of them received appropriate antifungal treatment; however, the treatment was delayed more than 3 days in 10 of them. Of the 11 patients receiving inappropriate antifungal treatment, 10 had CRBSIs, and all 11 had catheter removal. Only one patient died of persistent fungemia. Of note, in the 6 (15%) patients who did not receive any antifungals, fungemia cleared in three patients with CRBSIs after catheter removal; the remaining three patients with non-catheter-related infections died.

Disseminated infection

Most patients, 5 (83%) with disseminated infections had significantly been severely neutropenic compared to patients without disseminated infections ($P = .07$). *Trichosporon* significantly accounted disseminated infection in 4 (66%) compared to other yeast species ($P = .009$), whereas *S. cerevisiae* caused the other two. Breakthrough disseminated infections occurred in four (67%) patients. The infections manifested with skin rash, hepatosplenic or intra-abdominal abscesses, and pneumonia in these patients. Also, four patients had polymicrobial bloodstream infections (a vancomycin-resistant *Enterococcus* species, *Pseudomonas aeruginosa*, *Candida krusei*, and a *Fusarium* species).

Outcome of fungemia

Fourteen (34%) of 41 patients died within 30 days after ROYBSIs diagnosis (Table 4). The yeast-related death was 57% (8/14). Three (21%) patients underwent autopsies, and one of them had disseminated trichosporonosis. Patients with breakthrough infections had a higher mortality rate than did those without breakthrough infections (8/20 [40%] versus 6/21 [29%] patients; $P =$ not significant), which was related to fungemia in 4 of 8 patients. All patients with disseminated infections died within 30 days after diagnosis; in five of them, was yeast-related death. Most of the patients (5/6 [83%]) had active neutropenia at the time of death.

Univariate analysis showed that the risk factors associated with death were *S. cerevisiae*, *Geotrichum*, disseminated infections and intensive care unit admission (Table 5). In contrast, *Rhodotorula* infection was associated with improved survival rate as seen in CRBSI cases and with catheter removal. Resolution of neutropenia occurred in 11 of 20 (55%) patients. Seven of the nine patients without resolution of neutropenia died.

Multivariate Cox regression analysis revealed a significantly increased risk of death in patients with *S. cerevisiae* infection (hazard ratio, 3.7; 95% confidence interval [CI], 1.2-11.4), *Geotrichum* infection (hazard ratio, 111.3; 95% CI, 9.9-1255.2), or disseminated infection (hazard ratio, 33.4; 95% CI, 6.5-172.2) and a reduced risk in patients who had catheter removal (hazard ratio, 0.1; 95% CI, 0.03-0.50).

DISCUSSION

In contrast with more common *Candida* species, opportunistic non-*Candida* yeasts, including *Trichosporon*, *Saccharomyces*, and *Rhodotorula* spp., are emerging causes of fungemia and/or disseminated infections in immunosuppressed patients [1, 2]. Therefore, a better understanding of the clinical characteristics of ROYBSIs is required. The present study, to our knowledge, is the largest single-center contemporary series of consecutive ROYBSIs in patients with cancer to date. Our study uniquely provides in vitro antifungal susceptibility data that may guide selection of antifungal therapy for uncommonly encountered ROYBSIs.

In our series, the overall incidence of ROYBSIs remained relatively stable at 1.8-2.3 cases per 100,000 patient-days over final 6 years of the study period. Most patients with ROYBSIs had hematologic malignancies, and one third of them were hematopoietic stem cell transplant recipients. Catheters were common sources of ROYBSIs, especially with *Rhodotorula* spp., which were previously described as the fourth most common non-*Candida* and non-*Cryptococcus* yeasts isolated from clinical specimens in the ARTEMIS Global Antifungal Surveillance Program [2, 20-23]. *Rhodotorula* spp. can form biofilm [24], which may explain the frequent occurrence of catheter-associated *Rhodotorula* fungemia in our study. As with other fungal infections associated with indwelling catheters, catheter removal is frequently sufficient to resolve fungemia [20]. The second most common non-*Candida* yeasts in our study were *Trichosporon* spp., which we found only in patients with hematologic malignancies as described previously [1, 6]. Disseminated *Trichosporon* infections with skin, lung, liver, or spleen involvement occurred in 50% of such patients in a previous study, with a resultant high mortality rate [6]. The third most common yeast was *S. cerevisiae*. Although, Munoz *et al* [25] reported fungemia caused by *Saccharomyces* spp. which was contained in an orally administered probiotic, such infections may result from endogenous gastrointestinal translocation or due to contaminated catheters in immunosuppressed patients [7]. These two potential sources of infection seemed to be the main sources of fungemia in our study.

Not surprisingly, half of the ROYBSIs occurred as breakthrough infections in our series, typically in patients with hematologic malignancies and severe neutropenia in the setting of prior receipt of antifungals to which these yeasts frequently are not susceptible in vitro. Importantly, 67% of patients with disseminated infections had breakthrough infections, and all of them died. Also, catheters may be sources of breakthrough ROYBSIs similar to candidemia in patients with cancer [19]. Treatment of these infections remains challenging because of their rarity and resistance to standard antifungals and the compromised status of the host. According to our in vitro susceptibility testing, all *Trichosporon* and *Rhodotorula* isolates were resistant to echinocandins, which was similar to recent reports of breakthrough *Trichosporon* infection in leukemic patients while receiving caspofungin [1, 2, 4, 26, 27]. Of note is that azoles remained active against *Trichosporon* but not *Rhodotorula* spp. as described previously [1, 2, 28]. In our series, we noticed reduced susceptibility to amphotericin B at an MIC greater than 1 mg/L in 40% of *Trichosporon* isolates but these isolates remained susceptible to azoles as described previously [29]. Walsh *et al* and others have suggested that voriconazole is the most effective azole in the treatment of severe or disseminated trichosporonosis [29-35]. Overall, in our study, amphotericin B and

voriconazole remained active in vitro against most non-*Candida* yeast isolates, and they should be reasonable choices for pre-emptive treatment of these rare bloodstream infections, especially ROYBSIs.

Outcomes of disseminated ROYBSIs in our patients were poor. The crude 30-day mortality rate was rather high (34%), reflecting the hosts' immunosuppressed and debilitated states. However, as we recently have shown in most patients with candidiasis, mortality could not be solely related to fungemia [36]. The only independent factor associated with increased survival rate was catheter removal, as most non-*Candida* yeast infections originated from catheters.

Our retrospective single-institution study had several limitations. Specifically, the disease rarity resulted in a small number of patients, lack of molecular identification, also the correlation of in vitro susceptibility to antifungals with treatment response and/or outcome. Furthermore, the variety of these rare yeasts, heterogeneity of the hosts, and individualized management of infections limited the interpretation of the data.

In conclusion, ROYBSIs remain uncommon in patients with cancer, and catheters are common infection sources. Half of ROYBSIs occurred as breakthrough infections, and in vitro resistance to antifungals was not uncommon. Disseminated infections resulted in a high mortality rate. Future development of more rapid diagnostic techniques for identification of infecting pathogens for early targeted therapy would be useful.

Acknowledgments

The authors thank Cheryl Perego for useful information and Donald Norwood for editorial assistance.

Financial support. This research is supported in part by the National Institutes of Health through MD Anderson's Cancer Center Support Grant CA016672.

D.P.K. has received research support and honoraria from Schering-Plough; Pfizer; Astellas Pharma US, Inc.; Enzon Pharmaceuticals; and Merck and Co., Inc. R.E.L. has received research support and honoraria from Schering-Plough; Astellas Pharma US, Inc.; Enzon Pharmaceuticals; and Merck and Co., Inc.

References

1. Kontoyiannis DP, Torres HA, Chagua M, Hachem R, Tarrand JJ, Bodey GP, Raad II. Trichosporonosis in a tertiary care cancer center: risk factors, changing spectrum and determinants of outcome. *Scand J Infect Dis.* 2004; 36:564–9. [PubMed: 15370667]
2. Miceli MH, Diaz JA, Lee SA. Emerging opportunistic yeast infections. *Lancet Infect Dis.* 2011; 11:142–51. [PubMed: 21272794]
3. Goodman D, Pamer E, Jakubowski A, Morris C, Sepkowitz K. Breakthrough trichosporonosis in a bone marrow transplant recipient receiving caspofungin acetate. *Clin Infect Dis.* 2002; 35:35–6.
4. Matsue K, Uryu H, Koseki M, Asada N, Takeuchi M. Breakthrough trichosporonosis in patients with hematologic malignancies receiving micafungin. *Clin Infect Dis.* 2006; 42:753–7. [PubMed: 16477548]
5. Henrich TJ, Marty FM, Milner Jr DA, Thorner AR. Disseminated *Geotrichum candidum* infection in a patient with relapsed acute myelogenous leukemia following allogeneic stem cell transplantation and review of the literature. *Transplant Infectious Disease.* 2009; 11:458–62. [PubMed: 19804480]
6. Girmenia C, Pagano L, Martino B, D'Antonio D, Fanci R, Specchia G, et al. Invasive infections caused by *Trichosporon* species and *Geotrichum capitatum* in patients with hematological malignancies: a retrospective multicenter study from Italy and review of the literature. *J Clin Microbiol.* 2005; 43:1818–28. [PubMed: 15815003]

7. Cairoli R, Marengo P, Perego R, de Cataldo F. *Saccharomyces cerevisiae* fungemia with granulomas in the bone marrow in a patient undergoing BMT. *Bone Marrow Transplant*. 1995; 15:785–6. [PubMed: 7670407]
8. Vazquez, J. *Clinical Mycology*. Oxford University Press; New York: 2003. *Rhodotorula*, *Malassezia*, *Trichosporon* and other yeast-like fungi.; p. 203-17.
9. Bryce EA, Roberts FJ, Sekhon AS, Coldman AJ. Yeast in blood cultures. Evaluation of factors influencing outcome. *Diagn Microbiol Infect Dis*. 1992; 15:233–7. [PubMed: 1582167]
10. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis*. 2008; 46:1813–21. [PubMed: 18462102]
11. CLSI. CLSI document M27-A3. 3rd ed.. Clinical and Laboratory Standards Institute; Wayne, PA: 2008. Reference method for broth dilution antifungal susceptibility testing of yeasts; approved standard.
12. Pfaller MA, Diekema DJ, Ostrosky-Zeichner L, Rex JH, Alexander BD, Andes D, et al. Correlation of MIC with outcome for *Candida* species tested against caspofungin, anidulafungin, and micafungin: analysis and proposal for interpretive MIC breakpoints. *J Clin Microbiol*. 2008; 46:2620–9. [PubMed: 18579718]
13. Hazen, K.; Howell, SA. *Manual of Clinical Microbiology*. 9th ed.. ASM Press; Washington DC: 2007. *Candida*, *Cryptococcus* and other yeasts of medical importance..
14. Larone, D. 4th ed.. ASM Press; Washington, D.C: 2002. *Medically Important Fungi: A guide to identification*.
15. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009; 49:1–45. [PubMed: 19489710]
16. Duthie R, Denning DW. *Aspergillus* fungemia: Report of two cases and review. *Clinical Infectious Diseases*. 1995; 20:598–605. [PubMed: 7756482]
17. Lionakis MS, Bodey GP, Tarrand JJ, Raad II, Kontoyiannis DP. The significance of blood cultures positive for emerging saprophytic moulds in cancer patients. *Clin Microbiol Infect*. 2004; 10:922–5. [PubMed: 15373888]
18. Segal BH, Herbrecht R, Stevens DA, Ostrosky-Zeichner L, Sobel J, Viscoli C, et al. Defining Responses to Therapy and Study Outcomes in Clinical Trials of Invasive Fungal Diseases: Mycoses Study Group and European Organization for Research and Treatment of Cancer Consensus Criteria. *Clinical Infectious Diseases*. 2008; 47:674–83. [PubMed: 18637757]
19. Antoniadou A, Torres HA, Lewis RE, Thornby J, Bodey JP, Han XY, et al. Candidemia in a tertiary care cancer center: in vitro susceptibility and its association with outcome of initial antifungal therapy. *Medicine*. 2003; 82:309–21. [PubMed: 14530780]
20. Anatoliotaki M, Mantadakis E, Galanakis E, Samonis G. *Rhodotorula* species fungemia: a threat to the immunocompromised host. *Clin Lab*. 2003; 49:49–55. [PubMed: 12593475]
21. Kiehn TE, Gorey E, Brown AE, Edwards FF, Armstrong D. Sepsis due to *Rhodotorula* related to use of indwelling central venous catheters. *Clin Infect Dis*. 1992; 14:841–6. [PubMed: 1576278]
22. Tuon FF, de Almeida GM, Costa SF. Central venous catheter-associated fungemia due to *Rhodotorula* spp.-a systematic review. *Med Mycol*. 2007; 45:441–7. [PubMed: 17654271]
23. Pfaller MA, Diekema DJ, Gibbs DL, Newell VA, Ellis D, Bijie H, et al. Results from the ARTEMIS DISK Global Antifungal Surveillance study, 1997 to 2007: an 10.5-Year analysis of susceptibilities of *Noncandida* yeast species to Fluconazole and Voriconazole Determined by CLSI standardized disk diffusion testing. *J Clin Microbiol* 2009. 47:117–123.
24. Elvers KT, Leeming K, Lappin-Scott HM. Binary and mixed population biofilms: time-lapse image analysis and disinfection with biocides. *J Ind Microbiol Biotechnol*. 2002; 29:331–8. [PubMed: 12483475]

25. Munoz P, Bouza E, Cuenca-Estrella M, Eiros JM, Perez MJ, Sanchez-Somolinos, et al. *Saccharomyces cerevisiae* fungemia: an emerging infectious disease. *Clin Infect Dis*. 2005; 40:1625–34. [PubMed: 15889360]
26. Bayramoglu G, Sonmez M, Tosun I, Aydin K, Aydin F. Breakthrough *Trichosporon asahii* fungemia in neutropenic patient with acute leukemia while receiving caspofungin. *Infection*. 2008; 36:68–70. [PubMed: 17882360]
27. Diekema DJ, Petroelje B, Messer SA, Hollis RJ, Pfaller MA. Activities of available and investigational antifungal agents against *rhodotorula* species. *J Clin Microbiol*. 2005; 43:476–8. [PubMed: 15635020]
28. Lunardi LW, Aquino VR, Zimmerman RA, Goldani LZ. Epidemiology and outcome of *Rhodotorula* fungemia in a tertiary care hospital. *Clin Infect Dis*. 2006; 43:60–3.
29. Walsh TJ, Newman KR, Moody M, Wharton RC, Wade JC. *Trichosporonosis* in patients with neoplastic disease. *Medicine*. 1986; 65:268–79. [PubMed: 3523114]
30. Falk R, Wolf DG, Shapiro M, Polacheck I. Multidrug-resistant *Trichosporon asahii* isolates are susceptible to voriconazole. *J Clin Microbiol*. 2003; 41:911. [PubMed: 12574315]
31. Perparim K, Nagai H, Hashimoto A, Goto Y, Tashiro T, Nasu M. In vitro susceptibility of *Trichosporon beigeli* to antifungal agents. *J Chemother*. 1996; 8:445–8. [PubMed: 8981185]
32. Walsh TJ, Melcher GP, Rinaldi MG, Lecciones J, McGough DA, Kelly P, et al. *Trichosporon beigeli*, an emerging pathogen resistant to amphotericin B. *J Clin Microbiol*. 1990; 28:1616–22. [PubMed: 2380383]
33. Anaissie E, Gokaslan A, Hachem R, Rubin R, Griffin G, Robinson R, et al. Azole therapy for *trichosporonosis*: clinical evaluation of eight patients, experimental therapy for murine infection, and review. *Clin Infect Dis*. 1992; 15:781–7. [PubMed: 1445976]
34. Paphitou NI, Ostrosky-Zeichner L, Paetznick VL, Rodriguez JR, Chen E, Rex JH. In vitro antifungal susceptibilities of *Trichosporon* species. *Antimicrob Agents Chemother*. 2002; 46:1144–6. [PubMed: 11897610]
35. Pfaller M, Diekema D. Epidemiology of Invasive Mycoses in North America. *Crit Rev Microbiol*. 2010; 36:1–53. [PubMed: 20088682]
36. Sipsas NV, Lewis RE, Tarrand J, Hachem R, Rolston KV, Raad II, Kontoyiannis DP, et al. Candidemia in patients with hematologic malignancies in the era of new antifungal agents (2001-2007): stable incidence but changing epidemiology of a still frequently lethal infection. *Cancer*. 2009; 115:4745–52. [PubMed: 19634156]

Table 1

ROYBSIs in 41 Patients with Cancer

Species	Number of patients		
	Proven (n = 13 [32%])	Probable (n = 20 [49%])	Indeterminate (n = 8 [20%])
<i>Rhodotorula</i> (n = 21 [51%])	4	14	3
<i>Trichosporon</i> (n = 8 [20%])	5	2	1
<i>S. cerevisiae</i> (n = 8 [20%])	3	2	3
<i>Geotrichum</i> (n = 2 [5%])	1	0	1
<i>M. furfur</i> (n = 1 [2%])	0	1	0
<i>P. anomala</i> (n = 1 [2%])	0	1	0

NOTE. Catheter-related infections occurred in 16 (76%) *Rhodotorula* infections, 1 (13%) *Trichosporon* infection, 2 (25%) *S. cerevisiae* infections, and 1 (50%) *Geotrichum* infection.

Table 2

Characteristics of the 41 Study Patients with ROYBSIs.

Characteristic	Number of patients (%)
Median age, years (range)	51 (8-81)
Male sex	21 (51)
Malignancy	
Leukemia	22 (54)
Lymphoma	5 (12)
Solid tumor	14 (34)
Chemotherapy within 30 days after ROYBSIs diagnosis	31 (76)
Corticosteroid-based treatment within 30 days after ROYBSIs diagnosis	23 (56)
Prior HSCT ^a	12 (29)
Admission to ICU ^b	16 (39)
Presence of central venous catheter ^b	39 (95)
Neutropenia at diagnosis	
ANC <500 cells/ μ L	20 (49)
ANC <100 cells/ μ L	18 (44)
Breakthrough ROYBSIs	20 (49)
While receiving amphotericin B-based regimen	3/20 (15)
While receiving echinocandin-based regimen	5/20 (25)
While receiving azoles	16/20 (80)
Fluconazole	5/16 (31)
Posaconazole	3/16 (19)
Voriconazole	6/16 (38)
Itraconazole	2/16 (13)
While receiving combination antifungal treatment ^c	4/20 (20)

NOTE. HSCT, hematopoietic stem cell transplant; ICU, intensive care unit.^aAllogeneic transplant in 10 patients and autologous transplant in 2 patients.^bAt diagnosis.^cCombination of liposomal amphotericin B and voriconazole and of caspofungin and either voriconazole, posaconazole, or fluconazole.

Table 3

Susceptibility Data for ROYBSIs Isolates (n = 33)

Drug	Number (%)				
	<i>Trichosporon</i> (n = 5/8)	<i>Rhodotorula</i> (n = 17/21)	<i>S. cerevisiae</i> (n = 8/8)	<i>Geotrichum</i> (n = 2/2)	<i>P. anomala</i> (n = 1/1)
Amphotericin B					
No.	5	17	8	2	1
S	3 (60)	15 (88)	8 (100)	1 (50)	1 (100)
R	2 (40)	2 (12)	0	1 (50)	0
Fluconazole					
No.	3	17	8	2	1
S	3 (100)	3 (18)	6 (75)	2 (100)	1 (100)
R	0	14 (82)	2 (25)	0	0
Voriconazole					
No.	3	11	5	2	1
S	3 (100)	7 (64)	5 (100)	2 (100)	1 (100)
R	0	4 (36)	0	0	0
Itraconazole					
No.	4	17	8	2	1
S	4 (100)	6 (35)	7 (87)	2 (100)	1 (100)
R	0	11 (65)	1 (13)	0	0
Caspofungin					
No.	3	8	5	2	1
S	0	0	5 (100)	0	1 (100)
R	3 (100)	8 (100)	0	2 (100)	0
Posaconazole					
No.	3	11	5	2	1
S	3 (100)	6 (55)	5 (100)	2 (100)	1 (100)
R	0	5 (45)	0	0	0

NOTE. S, Susceptibility; R, Resistance. Breakpoints for susceptibility were adopted according to CLSI methodology [11].

Table 4

Treatment and Outcomes in the 41 Patients with ROYBSIs

Characteristic	Number of patients (%)
Antifungal treatment	35 (85)
Amphotericin B-based regimen	15/35 (43)
Echinocandin-based regimen	12/35 (34)
Azole-based monotherapy	8/35 (23)
Combination antifungal treatment	14 (34)
Median duration of treatment, days (range)	20 (2-75)
CVC removal	26/39 (67)
Median time to CVC removal, days (range)	4 (0-10)
Resolution of neutropenia	11/20 (55)
Growth factors ^a	13 (32)
Disseminated infection	6 (15)
Crude mortality rate at 30 days after ROYBSIs diagnosis	14 (34)
Attributable mortality rate	8/14 (57)
Median time to death, days (range)	5 (0-70)
Mortality rate according to yeast species	
<i>Rhodotorula</i>	1/21 (5)
<i>Trichosporon</i>	4/8 (50)
<i>S. cerevisiae</i>	6/8 (75)
<i>Geotrichum</i>	2/2 (100)
<i>M. furfur</i>	1/1 (100)
Outcome of breakthrough ROYBSIs	
Dissemination	4/20 (20)
Crude mortality rate at 30 days	8/20 (40)
Attributable mortality rate	4/8 (50)

NOTE. CVC, central venous catheter.^aGranulocyte colony-stimulating factor in 11 (27%), granulocyte-macrophage colony-stimulating factor in 2 (5%).

Table 5

Survival Analysis at 30 days of Patients with ROYBSIs

Variable	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	<i>P</i>	Hazard ratio (95% CI)	<i>P</i>
Admission to ICU at diagnosis	4.9 (1.6-14.6)	.004	--	NS
Presence of CVC	0.3 (0.06-1.1)	.070	--	NS
CRBSI	0.2 (0.05-0.6)	.006	--	NS
CVC removal	0.3 (0.1-0.8)	.020	0.1 (0.03-0.5)	.004
Resolution of neutropenia	0.3 (0.07-1.5)	.140	--	NS
Dissemination	10.6 (3.3-34.2)	<.001	33.4 (6.5-172.2)	<.001
<i>S. cerevisiae</i> infection	5.0 (1.7-14.2)	.003	3.7 (1.2-11.4)	.024
<i>Rhodotorula</i> infection	0.09 (0.02-0.4)	.001	--	NS
<i>Geotrichum</i> infection	5.8 (1.2-28.1)	.030	111.3 (9.9-1255.0)	<.001

NOTE. ICU, intensive care unit; NS, not significant; CVC, central venous catheter.