Candidemia in immunocompromised and immunocompetent critically ill patients: a prospective comparative study

G. Dimopoulos · A. Karabinis · G. Samonis · M. E. Falagas

Abstract The purpose of this study was to compare the risk factors, clinical manifestations, and outcome of candidemia in immunocompromised (IC) and nonimmunocompromised (NIC) critically ill patients. Data were collected prospectively over a 2-year period (02/2000–01/2002) from patients in a 25-bed, medical–surgical intensive care unit (ICU). Eligible for participation in this study were patients who developed candidemia during their ICU stay. Patients under antifungal therapy and with a confirmed systemic fungal infection prior to the diagnosis of candidemia were excluded. Cultures of blood, urine, and stool were performed for all patients in the study, and all patients underwent endoscopy/biopsy of the esophagus for detection of Candida. Smears and/or scrapings of oropharyngeal and esophageal lesions were examined for hyphae and/or pseudohyphae and were also cultured for yeasts. During the study period, 1,627 patients were hospitalized in the ICU, 57% for primary medical reasons and 43% for surgical reasons. After application of the study’s inclusion and exclusion criteria, 24 patients with candidemia (9 IC and 15 NIC) were analyzed. Total parenteral nutrition was more common in IC than in NIC patients (9/9 [100%] vs 8/15 [53%], \( p = 0.02 \)). Oropharyngeal candidiasis was detected in 5 of 9 (55.5%) IC patients and in 1 of 15 (6.5%) NIC patients (\( p = 0.015 \)). Esophageal candidiasis was also more common in IC than in NIC patients (4/9 [44%] vs 0/15 [0%], \( p = 0.012 \)). Among the 9 IC patients, all except 2 died, resulting in a crude mortality of 78%; among the 15 NIC patients, 9 died, resulting in a crude mortality of 60% (\( p > 0.05 \)). Autopsy was performed in two IC and in six NIC patients, with disseminated candidiasis found in one IC patient. Oropharyngeal and esophageal candidiasis are frequent in IC patients with candidemia. In contrast, this coexistence is rare in NIC critically ill patients with Candida bloodstream infections. A high mortality was noted in both IC and NIC critically ill patients with candidemia.

Introduction

Bloodstream infections (BSIs) due to Candida spp. have become common in both adult and pediatric intensive care units (ICUs), accounting for 10–15% of hospital-acquired BSIs [1–3]. This rising incidence has been attributed to several risk factors that are prevalent in critically ill patients, such as debility, underlying malignancy, blood and marrow transplantation, acquired immunodeficiency syndrome (AIDS), prolonged ICU and hospital stay, neutropenia, use of antibiotics and corticosteroids, and administration of parenteral alimentation [4–10]. In most
cases, the yeast’s portal of entry is the gut, yet in other patients, especially those with central venous catheters (CVCs), skin is the most likely culprit [11, 12].

Candidemia may occur in both immunocompromised (IC) and nonimmunocompromised (NIC) patients. The development of candidemia, however, strongly implies immunodeficiency, since it often occurs in IC patients and, more specifically, in 10–20% of those with myeloproliferative disorders or leukemia and in up to 74% of patients with AIDS [13]. In immunocompetent patients, Candida esophagitis is quite rare and is associated with certain predisposing factors, such as use of H2-receptor antagonists, antacids, prior vagotomy producing hypochlorydria, administration of antibiotics and systemic or inhaled corticosteroids, functional or mechanical obstruction of the esophagus, malnutrition, metabolic disorders, and alcoholism [14–16]. However, it is unclear if Candida esophagitis is unusual in the general population because its occurrence in that setting has never been investigated prospectively.

No study to date has been specifically designed to compare risk factors, manifestations, and outcome of candidemia in IC and NIC critically ill patients. Thus, we performed the present study to assess possible clinically significant differences between IC and NIC patients with candidemia receiving care in the ICU setting.

Materials and methods

Study design

This was a prospective study that was conducted over 2 years (February 2000–January 2002) in a 25-bed, medical–surgical ICU in a tertiary hospital in Greece. The “G. Gennimatas” General Hospital in Athens is a 750-bed general hospital that mainly serves the north-northeastern part of Athens. The study protocol was approved by the hospital’s ethics committee. Because of the patients’ inability to give informed consent for participation in the study, consent was obtained from their next of kin. Eligible for participation in the study were patients who had been hospitalized for >48 h and had developed candidemia during their ICU stay. Blood cultures were ordered at the discretion of the attending physicians, when clinically indicated. Patients with severe thrombocytopenia (platelets <60,000/μl) or coagulopathy were excluded because our study included a biopsy procedure. Patients receiving or who had received prior antifungal therapy the last month before the ICU admission and patients with a confirmed systemic fungal infection prior to the diagnosis of candidemia also were excluded because the focus of the study was to be a population with ICU-acquired candidemia.

Data collection

One of the authors (G.D.) collected the data in a standard manner and was responsible for the follow-up of the patients during the study period. Patients were evaluated in terms of age, Acute Physiology and Chronic Health Evaluation-II (APACHE II) and Sequestrial Organ Failure Assessment (SOFA) scores, mean duration of ICU stay, main predisposing factors for fungal infection development, and clinical outcome. For the purposes of the study, patients without underlying malignancy or neutropenia (leukocyte count >4,000/μl and neutrophil count >1,000/μl) and with human immunodeficiency virus (HIV) seronegative status who had not received corticosteroids orally, intravenously, or by nebulization within the last 30 days prior to ICU admission were defined as nonimmunocompromised (NIC). Patients who received systemic corticosteroids for ICU indications, such as sepsis or adult respiratory distress syndrome (ARDS), after their ICU admission were classified in the NIC group. The study population did not include transplant patients, since our center is a trauma-oriented general hospital. Oral thrush was clinically diagnosed by the presence of typical creamy lesions and whitish plaques or pseudomembranes in the oropharyngeal mucosa and on the tongue.

A complete laboratory evaluation, which included a hemogram as well as biochemical and coagulation profiles, urinalysis, serologic testing for HIV, radiological studies, and an electrocardiogram, was performed. Blood, urine, and stool cultures, in addition to cultures of scrapings obtained from the oropharynx, were performed for all study patients. Oropharyngeal scrapings were also immediately examined microscopically for the presence of yeasts and/or hyphae/pseudohyphae, using 10% potassium hydroxide.

The investigational work-up for invasive candidiasis in our patients (other than blood cultures, esophageal endoscopy, and oral scrapings) included (a) identification of predisposing factors, (b) surveillance cultures to detect possible colonization, (c) eye exam, and (d) CT scans of the suspected site of infection.

Pathological examinations

All endoscopies were performed by the same gastroenterologist. Endoscopies were performed during the first 24 h after the diagnosis of candidemia, using a Pentax EG 2901 videoscope. During endoscopy, brushing specimens and tissue biopsies were obtained for microbiological and histological examination. Candida esophagitis was diagnosed by the presence of visible esophageal lesions (white plaques with hyperemia and edema, linear and nodular elevated plaques with ulceration, plaques with increased friability of the mucous membrane) using a modified Kodsi...
method and was verified by biopsy showing hyphae in histological sections and/or *Candida* growth on agar plates [17, 18].

**Microbiological investigations**

Additionally, the brushing specimens were evaluated immediately for yeasts and hyphae/pseudohyphae after the addition of 10% potassium hydroxide and were cultured on Sabouraud dextrose agar plates for *Candida* growth. Biopsy samples were fixed with 10% formalin and paraffin followed by acid-Schiff staining to detect mucosal invasion by the fungus.

Cultures were considered positive if there was growth of *Candida* on Sabouraud dextrose agar plates. Yeasts were identified using the API 20C AUX system (bioMérieux, Marcy l’Etoile, France). Candidemia was defined by at least one positive blood culture for *Candida* spp., and candiduria by a urine culture with *Candida* spp. growth of ≥10⁵ cfu/ml. Candidemia was identified using BacTalert (bioMérieux, USA).

**Statistical analysis**

IC and NIC patients were compared for certain variables of interest by Mann–Whitney *U* test, chi-squared test, and Fisher exact test. The level of significance was set at *p*<0.05.

**Results**

During the study period, 1,627 patients were hospitalized in the ICU, 57% for primary medical reasons and 43% for primary surgical reasons. Twenty-four patients (9 IC and 15 NIC) met the eligibility criteria. Of these, 18 (75%) were

| Patient no. | Blood | Esophagus | Urine | Oropharynx | Stools | No. of sites (except blood) colonized |
|-------------|-------|-----------|-------|------------|--------|-------------------------------------|
| Immunocompromised |       |           |       |            |        |                                     |
| 01          | *C. albicans* | *C. albicans* | *C. albicans* | *C. albicans* | *C. albicans* | 4                                     |
| 02          | *C. albicans* | NG        | NG    | *C. albicans* | *C. albicans* | 2                                     |
| 03          | *C. albicans* | NG        | NG    | NG          | *C. albicans* | 1                                     |
| 04          | *C. krusei*  | *C. albicans* | *C. albicans* | *C. albicans* | NG    | 3                                     |
| 05          | *C. albicans* | NG        | NG    | *C. albicans* | NG    | 2                                     |
| 06          | *C. albicans* | NG        | NG    | NG          | NG    | 0                                     |
| 07          | *C. parapsilosis* | *C. albicans* | *C. parapsilosis* | *C. albicans* | *C. albicans* | 4                                     |
| 08          | *C. dubliniensis* | NG        | NG    | NG          | NG    | 0                                     |
| 09          | *C. lusitaniae* | NG        | NG    | NG          | *C. albicans* | 1                                     |
| Nonimmunocompromised |       |           |       |            |        |                                     |
| 10          | *C. albicans* | NG        | *C. albicans* | NG          | *C. albicans* | 2                                     |
| 11          | *C. albicans* | NG        | *C. albicans* | NG          | *C. albicans* | 3                                     |
| 12          | *C. albicans* | NG        | NG    | NG          | *C. albicans* | 1                                     |
| 13          | *C. albicans* | NG        | *C. albicans* | NG          | NG    | 1                                     |
| 14          | *C. albicans* | NG        | NG    | NG          | NG    | 0                                     |
| 15          | *C. albicans* | NG        | NG    | NG          | *C. albicans* | 1                                     |
| 16          | *C. albicans* | NG        | *C. albicans* | NG          | *C. albicans* | 2                                     |
| 17          | *C. albicans* | NG        | *C. albicans* | NG          | NG    | 1                                     |
| 18          | *C. albicans* | NG        | NG    | NG          | *C. albicans* | 1                                     |
| 19          | *C. albicans* | NG        | NG    | NG          | NG    | 0                                     |
| 20          | *C. tropicalis* | NG        | NG    | NG          | NG    | 0                                     |
| 21          | *C. tropicalis* | NG        | NG    | NG          | *C. albicans* | 1                                     |
| 22          | *C. tropicalis* | NG        | *C. albicans* | NG          | NG    | 0                                     |
| 23          | *C. parapsilosis* | NG        | *C. albicans* | NG          | NG    | 1                                     |
| 24          | *C. krusei*  | NG        | NG    | NG          | NG    | 0                                     |

*NG* Cultures with no growth
medical patients and 6 (25%) surgical patients. Their demographic and clinical characteristics are shown in Table 2. Among the IC and NIC patients, 6 (40%) and 4 (44%) were females, respectively ($p>0.05$). The median age of the IC and NIC patients was 50 years (range 34–55) and 52 years (range 34–68), respectively ($p>0.05$). The median duration of ICU stay for IC and NIC patients was 17.8 and 16.7 days, respectively ($p>0.05$).

Among the nine IC patients, all had underlying primary medical pathology, since three had leukaemia/lymphoma, three AIDS, and one each had liver cirrhosis complicated by septic shock, pneumonia following chemotherapy for lung cancer, and rheumatoid arthritis complicated by pneumonia. None of the patients in the study with leukemia/lymphoma received chemotherapy during the study or for 2 weeks prior to the diagnosis of candidemia. The patients with lung cancer and rheumatoid arthritis (patient nos. 2 and 3 in IC group, Table 1) received treatment with glucocorticosteroids. Among the 15 NIC patients, the underlying diagnosis was pneumonia/ARDS in 6, trauma/head injury in 3, peritonitis in 3, pancreatitis in 2, and pulmonary embolism in 1. Six of the 15 NIC patients had surgical pathology: three with trauma/head injury and three with peritonitis. Most patients with pneumonia had community-acquired infection but needed ICU admission due to respiratory failure. Patient numbers 19 and 23 in the NIC group (Table 1) developed ventilator-associated pneumonia.

The mean time from ICU admission to the isolation of Candida from blood specimens was 9 days (range 5–11 days). The mean time between drawing blood specimens for culture and isolation of Candida was 3 days. The presence of known predisposing factors for development of candidiasis in these patients is shown in Table 3. The 9 IC patients with candidemia had higher mean APACHE II (24±3 vs 20±3) and SOFA (8±1 vs 6±2) scores during ICU admission compared to the 15 NIC patients ($p=0.04$ for both scores). In addition, the administration of total parenteral nutrition was more common in IC patients ($p=0.02$).

Oropharyngeal candidiasis was detected in 5 of 9 (55.5%) IC patients and in 1 of 15 (6.5%) NIC patients ($p=0.015$). In the IC patients, the diagnosis of oral thrush was confirmed prior to the ICU admission, while in the single NIC patient with oral thrush, the diagnosis was established on the eighth ICU day. Four of the nine (44%) IC patients and none of the NIC patients presented with esophageal candidiasis ($p=0.012$). All patients with esophageal candidiasis manifested symptoms (mainly odynophagia; dysphagia in one patient) before ICU admission, but the diagnosis

| Patient no. | Sex | Age (years) | Comorbid factors                  |
|------------|-----|-------------|-----------------------------------|
| Immuno compromised                      |     |             |                                   |
| 01         | M   | 34          | AIDS, PCP                         |
| 02         | F   | 48          | Rheumatoid arthritis, pneumonia   |
| 03         | M   | 55          | Lung cancer, pneumonia            |
| 04         | F   | 53          | Leukemia, protein C deficiency    |
| 05         | M   | 38          | AIDS, MRSA bacteremia             |
| 06         | F   | 52          | Leukemia, pneumonia               |
| 07         | M   | 54          | AIDS, pneumonia                   |
| 08         | F   | 50          | Lymphoma, pneumonia               |
| 09         | M   | 50          | Alcoholic cirrhosis, sepsis       |
| Nonimmuno compromised                      |     |             |                                   |
| 10         | M   | 52          | Pneumonia/ARDS                    |
| 11         | F   | 62          | Pancreatitis                      |
| 12         | M   | 48          | Pneumonia/ARDS                    |
| 13         | M   | 53          | Trauma                            |
| 14         | M   | 34          | Peritonitis                        |
| 15         | M   | 34          | Cocaine overdose, ARDS            |
| 16         | M   | 54          | Trauma, splenectomy               |
| 17         | F   | 45          | Peritonitis                        |
| 18         | F   | 56          | Pneumonia                          |
| 19         | M   | 68          | Head injury, pneumonia             |
| 20         | F   | 54          | Pancreatitis, ARDS                |
| 21         | M   | 65          | Pulmonary embolism, PCD           |
| 22         | F   | 43          | Peritonitis                        |
| 23         | F   | 45          | Charcot disease, pneumonia         |
| 24         | M   | 34          | Heroin overdose, ARDS             |

ARDS Adult respiratory distress syndrome, MRSA methicillin-resistant Staphylococcus aureus, PCP Pneumocystis carinii pneumonia
of esophageal candidiasis was not confirmed until after their ICU admission.

Table 1 shows the results of the fungal cultures in IC and NIC patients. *C. albicans* was isolated from the blood in 5 of 9 (55.5%) IC patients and in 10 of 15 (66.5%) NIC patients, while non-*albicans* Candida spp. were isolated in the remaining 9 patients of the two study groups (*p* > 0.05). Among NIC patients, *C. tropicalis* was isolated from the blood of three patients and *Candida krusei* and *Candida parapsilosis* from one patient each. Among IC patients, *C. krusei*, *C. parapsilosis*, *Candida dubliniensis*, and *Candida lusitaniae* were isolated from the blood of one patient each. The same *Candida* spp. were isolated in at least two different body sites in eight of ten NIC patients and in four of five IC patients with candidemia due to *C. albicans*. There was one patient (Table 1) who had concomitant and persistent methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia during the ICU hospitalization.

Patients with *C. albicans* candidemia received fluconazole 400 mg every 12 h intravenously and patients with non-*albicans* candidemia liposomal amphotericin B intravenously (mean duration of therapy, 16.5 days; range 14–24 days).

No statistically significant difference in clinical outcome was detected between NIC and IC patients with candidemia. Among the nine IC patients, all except two (patient nos. 2 and 8; Table 1) died, resulting in a crude mortality of 78%. Among the 15 NIC patients, 9 (patient nos. 10, 11, 13, 14, 16, 17, 18, 20, and 24; Table 1) died, resulting in a crude mortality of 60% (*p* > 0.05). When IC and NIC patients were combined, the mortality among patients with primary medical pathology and patients with surgical pathology was identical, at 67%. More specifically, of the 18 patients with medical pathology (9 IC and 9 NIC), 12 (7 IC and 5 NIC) died, while 4 of the 6 patients with surgical pathology (all NIC) died. Autopsy after consent was performed in eight patients (two IC and six NIC) and showed disseminated candidiasis in one IC patient (oropharyngeal, esophageal, and gastric candidiasis).

### Discussion

The main findings of our study of critically ill patients with candidemia are that IC patients had higher APACHE II and SOFA scores and were more likely to receive total parenteral nutrition than NIC patients. In addition, oropharyngeal and esophageal candidiasis was considerably more common in IC than in NIC ICU patients with candidemia. Of importance, a high mortality was noted in both IC and NIC critically ill patients with candidemia.

The recent advances in intensive care have improved the survival of critically ill patients at the cost of the emergence of nosocomial infections of the bloodstream and other sites. Candidemia is the most common hematogenous fungal infection and the fourth most common BSI overall in the USA, accounting for 8% of all nosocomial BSIs [19]. In Greece, there are no relevant data from large multicenter studies regarding candidal BSI, although there are data from a single-center study reporting that 3.3–4.9% of BSIs during a 5-year period (2000–2005) were due to *Candida* spp. [20]. Risk factors for invasive candidiasis in the ICU have been defined by several studies and include a prolonged hospital stay; the use of broad-spectrum antibiotics, corticosteroids or other immunosuppressants; the administration of total parenteral nutrition, hemodialysis or multiple blood transfusions; prolonged mechanical ventilation; diabetes mellitus; gastrointestinal perforation or surgery; and pancreatitis [5, 7–10, 21].

*Candida* spp. colonize the gastrointestinal tract of healthy individuals and, although they are most frequently recovered from the oropharynx, they have also been isolated from the stool of 10–30% of healthy adults [22]. Colonization of the gastrointestinal tract or the oropharynx with *Candida* spp. has been shown to invariably precede hematogenous or systemic disease, although in recent years the improved survival of burn victims and the widespread use of CVCs has allowed direct invasion of the bloodstream by *Candida* spp. that colonize the skin [11, 12]. *Candida* colonization as a risk factor is still controversial. It has been

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**Table 3** Presence of factors predisposing to the development of candidemia in the study population

| Factor                                      | Immunocompromised patients (n=9) | Nonimmunocompromised patients (n=15) | *p* value |
|---------------------------------------------|----------------------------------|--------------------------------------|-----------|
| Age in years, mean±SD                       | 50±5.9                           | 58±9.6                               | >0.05     |
| Apache II score, mean±SD                    | 24±3                             | 20±3                                 | 0.04      |
| SOFA score, mean±SD                         | 8±1                              | 6±2                                  | 0.04      |
| Broad-spectrum antibiotics, no. (%)         | 9 (100)                          | 15 (100)                             | >0.05     |
| Central venous catheter, no. (%)            | 9 (100)                          | 15 (100)                             | >0.05     |
| Total parenteral nutrition, no. (%)         | 9 (100)                          | 8 (53)                               | 0.02      |
| CVVH, no. (%)                               | 4 (44)                           | 5 (33)                               | >0.05     |
| Diabetes mellitus, no. (%)                  | 1 (11)                           | 4 (27)                               | >0.05     |
| Systemic corticosteroids, no. (%)           | 7 (47)                           | 6 (40)                               | >0.05     |

SOFA Sequestrial Organ Failure Assessment score, CVVH continuous venovenous hemofiltration.
The development of sensitive marker for the presence of esophageal candidiasis. Candida concomitantly with bacteremia [33]. In our patients, fungemia due to C. tropicalis was not preceded by colonization with the same species. It is well known that C. tropicalis, part of the normal human mucocutaneous flora, is a major cause of septicemia/disseminated candidiasis, mainly in patients with lymphoma, leukemia, and diabetes [34]. Accordingly, a possible explanation for the development of C. tropicalis candidemia in our patients could be the uncontrolled diabetes combined with the severe septic syndrome.
We did not have any cases of candidemia due to Candida glabrata, a common pathogen in the USA and Israel [35, 36]. This finding is in accordance with the data of the Sentry Antimicrobial Surveillance Program, which surveyed episodes of BSI due to Candida spp. in patients hospitalized in European ICUs. Overall, 53% of the BSIs due to Candida spp. were attributable to C. albicans, followed by C. parapsilosis (21%), C. glabrata (12%), C. tropicalis (6%), C. famata (2%), C. krusei (1%), and Candida inconspicua (1%) [37].

With regards to C. albicans, our figures are very close to both European [37] and American studies. For example, Trick et al. [35], who described the secular trend of hospital-acquired candidemia among ICU patients in the USA during 1989–1999, found that among cases of monomicrobial and polymicrobial candidemia, C. albicans was isolated in 59 and 57%, respectively. The high crude mortality among our patients (60% for NIC and 78% for IC) was not unexpected, given the severity of their underlying diseases, and is comparable to the mortality rate for adults with candidemia reported by Lark et al. [38] (67%), Gudlaugsson et al. [39] (61%), Karlowsky et al. [40] (52%), Colombo et al. [41] (50%), and Pappas et al. [42] (47%). Although we saw no difference in outcome between medical and surgical patients, others have described a poorer outcome for medical patients with candidemia [43].

In our study population, patients with ARDS and sepsis were classified in the NIC group because we believe that these patients have a temporary immunosuppression (if they survive), while the patients classified in the IC group had a certain degree of chronic immunosuppression, despite the differences in the underlying disease. The patient with alcoholic cirrhosis and sepsis (Table 1) was classified in the IC group because he had received glucocorticosteroids due to exacerbations of chronic obstructive pulmonary disease for 2 months before admission to the ICU.

The design of the study did not allow for all patients admitted to the ICU to be evaluated for the presence of oropharyngeal and esophageal candidiasis. Additionally, we focused on a subset of patients with ICU-acquired candidemia without prior systemic fungal infection who had not been exposed to prophylactic antifungal drugs. Since, by definition, the term “ICU-acquired candidemia” means that the fungal infection is acquired in the ICU, we excluded from our study those patients with previous invasive fungal infection.

We should acknowledge that our study has several limitations. First, we were unable to pinpoint the exact time of onset of the esophageal candidiasis, especially since oral thrush was already present before admission to the ICU. Due to obvious ethical reasons, we evaluated our patients for esophageal candidiasis with endoscopy only once. Thus, we do not know if the esophagus was involved before or after the ICU admission. Second, it is unclear if the esophageal candidiasis resulted from hematogenous spread of the fungi in the esophagus, or if the bloodstream involvement was directly related to the oral thrush or the esophageal candidiasis. Third, we did not focus on the treatment administered to patients with candidemia, although we did report that patients with C. albicans and non-albicans candidemia received fluconazole and liposomal amphotericin B intravenously, respectively. Fourth, we do not have readily available data on the length of stay of all patients who received care in the ICU or the total number of cases of candidemia in the ICU, including those excluded, to know how common candidemia is among ICU patients. Fifth, there are no readily available data regarding the type of therapy and the removal of CVCs and the influence of either factor on outcome in the two patient groups studied. Sixth, the sample of our study population is relatively small (study population from a single center) and thus does not permit a powerful statistical analysis; unfortunately, various practical reasons prevented us from incorporating data from other large ICUs into our study. Finally, we do not have readily available data on MICs because the laboratory usually reported the results for an isolate as either “susceptible” or “not susceptible” to fluconazole.

In conclusion, we compared various characteristics, including risk factors, manifestations, and outcome of IC and NIC ICU patients with candidemia. We found that oropharyngeal and esophageal candidiasis frequently coexisted with candidemia in IC patients. Prospective, clinical studies are needed to better define the value of avoiding colonization and/or of treating oropharyngeal and esophageal candidiasis for the prevention of systemic disease in selected critically ill patients.

References

1. Edmond MB, Wallace SE, McClish DK, Pfaffer MA, Jones RN, Wenzel RP (1999) Nosocomial bloodstream infections in United States hospitals: a three-year analysis. Clin Infect Dis 29:239–244
2. National Nosocomial Infections Surveillance (1999) System report, data summary from January 1990–May 1999, issued June 1999. Am J Infect Control 27:520–532
3. Jarvis WR, Martone WJ (1992) Predominant pathogens in hospital infections. J Antimicrob Chemother 29(Suppl A):19–24
4. Ostrosky-Zeichner L (2003) New approaches to the risk of Candida in the intensive care unit. Curr Opin Infect Dis 16:533–537
5. Blumberg HM, Jarvis WR, Soucie JM, Edwards JE, Patterson JE, Pfaffer MA et al, for the National Epidemiology of Mycoses Survey (NEMIS) Study Group (2001) Risk factors for candidal bloodstream infections in surgical intensive care unit patients: the NEMIS prospective multicenter study. The National Epidemiology of Mycosis Survey. Clin Infect Dis 33:177–186
6. Verduyn Lunel FM, Meis JF, Voss A (1999) Nosocomial fungal infections: candidemia. Diagn Microbiol Infect Dis 34:213–220
7. Marr KA, Seidel K, White TC, Bowden RA (2000) Candidemia in allogeneic blood and marrow transplant recipients: evolution of risk factors after the adoption of prophylactic fluconazole. J Infect Dis 181:309–316
8. Fridkin SK, Jarvis WR (1996) Epidemiology of nosocomial fungal infections. Clin Microbiol Rev 9:499–511
9. Karabinis A, Hill C, Leclercq B, Tancrede C, Baume D, Andremont A (1988) Risk factors for candidemia in cancer patients: a case-control study. J Clin Microbiol 26:429–432
10. Viscoli C, Girmenia C, Marinus A, Collette L, Martino P, Vandercam B et al (1999) Candidemia in cancer patients: a prospective, multicenter surveillance study by the Invasive Fungal Infection Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC). Clin Infect Dis 28:1071–1079
11. Cole GT, Halawa AA, Anaissie EJ (1996) The role of the gastrointestinal tract in hematogenous candidiasis: from the laboratory to the bedside. Clin Infect Dis 22(Suppl 2):S73–S88
12. Nucci M, Anaissie E (2001) Revisiting the source of candidemia: skin or gut? Clin Infect Dis 33:1959–1967
13. Wilcox CM, Karowe MW (1994) Esophageal infections: etiology, diagnosis, and management. Gastroenterologist 2:188–206
14. Kochhar R, Talwar P, Singh S, Mehta SK (1988) Invasive candidiasis following cimetidine therapy. Am J Gastroenterol 83:102–103
15. Boero M, Pera A, Andriulli A, Ponti V, Canepa G, Palmas F et al (1983) Candida overgrowth in gastric juice of peptic ulcer subjects on short- and long-term treatment with H2-receptor antagonists. Digestion 28:158–163
16. Simon MR, Houser WL, Smith KA, Long PM (1997) Esophageal candidiasis as a complication of inhaled corticosteroids. Ann Allergy Asthma Immunol 79:333–338
17. Kodsi BE, Wickremesinghe C, Kozinn PJ, Iswara K, Goldberg PK (1976) Candida esophagitis: a prospective study of 27 cases. Gastroenterology 71:715–719
18. Wheeler RR, Peacock JE Jr, Cruz JM, Richter JE (1987) Esophagitis in the immunocompromised host: role of esophagoscopy in diagnosis. Rev Infect Dis 9:88–96
19. Pfaffer MA, Jones RN, Messer SA, Edmond MB, Wenzel RP (1998) National surveillance of nosocomial blood stream infection due to Candida albicans: frequency of occurrence and antifungal susceptibility in the SCOPE Program. Diagn Microbiol Infect Dis 31:327–332
20. Falagas ME, Kasiakou SK, Nikita D, Morfou P, Georgoulias G, Ralafidis P (2006) Secular trend of antimicrobial resistance of blood isolates in a newly founded Greek hospital. BMC Infect Dis 6:69
21. Roseff SA, Sugar AM (1993) Oral and esophageal candidiasis. In: Bodey GP (ed) Candidiasis: pathogenesis, diagnosis and treatment. Raven, New York, pp 185–203
22. Smits BJ, Prior AP, Arbakter PG (1966) Incidence of candida in hospital inpatients and the effects of antibiotic therapy. Br Med J 5481:208–210
23. Pittet D, Monod M, Suter PM, Frenk E, Auckenthaler R (1994) Candida colonization and subsequent infections in critically ill surgical patients. Ann Surg 220:751–758
24. Paphitiou NF, Ostrosky-Zeichner L, Rex JH (2005) Rules for identifying patients at increased risk for candidal infections in the surgical intensive care unit: approach to developing practical criteria for systematic use in antifungal prophylaxis trials. Med Mycol 43:235–243
25. Krause W, Matheis H, Wulf K (1969) Fungaemia and funguria after oral administration of Candida albicans. Lancet 1:598–599
26. Samonis G, Skordilis P, Maraki S et al (1998) Oropharyngeal candidiasis as a marker for esophageal candidiasis in patients with cancer. Clin Infect Dis 27:283–286
27. Wilcox CM, Straub RF, Clark WS (1995) Prospective evaluation of oropharyngeal findings in human immunodeficiency virus-infected patients with esophageal ulceration. Am J Gastroenterol 90:1938–1941
28. Antinori A, Antinori A, Ammassari A et al (1995) Presumptive clinical criteria versus endoscopy in the diagnosis of Candida esophagitis at various HIV-1 disease stages. Endoscopy 27:371–376
29. Sáfár A, Perin DS, Armstrong D (2002) Hematogenous infections due to Candida parapsilosis: changing trends in fungemic patients at a comprehensive cancer center during the last four decades. Diagn Microbiol Infect Dis 44:11–16
30. Levy I, Rubin LG, Vasishtha S, Tucci V, Sood SK (1998) Emergence of Candida parapsilosis as the predominant species causing candidemia in children. Clin Infect Dis 26:1086–1088
31. Nolla-Salas J, Sitges-Serra A, Martinez-Gonzalez J, Leon-Regidor MA, Ibanez-Lucia P, Torres-Rodrigue JM, for the Study Group of Fungal Infection in the ICU (1997) Candidemia in non-neutropenic critically ill patients: analysis of prognostic factors and assessment of systemic antifungal therapy. Intensive Care Med 23:23–30
32. Uzun O, Acioglu S, Anaissie EJ, Rex JH (2001) Risk factors and predictors of outcome in patients with cancer and breakthrough candidemia. Clin Infect Dis 32:1713–1717
33. Peres-Bota D, Rodrigues-Villalbos H, Dimopoulos G, Melot C, Vincent JL (2004) Infections with Candida spp. in critically ill patients are primarily related to the length of stay in the intensive care unit. Clin Microb Infect 10:550–555
34. Bodey GP (1993) Candidiasis: pathogenesis, diagnosis and treatment. Raven, New York, p 93
35. Trick WE, Fridkin SK, Edwards JR, Hajjeh RA, Gaynes RP, and the National Nosocomial Infections Surveillance System Hospitals (2002) Secular trend of hospital-acquired candidemia among intensive care unit patients in the United States during 1989–1999. Clin Infect Dis 35:627–630
36. Rennert G, Rennert HS, Pitlik S, Finkelson R, Kitzes-Cohen R (2000) Epidemiology of candidemia—a nationwide survey in Israel. Infection 28:26–29
37. Pfaffer MA, Jones RN, Doern GV et al (1999) International surveillance of blood stream infections due to Candida species in the European SENTRY Program: species distribution and antifungal susceptibility, including the investigational triazole and echinocandin agents. SENTRY Participant Group (Europe). Diagn Microbiol Infect Dis 35:19–25
38. Lark RL, Chenoweth C, Saint S, Finkelstein R, Kitzes-Cohen R (2000) Epidemiology of candidemia—a nationwide survey in Israel. Infection 28:26–29
39. Gudlaugsson O, Gillespie S, Lee K et al (2003) Attributable mortality of nosocomial candidemia, revisited. Clin Infect Dis 37:1172–1177
40. Karlosky JA, Zhanel GG, Klym KA, Hoban DJ, Kabani AM (1997) Candidemia in a Canadian tertiary care hospital from 1976 to 1996. Diagn Microbiol Infect Dis 29:5–9
41. Colombo AL, Nucci M, Salomao R et al (1999) High rate of non-albicans candidemia in Brazilian tertiary care hospitals. Diagn Microbiol Infect Dis 34:281–286
42. Pappas PG, Rex JH, Lee J et al, for the NIAID Mycoses Study Group (2003) A prospective observational study of candidemia: epidemiology, therapy, and influences on mortality in hospitalized adult and pediatric patients. Clin Infect Dis 37:634–643
43. Charles PE, Doise JM, Quenot JP et al (2003) Candidemia in critically ill patients: difference of outcome between medical and surgical patients. Intensive Care Med 29:2162–2169