Rev Iberoam Micol. 2009;**26(3)**:184–188

Revista Iberoamericana de Micología

www.elsevier.es/reviberoammicol

Original

Nosocomial candidemia at a general hospital: The change of epidemiological and clinical characteristics. A comparative study of 2 cohorts (1993–1998 versus 2002–2005)

Joaquín Gómez [a], Elisa García-Vázquez [a,*], Cristina Espinosa [a], Joaquín Ruiz [b], Manuel Canteras [c], Alicia Hernández-Torres [a], Victor Baños [a], José Antonio Herrero [a] and Mariano Valdés [d]

[a] *Internal Medicine-Infectious Diseases Department, University Hospital "Virgen de la Arrixaca", Murcia, Spain*
[b] *Microbiology Department, University Hospital "Virgen de la Arrixaca", Murcia, Spain*
[c] *Department of Biostatistics, Faculty of Medicine, University of Murcia, Spain*
[d] *Medicine Department, Faculty of Medicine, University of Murcia, Spain*

ARTICLE INFO

Article history:
Received 30 July 2008
Accepted 10 February 2009
Available online 18 de julio de 2009

Keywords:
Candidemia
Nosocomial
Epidemiology
Candida spp.

ABSTRACT

Background: Nosocomial candidemia (NC) is associated with high mortality, increased hospital stay and greater economical cost.

Aims: To evaluate epidemiological and clinical aspects of 2 different cohorts of non-paediatric patients with NC.

Methods: A retrospective observational and comparative study of patients with NC. Patients were identified by review of results of blood cultures from the hospital microbiology laboratory. We analysed epidemiological, clinical, microbiological and laboratory data and changes in the 2 cohorts: 1993–1998 (P1) and from 2002 to 2005 (P2).

Results: Eighty patients were studied during P1 and 107 during P2; incidence was 9/10,000 in P1 and 15.8/10,000 admitted patients in P2 ($p<0.05$). Mean age was 52 years in P1 and 61 years in P2 ($p<0.05$); 66% and 49% NC were due to *Candida albicans* in P1 and P2, respectively ($p<0.05$); diabetes was present in 12% in P1 and in 25% in P2 ($p<0.05$). All of the patients had previously received at least one course of broad-spectrum antibiotics. A statistically significant difference ($p<0.05$) in predisposing conditions was identified in central intravenous line rate (100% in P1 and 91% in P2) and previous surgery (43% in P1 and 78% in P2). Acute severity of illness at onset and complications were more frequent in P2 ($p<0.05$). Mortality rate was similar in P1 and P2 (51% and 49.5%, respectively).

Conclusions: Frequency of NC has increased and non-*albicans Candida* is now more frequent than *C. albicans*. Although acute severity of illness at onset and complications are now more frequent, mortality remains the same.

Candidemia nosocomial en un hospital general: cambios en las características epidemiológicas y clínicas. Estudio comparativo de dos cohortes (1993–1998 versus 2002–2005)

Palabras clave:
Candidemia
Nosocomial
Epidemiología
Candida spp.

RESUMEN

Antecedentes: La candidemia nosocomial (CN) se asocia a una elevada mortalidad y a un aumento de la estancia hospitalaria y del coste económico de la misma.

Objetivos: Analizar las características epidemiológicas y clínicas de dos cohortes de pacientes no pediátricos que desarrollaron CN.

Métodos: Estudio retrospectivo, observacional y comparativo de pacientes con CN. Los casos se identificaron a partir de los resultados de los hemocultivos (Laboratorio de Microbiología de nuestro centro). Se estudiaron las diferencias referentes a aspectos epidemiológicos, clínicos, microbiológicos y de laboratorio de las 2 cohortes: 1993–1998 (P1) y 2002–2005 (P2). Los paciente estudiados en P1 fueron 80, y 107 en P2.

Resultados: La incidencia fue 9/10000 en P1 y 15,8/10000 ingresos en P2 ($p<0,05$); la edad media fue 52 y 61 años en P1 y P2, respectivamente ($p<0,05$); 66% y 49% de los casos correspondían a *Candida albicans* en P1 y P2, respectivamente ($p<0,05$); 12% de los pacientes en P1 y 25% en P2 eran diabéticos ($p<0,05$). Todos

* Corresponding author.
E-mail address: elisag@eresmas.net (E. García-Vázquez).

1130-1406/$ - see front matter © 2009 Revista Iberoamericana de Micología. Publicado por Elsevier España, S.L. Todos los derechos reservados.
doi:10.1016/j.riam.2009.02.003

los pacientes habían recibido previamente al menos un ciclo de tratamiento antibiótico de amplio espectro. Hubo diferencias estadísticamente significativas ($p<0,05$) en los siguientes factores predisponentes: portadores de vía venosa central (100% en P1 y 91% en P2) y cirugía previa (43% en P1 y 78% en P2). La gravedad del diagnóstico y el desarrollo de complicaciones fue más frecuente en P2 ($p<0,05$). La mortalidad fue similar en P1 y P2 (51% y 49,5%, respectivamente).

Conclusiones: La frecuencia de CN ha aumentando y las especies de *Candida* no-C. *albicans* son ahora más frecuentes que C. *albicans*. Aunque la gravedad y el desarrollo de complicaciones son ahora más frecuentes, la mortalidad se ha mantenido estable.

Candidemia is related to high mortality with figures that oscillate between 40% and 60% according to different series. As well as with higher mortality, fungemia is associated with longer average hospital stays and an increase in the economic cost per process. In recent years, a higher frequency has been noticed in the prevalence study of nosocomial infection in Spanish hospitals (EPINE), reaching figures in some centres of even 50% out of the total of episodes of hospital bacteraemia, thus accounting for the sixth microorganism in frequency.[28] On the other hand, we have witnessed several epidemiological and clinical changes in the characteristics and risk factors of the patients, together with increasing resistance to fluconazole in relation to the higher representativity of non-*albicans Candida* in the total of episodes of candidemia.[17,19]

In view of these clinical problems, the aim of our study is to compare the changes in the epidemiological and clinical characteristics of 2 cohorts of patients with nosocomial candidemia (NC) in 2 different periods.

Patients and methods

Hospital characteristics

The Hospital Universitario Virgen de la Arrixaca, in Murcia (Spain), is a 944-bed facility, 611 of which belong to the general hospital. Its area of care encompasses a population of approximately 450,000 individuals. It is, in addition, a reference hospital in certain specialties such as neurosurgery, burn trauma, cardiovascular surgery and organ transplantation.

Study period

All episodes of bloodstream infection due to *Candida* species during the period from January 2002 to May 2005 (P2) were included and compared to our previous cohort of patients corresponding to the period 1993–1998 (P1).[7]

Microbiological study

The isolation and detection of the species of *Candida* were done following the microbiological protocols and in accordance with the international regulations of the Centres for Desease Control and Prevention.[30] During this study, blood cultures were collected as part of normal clinical practice and incubated for 5 days on the BACTALERT system. Yeasts were identified using the Vitek 2 YST card from bioMerieux (Durham, USA).

The study of susceptibility to amphotericin B and fluconazole was done by using the Yeast One method (TREK Diagnosis Systems, Cleveland, USA) following the NCCLS criteria.[14] Thus, *Candida* spp. was considered to be resistant to fluconazole in the case of MIC $>64\,\mu g/mL$, of intermediate susceptibility or of dose-dependent resistance if MIC was comprised between 16 and $32\,\mu g/mL$ and susceptible if MIC $<16\,\mu g/mL$. Resistance to amphotericin B was defined if MIC $>1\,\mu g/mL$. The quality control was carried out using *Candida parapsilosis* (ATCC 22019).

Patients' assessment

Candidemia was considered to be of community acquisition whenever *Candida* spp. were isolated within the first 72 h of hospital admission, provided the patient had not been hospitalised in the previous month. Candidemia was considered to be of nosocomial acquisition when a positive blood culture was obtained after the first 72 h of hospitalisation in patients who showed no symptoms or signs of infection at the time of hospital admission. Likewise, when a positive culture was obtained within the first 72 h of hospitalisation in a patient who had been hospitalised during the previous month, infection was understood to be of nosocomial acquisition. The retrospective review of the clinical records was done following a study protocol in which epidemiological, clinical and microbiological variables were collected.

Patients were assessed with regard to the prognosis of their underlying disease according to the criteria of McCabe and Jackson.[12] Their condition was then classified as "rapidly fatal" when death was expected to take place in days or weeks, "ultimately fatal" when death was likely to take place in some months or years, and "nonfatal" when death was not predictable. The severity of the patient's condition at presentation was assessed according to Winston et al.[31] as follows: "critical" when the patient's clinical condition was rapidly deteriorating and the probability of death during the first 24 h was high; "poor" when the clinical condition was deteriorating and death was probable but not imminent; "fair" when the clinical condition was deteriorating but death was not probable; and "good" when the clinical situation did not change during the first 24 h and death was not probable.

In the assessment of neoplasia, we considered patients with active solid organ cancer or with haematological malignancies.

Prognostic factors

In order to identify prognostic factors, and in accordance with previous works,[22] all clinical and epidemiological characteristics, all complications and the type of antifungal treatment were examined in relation to the final outcome of patients, with "recovery" understood to be the disappearance of all active signs and symptoms of infection.[13] When the physician considered the death of the patient to be related to the infection, it was designated as "death related to candidemia." If the physician considered that death had occurred after recovery from the infection and was related to the underlying disease or other medical or surgical complications, it was classified as "death not related to candidemia." The death of the patient was taken into consideration when it took place during admission to hospital, in accordance with previous studies.[22]

Among the epidemiological factors the presence of central venous and urinary catheters or nasogastric tube, the treatment with parenteral nutrition and the previous use of antibiotics were included. As for the latter, the type of agent and number of cycles received were taken into account, a cycle being considered when the patient had received antibiotic treatment with a minimum duration of 7 days in the previous 6 weeks before NC. The previous use of antifungal agents was defined as the administration of this type of drugs in the previous 6 weeks before candidemia. Origin of NC, complications and outcome were analysed according to standard criteria.[3]

Treatment

The antifungal used was considered active when, according to microbiological data, it presented *in vitro* activity (MIC that allowed to define the isolate as susceptible) against the *Candida* sp. isolated. We considered the initial empiric antifungal treatment to be appropriate when it exhibited *in vitro* activity against the corresponding *Candida* sp. isolated, when it was used in a correct dosage, and thus its use did not have to be modified after the antibiogram results were obtained. The efficacy of the treatment was considered to be assessable after at least 5 days of administration. The duration of the treatment was adjusted to the guidelines, requiring a minimum of 14 days to be considered as complete and up to 30–40 days in the case of development of complications.[15]

''Early'' treatment was defined as the empiric treatment initiated facing the presence of fever and before having any microbiological information or in the first 48 h after receiving the notification of positive blood culture for yeasts. On the other hand, treatment initiated after 48 h of receiving the microbiological information was estimated as ''late'' treatment.

The removal of the venous catheter was considered as appropriate when it was done in the first 48 h after having received the microbiological information.

Statistical study

Data were analysed using the statistics program SPSS 15.0 (SPSS Software, Chicago, USA). A descriptive study was performed for the clinical and epidemiological characteristics as well as for the prognostic factors of patients with NC. The relation or association between pairs of qualitative variables was determined through analyses of contingency tables by means of Pearson's χ^2 test, complemented by an analysis of residues with the aim of determining the directional dependence. In the case of quantitative variables, means have been compared using Student's t test. The difference was considered significant at $p<0.05$. The 2 cohorts of patients (P1 and P2) were statistically compared.

Results

During P2, the complete medical records of 107 patients with NC were available, out of which 79 were men and 28 women, with an average age of 61 years (range 17–87) (52 years—range 18–81 in P1; $p<0{,}05$); out of which 53 died (49.5%), against a mortality rate of 51% (41 out of 80) in P1. Annual incidence of the period of study was of 15.8 cases per 10,000 admitted patients while it was 9/10,000 patients/year in the historical series of P1.

In P2, *C. albicans* was isolated in 49 cases (45.8%) against 53 (66.2%) in P1 ($p<0{,}05$). In P2, 9 (8.4%) isolates of *Candida* were resistant to fluconazole (*C. glabrata* (8) and *C. krusei* (1)) and 8 (7.6%) presented intermediate or dose-dependent susceptibility (*C. glabrata* (6) and *C. parapsilosis* (2)) and there was only a blood culture whose isolate (*C. lusitaniae*) was resistant to amphotericin B. In the first study all the isolates were susceptible to fluconazole[25] except for the 2 isolates of *C. krusei*.

Among the predisposing factors for the development of candidemia in P2 the most outstanding were as follows: presence of central catheter (90.6%), parenteral nutrition (90.6%), urinary catheter (90.6%), previous use of 2 or more cycles of broad-spectrum antibiotics (80.4%), previous surgery (78.5%), mechanical ventilation (75.7%) and previous transfusions (70%).

As underlying diseases we highlight diabetes mellitus (25%) and neurological pathology of vascular origin (8.4%) as more prevalent in P2.

Acute severity of illness at onset in P2 was critical in 49.6% (only in 28.7% in P1). Complications turned up in 86 cases in P2 (80.4%) as against 65% in P1. The most statistically significant ones were respiratory distress (42.5%), renal failure (43%) and disseminated intravascular coagulation (DIC) (13%).

The comparative study of the clinical epidemiological pattern of the patients corresponding to P1 and P2 is detailed in Table 1.

Discussion

In our comparative study we found an increase of the incidence of candidemia in the second period, a greater clinical seriousness at onset, an increase of the percentage of candidemias caused by non-*albicans Candida*, and a higher frequency of patients with diabetes mellitus and neurological pathology of vascular origin, without all these differences producing significant changes in their outcome (similar mortality, 50%).

The increase of incidence from 9 to 15.8 per 10,000 admitted patients represents a phenomenon equally noticed in other studies of the literature; thus, in US series it oscillates between 19 and 24 cases per 10,000 hospital admissions.[19]

On the other hand, although in different series of the literature[2,9,13,17,19] *C. albicans* continues to be the most frequent isolate in nosocomial candidemias (50–60%), different studies[4,5,11,25,26] have already shown a higher incidence of non-*albicans Candida* than of *C. albicans*, as it happens in our cohorts (66.2% versus 45.8%). This phenomenon can be related to the demographic variables, the different groups of patients studied in different hospitals and countries and the previous use of antibiotics (fluoroquinolones) and antifungals (fluconazole). Thus, *C. krusei* has been related to the presence of acute leukemia as underlying disease, the previous use of fluoroquinolones and fluconazole, although we have not been able to clearly prove this latter aspect.[6,24,25] It is also remarkable the increase in the different series, as it happens in ours, of the frequency of isolations of *C. parapsilosis* in relation with the antecedent of parenteral nutrition and in other studies also in the paediatric population, a cohort that was not included in our study.[1,6]

In the second cohort we detected one case of candidemia by *C. lusitaniae* in a critically ill haematological patient who had been hospitalised for a long time, carried central venous catheter with parenteral nutrition, had received various cycles of broad-spectrum antibiotics and prophylaxis with fluconazole and who, as expected, showed bad outcome[29] and resistance to amphotericin B. The small number of candidemias by diverse *Candida* sp. (2–3%) is similar to the result found in longer cohorts (5%).[21] These cases are mainly noticed in oncological or haematological patients who carry central venous catheters or devices for the administration of chemotherapy.

In relation with the predisposing factors, we did not find differences between our results and those appearing in the medical literature with regard to seriousness of illness at onset,

Table 1
Clinical and epidemiological characteristics of nosocomial candidemia in P1 versus P2.

Variables	P1; $N = 80$ *n* (%)	P2; $N = 107$ *n* (%)	*p*
Incidence	9.1/10,000 admissions	15.8/10,000 admissions	<0.05
Mean age (years)	51.6	60.7	<0.05
Sex			
Male	51 (63.7)	79 (73.8)	ns
Female	29 (36.3)	28 (26.2)	
Services			
Medical	7 (8.7)	35 (32.7)	<0.05
Surgical	73 (91.3)	72 (67.3)	
Candida			
C. albicans	53 (66.2)	49 (45.8)	<0.05
Non-*albicans Candida*	27 (33.7)	58 (54.2)	
C. parapsilosis	13 (16.2)	26 (24.3)	
C. glabrata	5 (6.2)	13 (12)	
C. tropicalis	6 (7.5)	12 (11.2)	
C. krusei	2 (2.5)	2 (1.9)	
C. lusitaniae	0 (0)	1 (1)	
Various *Candida* sp.	1 (1.2)	4 (3.7)	
Associated bacteraemia	16 (20)	44 (41.2)	<0.05
Underlying disease			
Neoplasia	29 (36.2)	36 (33.6)	ns
Politraumatisms	18 (22.5)	21 (19.6)	ns
Diabetes mellitus	10 (12.5)	27 (25.2)	<0.05
Cardiocirculatory	9 (11.2)	9 (8.4)	ns
Brain strokes	0 (0)	9 (8.4)	<0.05
Other	14 (17.5)	5 (4.7)	<0.05
Predisposing Factors			
Central venous catheter	81 (100)	97 (90.6)	<0.05
Parenteral nutrition	81 (100)	97 (90.6)	<0.05
Previous use of antibiotics	81 (100)	107 (100)	ns
≥2 cycles	65 (80.2)	86 (80.4)	ns
1 cycle	16 (19.8)	21 (19.6)	ns
Urinary catheter	70 (86.4)	97 (90.6)	ns
Mechanical ventilation	66 (81.4)	81 (75.7)	ns
Blood transfusions	55 (67.9)	75 (70.1)	ns
Previous surgery	35 (43.2)	84 (78.5)	<0.05
Sources of infection			
Not clarified	44 (55)	26 (24.3)	<0.05
Central venous catheter	25 (31.2)	40 (37.4)	ns
Urinary	11 (13.7)	20 (18.7)	ns
Abdominal	0 (0)	8 (7.5)	<0.05
Surgical wounds	0 (0)	4 (3.7)	ns
Burns	0 (0)	6 (5.6)	ns
Respiratory	0 (0)	3 (2.8)	ns
Initial clinical condition[31]			
Critical	23 (28.7)	52 (49.6)	<0.05
Poor–fair	57 (71.3)	55 (51.4)	
Complications	52 (65)	86 (80.4)	<0.05
Shock	21 (26.2)	36 (33.6)	
Respiratory distress	13 (16.2)	32 (30)	
Renal failure	13 (16.2)	46 (43)	
DIC	0 (0)	14 (13.1)	
Endophtalmitis	5 (6.2)	0 (0)	
Evolution			
Recovery	39 (48.7)	54 (50.5)	ns
Exitus	41 (51.3)	53 (49.5)	

sources of infection and complications developed by patients with NC.[19]

As for the percentage of resistance of non-*albicans Candida* against fluconazole, there are differences among the series corresponding to different countries and hospitals, in such a way that in some cohorts[20,23,27] it does not exceed 5%. In our series we found significant resistance of *C. glabrata* to fluconazole (8%) and 7.6% of the isolates showed intermediate or dose-dependent susceptibility. These results are similar to those of other authors.[9,17–19] As previously mentioned, this fact has been related to the higher frequency of non-*albicans Candida* and to the increase of fluconazole consumption, mainly in hospitals with a high number of oncological or haematological patients and bone marrow transplants who are administered prophylaxis with fluconazole. In this sense, another azolic agent, voriconazole, shows a higher *in vitro*[10] activity against *C. glabrata* than fluconazole. Peman et al.[16] collected information from over 27,000 isolates of yeasts and found that 5683 isolates of *C. glabrata* had a voriconazole MIC90 < 1 μg/mL against a value > 32 μg/mL in the case of fluconazole. *C. glabrata* crossed resistance to azoles is variable and can increase with the previous use of fluconazole at subtherapeutic doses, by the induction of genetically codified expulsion pumps. Thus, in isolates with fluconazole MIC > 64 μg/mL the voriconazole MIC rises and, though 13% of the isolates resistant to fluconazole keep the susceptibility against voriconazole, it would be wise to limit its use as empiric treatment in these patients, specially when there is the antecedent of previous use of fluconazole.

Mortality in the different series[13,17,19] of patients with NC oscillates between 40% and 75%. In our experience it has remained at similar levels in both periods of study (around 50%), which highlights the great severity of these infections.[8]

In conclusion, the percentage of NC by *C.* non-*albicans* has increased throughout time and mortality has not varied. Therefore, we consider that constant monitorization of patients who develop candidemia is essential, in order to be able to detect the epidemiological changes and resistance patterns in each hospital, as well as to identify the risk factors that allow early detecting of these infections and thus improving the prognosis of the patients.

Authors' disclosure

Authors have nothing to declare.

References

1. Almirante B, Rodríguez D, Cuenca-Estrella M, Planes AM, Almela M, Sanchez F, and the Barcelona Candidemia Project Study Group. Epidemiology, risk factors, and prognosis of *Candida parapsilosis* bloodstream infection: case-control population-based surveillance study of patients in Barcelona, Spain, from 2002–2003. J Clin Microbiol. 2006;44:1681–5.
2. Almirante B, Rodriguez D, Park BJ, Cuenca-Estrella M, Planes AM, Almela M, and the Barcelona Candidemia Project Study Group, et al. Epidemiology and predictors of mortality in cases of *Candida* bloodstream infection: results from population-based surveillance, Barcelona, Spain, from 2002–2003. J Clin Microbiol. 2005;43:1829–35.
3. Alonso-Valle H, Acha O, García Palomo JD, Fariñas-Alvarez C, Fernández-Matarrasa C, Fariñas MC. Candidemia in a tertiary care hospital: epidemiology and factors influencing mortality. Eur J Clin Microbiol Infect Dis. 2003;22:254–7.
4. Bedini A, Venturelli C, Mussini C, Guaraldi G, Codeluppi M, Borghi V, et al. Epidemiology of candidemia and antifungal susceptibility patterns in a Italian tertiary-care hospital. Clin Microbiol Infect. 2006;12:75–80.
5. Colombo AL, Perfect J, DiNubile M, Bartizal K, Motyl M, Hicks P, et al. Global distribution and outcome for *Candida* sp. causing invasive candidiasis: results from an international randomized double-blind study of caspofungin versus amphotericin B for the treatment of invasive candidiasis. Eur J Clin Microbiol Infect Dis. 2003;22:470–4.
6. Girmenia C, Moleti ML, Micozzi A, Iori AP, Barberi W, Foa R, et al. Breakthrough *Candida krusei* fungemia during fluconazol prophylaxis followed by breakthrough zygomycosis during caspofungin therapy in a patient with severe aplastic anemia who underwent stem cell transplantation. J Clin Microbiol. 2005;43:5395–6.
7. Gómez J, Baños V, Simarro E, Ruiz J, Requena L, Pérez J, et al. Fungemias nosocomiales en un hospital general: epidemiología y factores pronóstico 1993–1998. Enf Inf Microbiol Clin. 2001;19:304–7.
8. Luzzati R, Allegranzi B, Antozzi L, Masala L, Pegoraro E, Azzini A, et al. Secular trends in nosocomial candidaemia in non-neutropenic patients in an Italian tertiary hospital. Clin Microbiol Infect. 2005;11:908–13.

9. Marchetti O, Bille J, Fluckiger U, Eggiman Ph, Ruef Ch, Garbino J, for the fungal infection Network of Switzerland (FUNGINOS), et al. Epidemiology of candidemia in Swiss tertiary care hospitals: secular trends, 1991–2000. Clin Infect Dis. 2004;38:311–20.
10. Marco F, Danes C, Almela M, Jurado A, Mensa J, Puig de la Bellacasa J, et al. Trends in frequency and in vitro susceptibilities to antifungal agents including voriconazole and anidalafungin, of *Candida* bloodstream isolates. Results from six years study (1996–2001). Diagn Microbiol Infect Dis. 2003;46:259–64.
11. Martin D, Persat F, Piens MA, Picot S. *Candida* species distribution in bloodstream cultures in Lyon, France, 1998–2001. Eur J Clin Microbiol Infect Dis. 2005;24:329–33.
12. McCabe WR, Jackson GG. Gram negative bacteremia: I. Ecology and etiology. Arch Intern Med. 1962;110:847–55.
13. Medoff G, Dismukes WE, Pappagianis D, Diamond R, Gallis HA, Drutz D. General guidelines for the evaluation of new antifungal drugs for the treatment of systemic fungal infections. Clin Infect Dis. 1992;15(Suppl. 1): S274–81.
14. National Committee for Clinical Laboratory Standards. Reference method for broth dilution antifungal susceptibility testing of yeast: approved standard. Document M27-A2, 2nd ed. National Committee for Clinical Laboratory Standard, Wayne, PA, 2002.
15. Oude-Lashof AML, Donnelly JP, Meis JFGM, Meer JWM, Kullberg BJ. Duration of antifungal treatment and development of delayed complications in patients with candidaemia. Eur J Clin Microbiol Infect Dis. 2003;22:43–8.
16. Peman J, Canton E, Calabuig E, Bosch M, Valentin M, Viudes A, et al. Actividad in vitro del voriconazol frente a levaduras y algas con los nuevos puntos de corte del patrón de resistencia. Rev Esp Quimioter. 2006;19:21–33.
17. Peman J, Canton E, Gobernado M, and the Spanish ECMM Working Group on Candidaemia. Epidemiology and antifungal susceptibility of Candida species isolated from blood: results of a 2-year multicentre study in Spain. Eur J Clin Microbiol Infect Dis. 2005;24:23–30.
18. Pfaller MA, Diekema DJ, for the Internacional Fangal Surveillance Participant Group. Twelve years of fluconazole in clinical practice: global trends in species distribution and fluconazole susceptibility of bloodstream isolates of *Candida*. Clin Microbio Infect. 2004;10(Suppl. 1):11–23.
19. Pfaller MA, Diekema DJ. Epidemiology of invasive candidiasis: a persistent public health problem. Clin Microbiol Rev. 2007;20:133–63.
20. Pfaller MA, Messer SA, Boyken L, Tendolkar S, Hollis RJ, Diekema DJ. Variation in susceptibility of bloodstream isolates of *Candida glabrata* to fluconazole according to patient age and geographic location. J Clin Microbiol. 2003;41: 2176–9.
21. Pulimood S, Ganesan L, Alangaden G, Chandrasekar P. Polymicrobial candidemia. Diagn Microbiol Infect Dis. 2002;44:353–7.
22. Rogers E, Bone RC. Clinical indicators in sepsis and septic adult respiratory distress syndrome. Med Clin North Am. 1986;70:921–32.
23. Samra Z, Yardeni M, Peled N, Bishara J. Species distribution and antifungal susceptibility of *Candida* bloodstream isolates in a tertiary medical center in Israel. Eur J Clin Microbiol Infect Dis. 2005;24:592–5.
24. San Miguel LG, Cobo J, Otheo J, Sanchez-Sousa A, Abraira V, Moreno S. Secular trends of candidemia in a large tertiary-care hospital from 1988–2000: emergence of *Candida parapsilosis*. Infect Control Hosp Epidemiol. 2005;26: 548–52.
25. Swinne D, Watelle M, Suetens C, Mertens K, Fonteyne PA, Nolard N. A one-year survey of candidemia in Belgium in 2002. Epidemiol Infect. 2004;132: 1175–80.
26. Tortorano AM, Peman J, Bernhardt H, Klingspor L, Kibbler CC, Faure O, the ECMM Working Group on Candidaemia, et al. Epidemiology of candidaemia in Europe: results of 28-month European Confederation of Medical Mycology (ECMM) hospital-based surveillance study. Eur J Clin Microbiol Infect Dis. 2004;23:317–22.
27. Tortorano AM, Rigoni AL, Biraghi E, Prigitano A, Viviani MA, and the FIMUA-ECMM cadidaemia study group. The European Confederation of Medical Mycology (ECMM) survey of candidaemia in Italy: antifungal susceptibility patterns of 261 non-*albicans Candida* isolates from blood. J Antimicrob Chemother. 2003;52:679–82.
28. Vaqué J, y grupo de trabajo EPINE. Evolución de la prevalencia de las infecciones nosocomiales en los hospitales españoles. EPINE 1990–2003. Sociedad Española de Medicina Preventiva, Salud Pública e Higiene (SEMPSPH), 2004. p. 73–128.
29. Viudes A, Peman J, Canton E, Salavert M, Ubeda P, Lopez-Ribot JL, et al. Two cases of fungemia due to *Candida lusitaniae* and a literature review. Eur J Clin Microbiol Infect Dis. 2002;21:294–9.
30. Warren NG, Hazen KC. *Candida*, *Cryptococcus* and others yeast of medical importance. In: Murray RP, Baron EJ, Pfaller MA, Tenover FC, Yolken RH, editors. Manual of clinical microbiology, 7th ed. Washington, DC: American Society for Microbiology; 1999. p. 1184–99.
31. Winston DJ, Murphy W, Young LS. Piperacillin therapy for serious bacterial infections. Am J Med. 1980;69:225–31.