*Infectious Disorders*

## Candidemia in patients with hematologic malignancies: analysis of 7 years' experience in a single center

**We report 45 incidents of candidemia in 45 patients diagnosed with hematologic malignancies between 1997 and 2004. A large majority of species isolated were non-*albicans* and there was an unexpectedly high incidence of *Candida tropicalis*. The attributable mortality (15%) was interestingly low in this population of severely immunocompromised patients.**

**Haematologica 2006;** 91:717-718
(*http://www.haematologica.org/journal/2006/05/717.html*)

Candidemia is a frequent infection in patients with hematologic malignancies. However, attributable mortality and appropriate management of central venous catheters (CVC) in such patients remain controversial. Using a database in the Department of Microbiology of Nantes hospital, we reviewed 45 incidents of candidemia involving 45 patients in our department of hematology between 1997 and 2004. Candidemia was defined as positivity of at least one blood culture associated with clinical symptoms of bloodstream infection such as fever or hypotension. Mortality attributable to candidemia was defined as death within 30 days after the first positive blood culture in a context of stable hematologic disease and no other possible cause of death. Heart and abdominal ultrasounds were always performed at diagnosis and repeated after neutrophil recovery if symptoms appeared.

The median age of the population was 57 years (range: 5 to 80 years). Forty-one patients were adults. As shown in Table 1, acute leukemia was the predominant underlying malignancy. Candidemia occurred during the first line treatment in 64% of leukemia patients, in 90% of myeloma patients while 78% of lymphoma patients became infected after a relapse. Nine patients developed candidemia after allogeneic stem cell transplantation. *Candida* species isolated were *C. albicans* (n=13), *C. tropicalis* (n=12), *C. krusei* (n=6), *C. parapsilosis* (n=5), *C. kefyr* (n=5), *C. glabrata* (n=3) and *C. pelliculosa* (n=1). We did not observe any significant association between age and species. Antifungal treatments were amphotericin B (n=11), amphotericin B+flucytosine (n=19), fluconazole (n=8), fluconazole+flucytosine (n=3), and caspofungin (n=3). One patient was untreated because he died the day of the first positive blood culture. Cutaneous candidiasis was microbiologically proven in nine patients (20%). Neither endocarditis nor hepatosplenic candidiasis was observed.

Several previously identified risk factors for candidemia[1] were present in our patients. They are listed in Table 2. All central venous catheters (CVC) were removed at a median time of 2 days (range: 1 to 7 days) after the first positive blood culture. Results of CVC culture were available in 34 patients and showed that nine had an infected CVC (26%). By day 30, 11 patients (24%) had died. The causes of death were candidemia (n=7, attributable mortality=15%), proven aspergillosis (n=1), lymphoma progression (n=2), and hyperkalemia (n=1). The seven patients who died of candidemia did so at a median of 7 days (range: 1 to 18 days) after the first positive blood culture. No significant predictors of death were identified when considering age, *Candida* species, allogeneic stem cell transplantation, time of CVC removal, neutropenia, or antifungal treatment. However, a distinct trend emerged when considering the stage of hematologic disease. Indeed, death occurred in six of the 19 patients whose infection was diagnosed during relapse but in only one of the 26 patients who developed candidemia during first-line treatment ($p$=0.01).

A striking result of this study was the emergence of a large proportion of species other than *C. albicans* (71%), particularly the high incidence of *C. tropicalis* (27%). This peculiar epidemiology might be explained by the predominance of leukemias, the majority of neutropenic patients, and the large number of patients treated with cytotoxic agents known to alter the gastrointestinal tract (GIT). The increased invasiveness of *C. tropicalis* in the GIT of neutropenic patients with mucositis was demonstrated by Walsh *et al.*[2] Moreover, Kontoyiannis *et al.*[3] have shown that predominant risk factors for *C. tropicalis* fungemia are leukemia and prolonged neutropenia.

Our study, focusing on an homogeneous population treated for hematologic malignancies, displayed a low

**Table 1.** The number of patients at different stages of treatment of their hematologic malignancy (first line, first relapse, second or subsequent relapse) in whom candidemia occurred.

| | *Treatment* | | | |
|---|---|---|---|---|
| | *First line* | *1st relapse* | *≥2 relapse* | *Total* |
| Acute leukemia | 14 | 5 | 3 | 22 |
| Myeloma | 9 | 1 | 0 | 10 |
| Lymphoma | 2 | 4 | 3 | 9 |
| Chronic myeloid leukemia | 1 | 2 | 1 | 4 |
| **Total** | **26** | **12** | **7** | **45** |

**Table 2.** The frequencies of several potential risk factors for candidemia in the population studied (n=45).

| | *n (%)* |
|---|---|
| Digestive tract colonization (mouth or stools) | 26 (58%) |
| Broad spectrum antibiotics | 39 (87%) |
| Median duration of treatment before first PBC | 13 days (range, 1 to 90 d.) |
| Neutropenia (<500/mm$^3$) | 37 (82%) |
| Median duration before first PBC | 11 days (range, 2 to 100 d.) |
| Median duration after first PBC | 9 days (range, 1 to 37 d.) |
| Chemotherapy in the month prior to candidemia | 39 (87%) |
| Total parenteral nutrition | 33 (73%) |
| Central venous catheter | 41 (90%) |
| Steroids | 9 (20%) |
| Cyclosporine | 4 (9%) |
| Graft-versus-host disease | 2 (4%) |
| Human immunodeficiency virus | 0 |

*PBC: positive blood culture.*

percentage of *Candida*-attributable mortality (15%). This interesting result could be explained by the relative young age of the population (median age: 57 years) and the good performans status of the majority of patients who were suitable for chemotherapy. Mortality among immunocompromised patients is difficult to assess from the existing literature because most of the recent studies included patients with heterogeneous underlying diseases.[4,5,6]

The management of CVC has been discussed by several experts in the field.[7,8] Removal remains controversial in neutropenic patients[7] because several studies have identified the gut as the major source of infection.[8,9] Some investigators consider that removing a CVC in this setting might be pointless and hazardous because of the potential complications associated with catheter replacement. In our study, 26% of cultured CVC were infected, indicating that even if candidemia originates from the gut, the catheter can be a secondary source of infection for as many as one in four patients. It is also noteworthy that *Candida* biofilms on CVC are resistant to amphotericin B and fluconazole.[10] Consequently, it is our opinion that immediate removal of CVC is advisable for *Candida*-positive neutropenic patients regardless of whether chemotherapy has altered the digestive tract.

*Stéphane Vigouroux,* Odile Morin,° Philippe Moreau,* Jean-Luc Harousseau,* Noël Milpied**

**Service d'Hématologie Clinique and °Laboratoire de Parasitologie-Mycologie, CHU Hôtel Dieu, Nantes, France*

*Key words: hematologic malignancies, candidemia.*

*Correspondence: Stéphane Vigouroux, MD, Service d'Hématologie Clinique, CHU Hôtel Dieu, 1 Place Alexis Ricordeau, 44000 Nantes. Phone: international +33.2.40083271. Fax: international +33.2.40083250.E-mail: vigouroux.st@wanadoo.fr*

## References

1. Fraser VJ, Jones M, Dunkel J, Storfer S, Medoff G, Dunagan WC. Candidemia in a tertiary care hospital: epidemiology, risk factors, and predictors of mortality. Clin Infect Dis 1992; 15: 414-21.
2. Walsh TJ, Merz WG. Pathologic features in the human alimentary tract associated with invasiveness of Candida tropicalis. Am J Clin Pathol 1986;85:498-502.
3. Kontoyiannis DP, Vaziri I, Hanna HA, Boktour M, Thornby J, Hachem R, et al. Risk factors for Candida tropicalis fungemia in patients with cancer. Clin Infect Dis 2001;33:1676-81.
4. Gudlaugsson O, Gillespie S, Lee K, Vande Berg J, Hu J, Messer S, et al. Attributable mortality of nosocomial candidemia, revisited. Clin Infect Dis 2003;37:1172-7.
5. Mora-Duarte J, Betts R, Rotstein C, Colombo AL, Thompson-Moya L, Smietana J, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. The Caspofungin Invasive Candidiasis Study Group. N Engl J Med 2002; 347: 2020-9.
6. Pappas PG, Rex JH, Lee J, Hamill RJ, Larsen RA, Powderly W, et al. A prospective observational study of candidemia: epidemiology, therapy, and influences on mortality in hospitalized adult and pediatric patients. The NIAID Mycoses Study Group. Clin Infect Dis 2003;37:634-43.
7. Pappas PG, Rex JH, Sobel JD, Filler SG, Dismukes WE, Walsh TJ, et al. Guidelines for treatment of candidiasis. The Infectious Diseases Society of America. Clin Infect Dis 2004; 38:161-89.
8. Walsh TJ, Rex JH. All catheter-related candidemia is not the same: assessment of the balance between the risks and benefits of removal of vascular catheters. Clin Infect Dis 2002; 34:600-2.
9. Blijlevens NM, Donnelly JP, de Pauw BE. Impaired gut function as risk factor for invasive candidiasis in neutropenic patients. Br J Haematol 2002;117:259-64.
10. Douglas LJ. Candida biofilms and their role in infection. Trends Microbiol 2003;11:30-6.