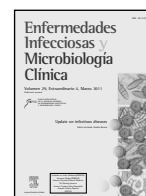




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Update on fungemia in oncology and hematology

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ABSTRACT

Keywords:
Fungemia
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The present article is an update of the literature on fungemia in onco-hematologic patients. A multidisciplinary group of Spanish physicians with an interest in this field selected the most important papers published lately. Papers from the fields of epidemiology, risk factors, pathogenesis, diagnosis, outcome, prevention and treatment are discussed. Important aspects of these studies include the assessment of different strategies in the management of fever in neutropenic patients. Moreover, early identification of patients at risk of fungal infections, as well as identification of patients at risk for fluconazole-resistant strains are topics of increasing interest.

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Actualización en fungemia en oncohematología

RESUMEN

Palabras clave:
Fungemia
Oncología
Hematología

El trabajo que se presenta es una revisión de la bibliografía reciente más relevante del último año publicada en relación con la funginemia en pacientes oncohematológicos. Un grupo multidisciplinar compuesto por diferentes especialistas españoles con interés en este campo revisan los artículos más novedosos. Los trabajos pertenecen a áreas de epidemiología, factores de riesgo, patogénesis, diagnóstico, evolución, prevención y tratamiento. Se analizan diferentes aspectos, incluyendo estrategias del manejo de la fiebre en el paciente neutropénico. La identificación precoz de factores de riesgo de infección fúngica, así como de los factores de riesgo de infección por cepas resistentes a fluconazol es objetivo de especial interés.

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Introduction

Candida is the fourth leading cause of blood stream infection, mainly affecting patients with hematologic malignancies and solid tumors, organ transplant recipients and patients admitted to intensive care units^{1,2}. Although the last twenty years have seen a trend towards declining infections by opportunistic yeasts and rising mould infections, particularly those caused by *Aspergillus* spp., invasive candidiasis continues to be a cause of concern with a crude mortality estimated at 40%.

The prophylactic use of fluconazole in persistently febrile neutropenic patients or those with a hematological malignancy who

may have received a hematopoietic stem cell transplant has achieved an incidence of invasive candidiasis approaching 5%. However, the emergence of *Candida* strains resistant to fluconazole has recently complicated the management of this infection. Risk factors for *Candida* infection include gastrointestinal tract colonization, cytomegalovirus disease, prior wide-spectrum antibiotic therapy, radiotherapy and a prior episode of bacteremia.

During induction chemotherapy, prophylactic fluconazole, posaconazole or caspofungin are recommended until neutropenia ceases. For stem cell transplant recipients with neutropenia, recommended prophylactic antifungals are fluconazole, posaconazole or micafungin. In neutropenic patients with suspected invasive candidiasis, empirical therapy with liposomal amphotericin B, caspofungin or an azole (if the patient has not already received azole prophylaxis) should be started. For treatment in this subset of patients, an equinocandin is usually recommended in most cases.

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Definition

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;46:1813-21.³

Invasive fungal diseases are important causes of morbidity and mortality. Clarity and uniformity in defining these infections are important factors in improving the quality of clinical studies. A standard set of definitions strengthens the consistency and reproducibility of such studies.

After the introduction of the original 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 definitions, advances in diagnostic technology and the recognition of areas in need of improvement led to a revision of this document. The revised definitions retain the original classifications of "proven," "probable," and "possible" invasive fungal disease, but the definition of "probable" has been expanded, whereas the scope of the category "possible" has been diminished. The category of proven invasive fungal disease can apply to any patient, regardless of whether the patient is immunocompromised, whereas the probable and possible categories are proposed for immunocompromised patients only.

Comments. These revised definitions of invasive fungal disease are intended to advance clinical and epidemiological research and may serve as a useful model for defining other infections in high-risk patients. Regarding candidemia, the clinical criteria for probable disseminated candidiasis include at least 1 of the following 2 entities after an episode of candidemia within the previous 2 weeks: small, target-like abscesses (bull's-eye lesions) in liver or spleen, or progressive retinal exudates on ophthalmologic examination. The presence of signs and symptoms consistent with sepsis syndrome indicates acute disseminated disease, whereas their absence denotes chronic disseminated disease. The mycological criteria for probable IFI includes beta-D-glucan detected in serum.

Epidemiology

Pagano L, Caira M, Nosari A, Van Lint MT, Candoni A, Offidani M, et al. Fungal infections in recipients of hematopoietic stem cell transplants: results of the SEIFEM B-2004 study –Sorveglianza Epidemiologica Infezioni Fungine Nelle Emopatie Maligne. *Clin Infect Dis*. 2007;45:1161-70.⁴

This study evaluates the incidence and outcome of invasive fungal infection (IFI) among patients who underwent autologous or allogeneic haematopoietic stem cell transplantation (HSCT) at 11 Italian transplantation centres. This cohort-retrospective study, conducted during 1999-2003, involved HSCT patients admitted to 11 tertiary care centres or university hospitals in Italy, who developed IFIs (proven or probable). Among 3,228 patients who underwent HSCT (1,249 allogeneic HSCT recipients and 1,979 autologous HSCT recipients), IFI occurred in 121 patients (overall incidence, 3.7%). Ninety-one episodes (2.8% of all patients) were due to moulds, and 30 (0.9%) were due to yeasts. Ninety-eight episodes (7.8%) occurred among the 1,249 allogeneic HSCT recipients, and 23 (1.2%) occurred among the 1,979 autologous HSCT recipients. The most frequent etiological agents were *Aspergillus* species (86 episodes) and *Candida* species (30 episodes). The overall mortality rate was 5.7% among allogeneic HSCT recipients and 0.4% among autologous HSCT recipients, whereas the attributable mortality rate registered in their population was 65.3% (72.4% for allogeneic HSCT recipients and

34.7% for autologous HSCT recipients). Aetiology influenced the patients' outcomes: the attributable mortality rate for aspergillosis was 72.1% (77.2% and 14.3% for allogeneic and autologous HSCT recipients, respectively), and the rate for *Candida* IFI was 50% (57.1% and 43.8% for allogeneic and autologous HSCT recipients, respectively).

Comments. IFI represents a common complication for allogeneic HSCT recipients. *Aspergillus* species is the most frequently detected agent in these patients, and aspergillosis is characterized by a high mortality rate. Conversely, autologous HSCT recipients rarely develop aspergillosis, and the attributable mortality rate is markedly lower. Candidemia was observed less often than aspergillosis among both allogeneic and autologous HSCT recipients; furthermore, there was no difference in either the incidence of or the attributable mortality rate for candidemia among recipients of the 2 transplant types.

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;112:2493-9.⁵

The objective of the current retrospective study was to compare the epidemiology of candidemia and its risk factors in patients who had hematologic malignancies (HM) with those in patients who had solid tumors (ST). The medical and electronic records of all patients with cancer who had candidemia at the authors' institution (M. D. Anderson Cancer Center, Houston) from 1993 to 2003 were reviewed for demographic data and clinical information, including the use of prophylactic fluconazole, the infecting *Candida* species, and the source of candidemia (catheter-related vs other apparent sources). Six hundred thirty-five patients with candidemia were analyzed. *C. glabrata* and *C. krusei* were the leading causes of candidemia in 31% and 24% of patients with HM, respectively, and in 18% and 2% of patients with ST, respectively ($P < .001$). A catheter was the source of candidemia in 36% of the patients with ST and in 12% of the patients with HM ($P < .001$). Response to antifungal therapy occurred in 73% of the ST group compared with 49% of the HM group ($P < .001$). Multivariate logistic regression analysis revealed that fluconazole prophylaxis was a risk factor for both *C. glabrata* and *C. krusei* candidemia. The analysis also identified neutropenia as a risk factor for all candidemia and catheter-related infection as a risk factor for *C. parapsilosis* candidemia.

Comments. The results of this study indicated that *C. glabrata* and *C. krusei* were the leading causes of candidemia in patients with HM. Neutropenia was the leading risk factor for all candidemia, whereas the catheter was the leading risk factor for *C. parapsilosis* candidemia. Correct initial treatment in patients with candidemia is a crucial factor for a successful outcome. The selection of initial treatment should be based on factors that include prior antifungal exposure, the clinical status of the patient, and the epidemiology of candidemia at individual institutions.

Kontoyiannis DP, Marr KA, Park BJ, Alexander BD, Anaissie EJ, Walsh TJ, et al. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001-2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. *Clin Infect Dis*. 2010;50:1091-100.⁶

The incidence and epidemiology of invasive fungal infections (IFIs), a leading cause of death among hematopoietic stem cell transplant (HSCT) recipients, are derived mainly from single-institution retrospective studies. The Transplant Associated Infections Surveillance Network, a network of 23 US transplant centers, prospectively enrolled HSCT recipients with proven and probable IFIs occurring between March 2001 and March 2006. Denominator data on all HSCTs performed at each site and clinical, diagnostic, and

outcome information for each IFI case were collected. To estimate trends in IFI, they calculated the 12-month cumulative incidence among 9 sequential subcohorts. 983 IFIs were identified among 875 HSCT recipients. The median age of the patients was 49 years; 60% were male. Invasive aspergillosis (43%), invasive candidiasis (28%), and zygomycosis (8%) were the most common IFIs. Fifty-nine percent and 61% of IFIs were recognized within 60 days of neutropenia and graft-versus-host disease, respectively. Median onset of candidiasis and aspergillosis after HSCT was 61 days and 99 days, respectively. Within a cohort of 16,200 HSCT recipients who received their first transplants between March 2001 and September 2005 and were followed up through March 2006, they identified 718 IFIs in 639 persons. Twelve-month cumulative incidences, based on the first IFI, were 7.7 cases per 100 transplants for matched unrelated allogeneic, 8.1 cases per 100 transplants for mismatched-related allogeneic, 5.8 cases per 100 transplants for matched-related allogeneic, and 1.2 cases per 100 transplants for autologous HSCT.

Comments. In this national prospective surveillance study of IFIs in HSCT recipients, the cumulative incidence was highest for aspergillosis, followed by candidiasis. Understanding the epidemiologic trends and burden of IFIs may lead to improved management strategies and study design.

Etiology

Nucci M, Anaissie E. *Fusarium* infections in immunocompromised patients. *Clin Microbiol Rev.* 2007;20**:695-704.⁷**

Fusarium species cause a broad spectrum of infections in humans, including superficial, locally invasive, and disseminated infections. The clinical form of fusariosis depends largely on the immune status of the host and the portal of entry of the infection. Infections by *Fusarium* species can be superficial or limited to single organs in otherwise healthy patients. Such infections are rare and tend to respond well to therapy. By contrast, disseminated fusariosis affects the immunocompromised host, especially HSCT recipients and patients with severe and prolonged neutropenia. Infection in this setting is frequently fatal, and successful outcome is determined largely by the degree and persistence of immunosuppression and the extent of infection, with virtually a 100% death rate for persistently neutropenic patients with disseminated disease. These infections may be clinically suspected on the basis of a constellation of clinical and laboratory findings, which should lead to prompt therapy. Treatment options include the lipid formulations of amphotericin B, voriconazole, and posaconazole. Prevention of fusarial infection among high-risk patients should be considered.

Suzuki K, Nakase K, Kyo T, Kohara T, Sugawara Y, Shibasaki T, et al. Fatal *Trichosporon* fungemia in patients with hematologic malignancies. *Eur J Haematol.* 2010;84**:441-7.⁸**

Invasive *Trichosporon* infection has been increasingly recognized in patients with hematologic malignancies. This study aims to clarify the clinical characteristics of this disease and factors influencing patient prognosis. The authors retrospectively analyzed 33 cases of *Trichosporon* fungemia (TF) in patients with hematologic malignancies treated at their collaborating five hospitals in Japan between 1992 and 2007. The majority of these patients had acute leukemia (82%), neutropenia (85%), and a history of intensive chemotherapy (91%). TF occurred as a breakthrough infection during antifungal therapy in 30 patients (91%), 18 of whom were receiving micafungin. The surveillance cultures of most patients were negative for *Trichosporon*. Only a few patients exhibited elevated levels of 1,3-beta-D-glucan before positive blood culture. Twenty-five patients (76%) died of this infection. The resolution of infection was associated with granulocyte recovery ($P = .0001$), absence of hyperglycemia ($P = .023$), and azole inclusive therapy ($P = .031$). Survival was significantly longer in

patients receiving antifungal therapies containing azole than in those who did not receive azole treatment ($P = .0034$).

Comments. At present, the diagnosis of invasive trichosporonosis depends on blood culture studies, and the mortality of this disease is high; however, azole therapy and control of blood glucose level, together with hematopoietic recovery (GM-CSF in neutropenic patients) could help in improving the clinical outcome. When antifungals lacking anti-*Trichosporon* activity are used, sufficient care should be taken to prevent the development of breakthrough trichosporonosis.

Jensen J, Muñoz P, Guinea J, Rodríguez-Creixems M, Peláez T, Bouza E. Mixed fungemia: incidence, risk factors, and mortality in a general hospital. *Clin Infect Dis.* 2007;44**:109-14.⁹**

The detection of >1 species of yeast in blood is uncommon. The authors describe episodes of mixed fungemia (MF), detected between 1985 and 2006, in a large teaching hospital. The study was divided into 2 periods that were separated by the introduction, in January 2005, of the CHROMagar *Candida* medium (CHROMagar) for the routine subculturing of blood cultures in which yeasts had been identified.

Overall, there were 747 cases of fungemia. During the first period (1985-1994), 217 episodes of fungemia were identified and no single episode of MF; during the second period (1995-2006), 15 episodes of MF were detected among 530 episodes of fungemia (2.8%). *Candida albicans* was isolated in 13 patients, non-*albicans* species of *Candida* in 16 patients, and *Saccharomyces cerevisiae* in 1 patient. Each episode of MF was compared with 2 control episodes of monomicrobial fungemia. Patients with MF had more frequently experienced organ transplantation (13% vs. 0%) and surgery (60% vs. 27%), had less frequently received parenteral nutrition (40% vs. 70%) or had intravenous lines (80% vs. 100%), and had a lower incidence of shock (6% vs. 37%) and a lower mortality (20% vs. 53%).

Comments. Mixed fungemia is still an uncommon disease and has a less severe outcome than does monomicrobial candidemia.

Risk factors

Slavin MA, Sorrell TC, Marriott D, Thursky KA, Nguyen Q, Ellis DH, et al. Candidaemia in adult cancer patients: risks for fluconazole-resistant isolates and death. *J Antimicrob Chemother.* 2010;65**:1042-51.¹⁰**

Candidaemia in cancer patients is associated with increasing fluconazole resistance. Models for predicting such isolates and their clinical impact are required. Clinical, treatment and outcome data from a population-based candidaemia survey (2001-2004) were collected at 5 and 30 days after diagnosis. Speciation and antifungal susceptibility testing was performed. There were 138 candidaemia episodes (33% *Candida albicans*) in adults with haematological malignancies and 150 (51% *C. albicans*) in adults with solid organ malignancies. Thirty-nine isolates had fluconazole MICs of ≥ 64 mg/L and 40 had MICs of 16-32 mg/L (predominantly *Candida glabrata* and *Candida krusei*). By multivariate analysis, triazole therapy, gastrointestinal tract (GIT) surgery in the 30 days before candidaemia and age >65 years were predictive of fluconazole-resistant candidaemia. Thirty day crude mortality was 40% in haematology patients and 45% in oncology patients. Fluconazole-resistant isolates were associated with increased risk of mortality by univariate ($P = .04$) and Kaplan-Meier survival analyses. By Cox proportional hazards modelling, the strongest predictors of mortality at onset of candidaemia were invasive ventilation, elevated creatinine, intensive care unit (ICU) admission and receipt of systemic triazoles or corticosteroids in the previous 30 days. Removal of a central venous access device (CVAD) at or within 5 days of onset was associated with decreased mortality.

Comments. Risk factors for fluconazole-resistant candidaemia in adults with cancer include fluconazole/triazole exposure and GIT surgery. ICU admission, invasive ventilation, renal impairment, age >65 years and prior exposure to corticosteroids and triazoles are risk factors for death. CVAD removal reduced mortality. These findings should be integrated into surveillance and treatment algorithms.

Pathogenic mechanisms

Hope WW, Drusano GL, Moore CB, Sharp A, Louie A, Walsh TJ, et al. Effect of neutropenia and treatment delay on the response to antifungal agents in experimental disseminated candidiasis. *Antimicrob Agents Chemother*. 2007;51:285-95.¹¹

The association between neutropenia and disseminated candidiasis was recognized nearly 40 years ago. Subsequently, neutropenia has been consistently implicated as a risk factor for the development of disseminated candidiasis and, more recently, has been demonstrated to be an important determinant of the likelihood of breakthrough infections, relapsing disease, chronic dissemination, and a poor prognostic marker for patients with candidemia. There is a progressive understanding of critical events in the interaction between *Candida* and neutrophils including signaling, recruitment, phagocytosis, and intracellular killing. The combined pharmacokinetic and pharmacodynamic model used in the current study provides a number of clinically relevant insights. Firstly, the experimental data and the combined mathematical model provide a basis for a further understanding of the clinical adage that antifungal agents merely prevent progressive infection. Although only the antifungal effect following the administration of a single dose of amphotericin B was studied, the data and model simulations support the notion that a critical factor in terms of the elimination of the infection is neutrophil recovery. The model simulations demonstrate the relatively modest antifungal effect of amphotericin B when administered to neutropenic mice compared with the significantly greater killing which results when the drug is administered in the presence of neutrophils. In neutropenic mice, the administration of amphotericin B serves only to prevent progressive growth, while in nonneutropenic mice there is a sustained decrement in the fungal burden within the kidney.

Comments. These analyses support the concept that factors which are extraneous to the inherent activity of antifungal agents may be equally, if not more, important in determining the ultimate therapeutic outcome. Thus, strategies to optimize the number and function of neutrophils, as well as delivering appropriate antifungal agents at the earliest possible time in the infectious process, are critical issues in order to improve the therapeutic outcome of patients with disseminated candidiasis.

Netea MG, Van de Veerdonk F, Verschueren I, Van der Meer JW, Kullberg BJ. Role of TLR1 and TLR6 in the host defense against disseminated candidiasis. *FEMS Immunol Med Microbiol*. 2008;52:118-23.¹²

Safdar A. Antifungal immunity and adjuvant cytokine immune enhancement in cancer patients with invasive fungal infections. *Clin Microbiol Infect*. 2007;13:1-4.¹³

Invasive fungal infections have a high mortality and their response to antifungal treatment is limited. New therapies are needed and adjunctive immunotherapy is promising. Understanding the mechanisms through which the host immune system recognize and eliminates fungal pathogens is an important step previously to the development of this kind of therapy. Toll-like receptors molecules have been demonstrated to play an important role in the host defence against candidosis. Netea et al explore the role of TLR1 and TLR6 in the recognition of *C. albicans* and the antifungal host defence by means of an experimental model with TLR1 -/- and TLR6 -/- mice

and controls. The results showed TLR6 is involved in the recognition of *C. albicans* and modulates the Th1/Th2 cytokine balance. In a more practical way, Safdar et al review the use of recombinant cytokines as adjuvant therapy to antifungals for the treatment in patients with invasive fungal infections. Thus, G-CSF and/or GM-CSF should be considered to use together with antifungals for select immunosuppressed patients with serious fungal infections and/or drug refractory diseases. The use of GM-CSF therapy should be limited because the risk of serious capillary leak syndrome. Recombinant humanised IFN- γ 1b has been used to patients with invasive fungal infection. No major side effects have been detected. Although a more extensive research has to be done, the potential of recombinant cytokines as adjuvant therapy for invasive fungal infections is promising.

Diagnosis

Guinea J, Recio S, Escribano P, Torres-Narbona M, Peláez T, Sánchez-Carrillo C, et al. Rapid antifungal susceptibility determination for yeast isolates by use of Etest performed directly on blood samples from patients with fungemia. *J Clin Microbiol*. 2010;48:2205-12.¹⁴

The authors prospectively determined the antifungal susceptibility of yeast isolates causing fungemia using the Etest on direct blood samples (195 prospectively collected and 133 laboratory prepared). They compared the Etest direct (24 h of incubation) with CLSI M27-A3 and the standard Etest methodologies for fluconazole, voriconazole, posaconazole, isavuconazole, caspofungin, and amphotericin B. Strains were classified as susceptible, resistant, or nonsusceptible using CLSI breakpoints (voriconazole breakpoints were used for posaconazole and isavuconazole). Categorical errors between Etest direct and CLSI M27-A3 for azoles were mostly minor. No errors were detected for caspofungin, and high percentages of major errors were detected for amphotericin B. For the azoles, false susceptibility (very major errors) was found in only two (0.6%) isolates (*Candida tropicalis* and *C. glabrata*). False resistance (major errors) was detected in 46 (14%) isolates for the three azoles (in 23 [7%] after excluding posaconazole). Etest direct of posaconazole yielded a higher number of major errors than the remaining azoles, especially for *C. glabrata*, *Candida* spp., and other yeasts. Excluding *C. glabrata*, *Candida* spp., and other yeasts, the remaining species did not yield major errors.

Comments. Etest direct for fluconazole, voriconazole, isavuconazole, and caspofungin shows potential as an alternative to the CLSI M27-A3 procedure for performing rapid antifungal susceptibility tests on yeast isolates from patients with fungemia. Etest direct is a useful tool to screen for the presence of azole-resistant and caspofungin-nonsusceptible strains.

Prophylaxis and treatment

Pappas PG, Kauffman CA, Andes D, Benjamin DK Jr, Calandra TF, Edwards JE Jr, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;48:503-35.¹⁵

Guidelines for the management of patients with invasive candidiasis and mucosal candidiasis were prepared by an Expert Panel of the Infectious Diseases Society of America. These updated guidelines replace the previous guidelines published in the 15 January 2004 issue of Clinical Infectious Diseases and are intended for use by health care providers who care for patients who either have or are at risk of these infections. Since 2004, several new antifungal agents have become available, and several new studies have been published relating to the treatment of candidemia, other forms of invasive candidiasis, and mucosal disease, including

oropharyngeal and esophageal candidiasis. There are also recent prospective data on the prevention of invasive candidiasis in high-risk neonates and adults and on the empiric treatment of suspected invasive candidiasis in adults. This new information is incorporated into this revised document.

Comments. These guidelines address specifically the empirical treatment for suspected invasive candidiasis in neutropenic patients, the treatment for candidemia in neutropenic patients and the administration of antifungal prophylaxis in neutropenic patients and in stem cell transplant recipients at risk of candidiasis.

Pappas PG, Rotstein CM, Betts RF, et al. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. *Clin Infect Dis.* 2007;45**:883-93.¹⁵**

Invasive candidiasis is an important cause of morbidity and mortality among patients with health care-associated infection. The echinocandins have potent fungicidal activity against most *Candida* species, but there are few data comparing the safety and efficacy of echinocandins in the treatment of invasive candidiasis. This was an international, randomized, double-blind trial comparing micafungin (100 mg daily) and micafungin (150 mg daily) with a standard dosage of caspofungin (70 mg followed by 50 mg daily) in adults with candidemia and other forms of invasive candidiasis. The primary end point was treatment success, defined as clinical and mycological success at the end of blinded intravenous therapy. A total of 595 patients were randomized to one of the treatment groups and received at least 1 dose of study drug. In the modified intent-to-treat population, 191 patients were assigned to the micafungin 100 mg group, 199 to the micafungin 150 mg group, and 188 to the caspofungin group. Demographic characteristics and underlying disorders were comparable across the groups. Approximately 85% of patients had candidemia; the remainder had noncandidemic invasive candidiasis. At the end of blinded intravenous therapy, treatment was considered successful for 76.4% of patients in the micafungin 100 mg group, 71.4% in the micafungin 150 mg group, and 72.3% in the caspofungin group. The median time to culture negativity was 2 days in the micafungin 100 mg group and the caspofungin group, compared with 3 days in the micafungin 150 mg groups. There were no significant differences in mortality, relapsing and emergent infections, or adverse events between the study arms.

Comments. Dosages of micafungin 100 mg daily and 150 mg daily were noninferior to a standard dosage of caspofungin for the treatment of candidemia and other forms of invasive candidiasis

Reboli AC, Rotstein C, Pappas PG, Chapman SW, Kett DH, Kumar D, et al. Anidulafungin Study Group. Anidulafungin versus fluconazole for invasive candidiasis. *N Engl J Med.* 2007;356**:2472-82.¹⁶**

Anidulafungin, a new echinocandin, has potent activity against *Candida* species. This was a study which compared anidulafungin with fluconazole in a randomized, double-blind, noninferiority trial of treatment for invasive candidiasis. Adults with invasive candidiasis were randomly assigned to receive either intravenous anidulafungin or intravenous fluconazole. All patients could receive oral fluconazole after 10 days of intravenous therapy. The primary efficacy analysis assessed the global response (clinical and microbiologic) at the end of intravenous therapy in patients who had a positive baseline culture. Efficacy was also assessed at other time points. Eighty-nine percent of the 245 patients in the primary analysis had candidemia only. *Candida albicans* was isolated in 62% of the 245 patients. In vitro fluconazole resistance was infrequent. Most of the patients (97%) did not have neutropenia. At the end of intravenous therapy, treatment was successful in 75.6% of patients treated with anidulafungin, as

compared with 60.2% of those treated with fluconazole (difference, 15.4 percentage points; 95% confidence interval [CI], 3.9 to 27.0). The results were similar for other efficacy end points. The statistical analyses failed to show a "center effect"; when data from the site enrolling the largest number of patients were removed, success rates at the end of intravenous therapy were 73.2% in the anidulafungin group and 61.1% in the fluconazole group (difference, 12.1 percentage points; 95%CI, -1.1 to 25.3). The frequency and types of adverse events were similar in the two groups. The rate of death from all causes was 31% in the fluconazole group and 23% in the anidulafungin group ($P=.13$).

Comments. Anidulafungin was shown to be noninferior to fluconazole in the treatment of invasive candidiasis.

Outcome

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**:223-9.¹⁷**

Crude and attributable mortality rates in patients with candidemia and invasive candidiasis remain unacceptably high. It is important to reach a more complete understanding of the risk factors underlying poor outcomes in patients with invasive *Candida* infections. Micafungin therapy has been assessed in two phase 3 trials compared to either liposomal amphotericin B or caspofungin. The availability of this large dataset allows the analyses of non-drug factors associated with survival and treatment success. A multivariate regression analysis was performed on data from the two trials separately and as a pooled analysis ($n=1,070$). Analysis outcomes were survival at 42 days post-initiation of therapy and treatment success. For the pooled analysis, treatment success was significantly more likely for candidemia than invasive candidiasis. Both survival and treatment success were significantly less likely for the non-removal of catheter versus removal, Asian-Indians versus Caucasians, APACHE II score >20 to ≤ 30 and >30 versus ≤ 20 , age ≥ 70 years versus <50 years, baseline corticosteroids, and persistent neutropenia. Survival was also significantly less likely for treatment in other regions versus North America and for patients with renal failure at baseline.

Comments. These findings help to define non-antifungal drug factors that may impact survival and treatment success in invasive candidiasis or candidemia.

Conflict of interest

R. de la Cámara has received fees for participating in symposiums organized by Pfizer, Merck Sharp & Dohme (MSD), Schering-Plough, Astellas and Gilead Science, and has participated in advisory committees on antifungal agents organized by MSD, Schering-Plough, Pfizer, Astellas and Gilead.

The remaining authors have not declared any conflict of interest.

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