Jesús Fortún
Francesca Gioia

Invasive candidiasis in the neutropenic patient

Infectious Diseases Service, Hospital Ramón y Cajal, Madrid

ABSTRACT

There are major differences in the epidemiology and prognosis of invasive candidiasis and candidemia in the neutropenic patient; however, a recent study performed in Spanish hospitals (Candipop) confirmed that mortality at 1 month is 30%, which is similar to that observed in the general population. Although *Candida albicans* is the most frequently isolated species, *C. tropicalis*, *C. glabrata*, and *C. krusei* are more prevalent than in non-neutropenic patients. The benefit of neutrophil transfusion is unclear, and catheter withdrawal must be tailored and based on confirmation of the diagnosis. Echinocandins are the first-line option for therapy and have a better safety profile than other agents.

Candidasis invasiva en el paciente neutropénico

RESUMEN

Existen diferencias significativas en la epidemiología y pronóstico de la candidemia y candidiasis invasiva en el paciente neutropénico, aunque una similar mortalidad a la observada en la población general (30% al mes) ha sido notificada en un reciente estudio nacional (Candipop). *Candida albicans* es la especie más frecuente pero *C. tropicalis*, *C. glabrata* y *C. krusei* tienen una mayor prevalencia que en los pacientes no neutropénicos. No está claro el beneficio de la transfusión de neutrófilos y la retirada de catéter debe ser individualizada. Las equinocandinas suponen el tratamiento de elección dada su eficacia y perfil de toxicidad en relación a otros antifúngicos.

Correspondence:
Jesús Fortún
Infectious Diseases Service, Hospital Ramón y Cajal, Madrid
E-mail: fortunabete@gmail.com

EPIDEMIOLOGY

The Candipop study, which recently analysed 752 episodes of candidemia in 29 Spanish hospitals between April 2010 and March 2011, confirmed that mortality was 30% during the first 30 days and 13% during the first week after diagnosis. The independent factors associated with mortality during the first 7 days were age, primary origin of candidemia, presence of septic shock, and administration of the appropriate antifungal drug. Withdrawal of the catheter did not reduce mortality overall, although early withdrawal did (first 48 hours)[1].

In patients with oncologic-hematologic conditions, the factors associated with mortality were similar to those of the general population. However, compared with patients with solid tumours, patients with hematologic neoplasms had a significantly higher incidence of neutropenia and mucositis and a lower frequency of catheter-associated candidemia and required the catheter to be withdrawn less often[2]. This less relevant role of the catheter as the origin of candidemia in patients with haematological disease has also been confirmed elsewhere[3].

The species causing candidemia also differs in patient with hematologic conditions. As in the general population, *Candida albicans* and *C. parapsilosis* are the most common species, although endogenous species (*C. tropicalis*, *C. glabrata*, and *C. krusei*) are much more prevalent than in the general population[4]. The greater mortality caused by these three species has been confirmed in many studies, some of which established an association with greater virulence or greater resistance to azoles. However, it is not easy to separate this higher species-dependent mortality from host-dependent mortality. The above mentioned species are more frequent in patients with profound and severe neutropenia, which, together with a high APACHE score, are the factors most significantly associated with mortality in many candidemia series[5,6].

RECOMMENDATIONS ON TREATMENT OF INVASIVE CANDIDIASIS AND CANDIDEMIA IN PATIENTS WITH ONCOLOGIC-HAEMATOLOGIC DISORDERS

Several clinical guidelines and national and international consensus statements have been published in recent years[7-12].

In 2012, ESCMID published specific guidelines on the management of candidemia in patients with hematologic cancer who had undergone bone marrow transplantation[9]. The guidelines do not recommend prophylaxis for post-chemotherapy neutropenia or in autologous transplantation. However, they do justify prophylaxis in allogenic transplantation in the following situations: neutropenia (recommendation grade AI for fluconazole, posaconazole, voriconazole, and micafungin), during the first 100 days in the absence of graft-versus-host disease (GVHD) (recommendation grade AI for fluconazole and posaconazole) and in the presence of GVHD (recommendation AI for fluconazole and posaconazole). In the case of empiric treatment for patients with long-term neutropenia, their highest recommendation is caspofungin (AII_t) and micafungin (AII_t), followed by liposomal amphotericin B (BII_t), fluconazole (CII_t), voriconazole (CII_t), and posaconazole (DII_t). For targeted treatment, the guidelines suggest caspofungin (AI) or liposomal amphotericin B (AI) and recommend catheter withdrawal (AII_u). Lastly, transfusion of granulocytes is considered a last resort in some cases of candidemia/candidiasis in neutropenic patients (CIII).

In 2016, the Infectious Diseases Society of America (IDSA) re-edited its guidelines on candidemia in the general population and for different conditions, including neutropenia[12]. Table 1 summarizes the main recommendations. Of particular interest is the recommendation of echinocandins as initial therapy and stepping down to fluconazole after recovery from neutropenia in clinically stable patients infected by a sensitive strain. The recommendations give more weight to transfusion of granulocytes, although the recommendation is weak and the level of evidence low; however, withdrawal of the catheter is recommended on an individual basis (strong recommendation, low level evidence).

ROLE OF WITHDRAWAL OF INTRAVENOUS CATHETER IN PATIENTS WITH ONCOLOGIC-HAEMATOLOGIC DISEASES AND CANDIDEMIA

Various studies have confirmed that systematic early withdrawal of vascular catheters in patients with candidemia reduces mortality[13-16], and this recommendation is included in most guidelines[7-12].

However, systematic withdrawal of vascular catheters has been criticized in patients with candidemia. Nucci et al analysed the impact of catheter withdrawal in two multicentre studies[17]: a 2-armed study comparing micafungin and liposomal amphotericin B[18] and a 3-arm study comparing 2 doses of micafungin (100 mg/d and 150 mg/d) with caspofungin 50 mg/d[19]. The catheter was removed during the first 48 hours in 354 of 842 evaluable patients and after 48 hours in 180 patients; it was left in place in 308 patients. The univariate analysis showed this approach to be successful and survival at 28 and 42 days to be higher in cases where the catheter was left in place. However, catheter removal did not affect control of recurrent candidemia or microbiological eradication. Finally, the multivariate analysis did not confirm an independent association between catheter withdrawal and success of therapy or survival at 28 or at 42 days. Only neutropenia, a high APACHE score, and advanced age were significant.

The apparent discrepancy between the results of this study and other similar studies lies in the differences in prevalence of the intravenous catheter as the source of candidemia. Studies in which the intravascular catheter is the main source of candidemia in >40% of cases (eg, on medical wards or in intensive care units) show that controlling the site of infection by withdrawing the catheter provides clear benefits. However, in situations where the

Table 1 **Recommendations on treatment of candidemia in neutropenic patients (adapted from reference 12; IDSA 2016 guidelines, GRADE protocol)**

		Recommendation	Evidence
1	Echinocandins: initial treatment	Strong	Moderate
2	Lipid amphotericin B: alternative (greater toxicity)	Strong	Moderate
3	Fluconazole: alternative (no previous azole therapy, noncritical patient)	Weak	Low
4	Fluconazole/voriconazole: step down (if sensitive strain, no neutropenia, control of candidemia, noncritical patient)	Weak	Low
5	Voriconazole: alternative (if also necessary to cover filamentous fungi)	Weak	Low
6	If *Candida krusei*: echinocandins, lipid amphotericin B, or voriconazole	Strong	Low
7	Duration of treatment: 2 weeks (if candidemia is controlled, no distant foci, clinical improvement)	Strong	Low
8	Ophthalmological examination after resolution of neutropenia	Strong	Low
9	Withdrawal of venous catheter on an individual basis	Strong	Low
10	Granulocyte transfusion: if persistent candidemia and neutropenia	Weak	Low

origin of candidemia may be endogenous and not vascular, such as in the neutropenic patient or in patients admitted to surgical wards, prevalence is lower, and recommendations on catheter withdrawal should be tailored after application of diagnostic techniques, including differential blood cultures.

NEUTROPHIL TRANSFUSION

Three single-centre retrospective studies have highlighted the key role of neutrophil transfusion in control of candidemia in the neutropenic patient[20-22]. A similar protocol was applied in all three studies, namely, donors received granulocyte colony-stimulating factor (600 µg), dexamethasone (8 mg), and a high number of transfusions (>8 per patient) with a high neutrophil count (>50 x 10^9). All 3 studies reported control of candidemia in >50% of cases and a frequency of adverse effects <10% with respect to the low baseline percentage of cross-matching and anti-polymorphonuclear antibodies.

The only multicentre randomized trial to evaluate the role of granulocyte transfusion in neutropenic patients with candidemia was performed with 74 adult patients in Germany[23]. Dexamethasone was not used, and the richness of the polymorphonuclear cells in the units transfused and the frequency of transfusion were lower than in previous studies. The study did not establish significant differences in control of candidemia, and survival at 28 days was similar to that of the control group (82% vs. 84%). In addition to these limitations, the authors also report major limitations (eg, low-risk population, delay between randomization and transfusion), which made it difficult to reach robust conclusions, and agree that new studies are necessary.

KEY ROLE OF ECHINOCANDINS IN THE TREATMENT OF CANDIDEMIA IN THE NEUTROPENIC PATIENT

A recent meta-analysis of 1,915 patients with candidemia confirmed that treatment with echinocandins was an independent factor associated with low mortality (OR, 0.65; 95%CI, 0.45-0.94), as was catheter withdrawal (OR, 0.50; 95%CI, 0.35-0.72)[24].

Most clinical trials on administration of fluconazole to treat candidemia carried out some years ago excluded neutropenic patients, and no controlled clinical trials with lipid amphotericin were performed before the advent of the echinocandins.

In the study by Mora et al (caspofungin vs conventional amphotericin to treat candidemia), 13% and 9% of patients, respectively, were neutropenic, and the response in this subgroup was 50% and 40%, which was slightly lower than that observed in the overall population (73% and 62%, respectively[25].

Kuse et al (micafungin vs liposomal amphotericin in candidemia) also included a significant number of neutropenic patients (12% and 8%, respectively) and confirmed a response of 75% and 80%, which was similar to that obtained in the overall population[18].

Papas et al (micafungin 100 mg/d vs micafungin 150 mg/d vs caspofungin 50 mg/d in patients with candidemia) found that 11%, 9%, and 6% of patients were neutropenic, with a response of 82%, 53%, and 64%, respectively[19].

Reboli et al (anidulafungin vs fluconazole for treatment of candidemia) found that the number of neutropenic patients in both arms was ≤3%, thus precluding evaluation of the role of anidulafungin in this type of patient[26].

Finally, Walsh et al found a 67% response to caspofungin (vs 50% for liposomal amphotericin B) in neutropenic patients with confirmed candidemia and fever receiving empirical treatment[27].

A recent meta-analysis including various of the studies mentioned above specifically analysed the key role of echinocandins in patients with neutropenia[28] and revealed a nonsignificant difference in favour of treatment with echinocandins (OR, 0.73; 95%CI, 0.42-1.29), with a clearly beneficial safety profile.

REFERENCES

1. Puig-Asensio M, Padilla B, Garnacho-Montero J, Zaragoza O, Aguado JM, et al. CANDIPOP Project.; GEIH-GEMICOMED (SEIMC).; REIPI. Epidemiology and predictive factors for early and late mortality in Candida bloodstream infections: a population-based surveillance in Spain. Clin Microbiol Infect 2014 ;20(4):O245-54.
2. Puig-Asensio M, Ruiz-Camps I, Fernández-Ruiz M, Aguado JM, Muñoz P, Valerio M, et al; CANDIPOP Project,.; GEIH-GEMICOMED SEIMC.; REIPI. Epidemiology and outcome of candidaemia in patients with oncological and haematological malignancies: results from a population-based surveillance in Spain. Clin Microbiol Infect 2015;21(5):491.e1-10.
3. Hachem R, Hanna H, Kontoyiannis D, Jiang Y, Raad I. The changing epidemiology of invasive candidiasis: Candida glabrata and Candida krusei as the leading causes of candidemia in hematologic malignancy. Cancer 2008;112(11):2493-9.
4. Pfaller M, Neofytos D, Diekema D, Azie N, Meier-Kriesche HU, Quan SP, et al. Epidemiology and outcomes of candidemia in 3648 patients: data from the Prospective Antifungal Therapy (PATH Alliance®) registry, 2004-2008. Diagn Microbiol Infect Dis 2012;74(4):323-31.
5. Viscoli C, Girmenia C, Marinus A, Collette L, Martino P, Vandercam B, et al. 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 1999;28(5):1071-9.
6. Horn DL, Ostrosky-Zeichner L, Morris MI, Ullmann AJ, Wu C, Buell DN, et al. Factors related to survival and treatment success in invasive candidiasis or candidemia: a pooled analysis of two large, prospective, micafungin trials. Eur J Clin Microbiol Infect Dis 2010;29(2):223-9.

7. Pappas PG, Kauffman CA, Andes D, Benjamin DK Jr, Calandra TF, Edwards JE Jr, et al; Infectious Diseases Society of America.. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 2009;48(5):503-35.
8. Aguado JM, Ruiz-Camps I, Muñoz P, Mensa J, Almirante B, Vázquez L, et al. Grupo de Estudio de Micología Médica de la SEIMC (GEMICOMED).. [Guidelines for the treatment of Invasive Candidiasis and other yeasts. Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC). 2010 Update]. Enferm Infecc Microbiol Clin 2011;29(5):345-61
9. Ullmann AJ, Akova M, Herbrecht R, Viscoli C, Arendrup MC, Arikan-Akdagli S, Bassetti M, et al. ESCMID Fungal Infection Study Group.. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: adults with haematological malignancies and after haematopoietic stem cell transplantation (HCT). Clin Microbiol Infect 2012;18 Suppl 7:53-67.
10. Arendrup MC, Bille J, Dannaoui E, Ruhnke M, Heussel CP, Kibbler C. ECIL-3 classical diagnostic procedures for the diagnosis of invasive fungal diseases in patients with leukaemia. Bone Marrow Transplant 2012;47(8):1030-45.
11. Baden LR, Swaminathan S, Angarone M, Blouin G, Camins BC, Casper C, et al. Prevention and Treatment of Cancer-Related Infections, Version 2.2016, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2016;14(7):882-913
12. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis 2016;62(4):e1-50.
13. Liu CY, Huang LJ, Wang WS, Chen TL, Yen CC, Yang MH, Hsiao LT, et al. Candidemia in cancer patients: impact of early removal of non-tunneled central venous catheters on outcome. J Infect 2009;58(2):154-60.
14. Yin M, Li C, Wu D, Wang H. Catheter Removal Does Matter but Should Be Individualized for Patients with Candidemia. Intern Med 2016;55(15):2133.
15: Yaita K, Onozawa K. Does Catheter Removal not Matter in Candidemia Patients? Intern Med 2016;55(15):2131.
16. Hsu HY, Chao CM. What is the impact of catheter removal on the outcome of non-catheter-related candidemia? Crit Care Med 2014;42(9):e629.
17. Nucci M, Anaissie E, Betts RF, Dupont BF, Wu C, Buell DN, Kovanda L, Lortholary O. Early removal of central venous catheter in patients with candidemia does not improve outcome: analysis of 842 patients from 2 randomized clinical trials. Clin Infect Dis 2010;51(3):295-303.
18. Kuse ER, Chetchotisakd P, da Cunha CA, Ruhnke M, Barrios C, Raghunadharao D, et al. Micafungin Invasive Candidiasis Working Group.. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. Lancet 2007;369(9572):1519-27.
19. Pappas PG, Rotstein CM, Betts RF, Nucci M, Talwar D, De Waele JJ, Vazquez JA, Dupont BF, Horn DL, Ostrosky-Zeichner L, Reboli AC, Suh B, Digumarti R, Wu C, Kovanda LL, Arnold LJ, Buell DN. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. Clin Infect Dis. 2007 Oct 1;45(7):883-93. Epub 2007 Aug 29. Erratum in: Clin Infect Dis. 2008 Jul 15;47(2):302.
20. Price TH, Boeckh M, Harrison RW, McCullough J, Ness PM, Strauss RG, Nichols WG, et al. Efficacy of transfusion with granulocytes from G-CSF/dexamethasone-treated donors in neutropenic patients with infection. Blood 2015;126(18):2153-61.
21. Grigull L, Pulver N, Goudeva L, Sykora KW, Linderkamp C, Beilken A, et al. G-CSF mobilised granulocyte transfusions in 32 paediatric patients with neutropenic sepsis. Support Care Cancer 2006;14(9):910-6.
22. Safdar A, Hanna HA, Boktour M, Kontoyiannis DP, Hachem R, Lichtiger B, Freireich EJ, Raad II. Impact of high-dose granulocyte transfusions in patients with cancer with candidemia: retrospective case-control analysis of 491 episodes of Candida species bloodstream infections. Cancer 2004;101(12):2859-65.
23. Seidel MG, Peters C, Wacker A, Northoff H, Moog R, Boehme A, Silling G, Grimminger W, Einsele H. Randomized phase III study of granulocyte transfusions in neutropenic patients. Bone Marrow Transplant 2008;42(10):679-84.
24. Andes DR, Safdar N, Baddley JW, Playford G, Reboli AC, Rex JH, Sobel JD, et al. Mycoses Study Group.. Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: a patient-level quantitative review of randomized trials. Clin Infect Dis 2012;54(8):1110-22.
25. Mora-Duarte J, Betts R, Rotstein C, Colombo AL, Thompson-Moya L, Smietana J, et al. Caspofungin Invasive Candidiasis Study Group.. Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med 2002;347(25):2020-9.
26. Reboli AC, Rotstein C, Pappas PG, Chapman SW, Kett DH, Kumar D, Betts R, et al. Anidulafungin Study Group. Anidulafungin versus fluconazole for invasive candidiasis. N Engl J Med 2007;356(24):2472-82.
27. Walsh TJ, Teppler H, Donowitz GR, Maertens JA, Baden LR, Dmoszynska A, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. N Engl J Med 2004;351(14):1391-402.
28. Kanji JN, Laverdière M, Rotstein C, Walsh TJ, Shah PS, Haider S. Treatment of invasive candidiasis in neutropenic patients: systematic review of randomized controlled treatment trials. Leuk Lymphoma 2013;54(7):1479-87.