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Potential risk factors for infection with *Candida* spp. in critically ill patients

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ABSTRACT

The incidence, risk factors and prognostic factors for candidal infection were determined in a prospective study of 280 infected patients. Thirty-one (11%) patients were infected with *Candida* spp., sub-divided into 18 (58%) with *C. albicans*, and 13 (42%) with non-*albicans* spp. (six *C. glabrata*, three *C. parapsilosis*, and one each of *C. krusei*, *C. tropicalis*, *C. guilliermondii* and *C. lusitaniae*). Infection with *Candida* spp. was always associated with concurrent bacterial infection. By univariate logistic regression analysis, the degree of morbidity and the duration of mechanical ventilation were independent predictive factors for death, but infection with *Candida* spp., was not. Factors associated with *Candida* spp. infection were the degree of morbidity, intensive care unit length of stay, alterations of immune response, and the number of medical devices involved. By multivariate logistic regression analysis, the only independent risk factor for candidal infection was intensive care unit length of stay.

Keywords Antifungal resistance, antifungal therapy, *Candida*, infection, mortality

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INTRODUCTION

The incidence of fungal infections in intensive care units (ICUs) has increased dramatically in recent years. The National Nosocomial Infections Surveillance system in the USA reported an overall increase in the rate of fungal infections from 2.0 infections/1000 patients discharged in 1980 to 3.8 infections/1000 patients discharged in 1990 [1]. Similarly, Voss *et al.* [2] noted an increased incidence of candidaemia, from 4.7 cases/10 000 patient-days in 1987 to 7.4 cases/10 000 patient-days in 1994, at a large Dutch university hospital. Studies now report that fungi are involved in up to 17% of all nosocomial infections [3,4], and 9–12% of nosocomial bloodstream infections [5–7]. This increase in fungal infections is multifactorial and reflects an increased number of immunocompromised and elderly patients requiring intensive care, increased recognition, better diagnostic testing, greater use of antibiotic drugs, improvements in life-support systems, and frequent use of invasive procedures [8].

Candida spp. are the most common cause of fungal infection in critically ill patients, accounting for 85% of fungal isolates in the National Nosocomial Infections Surveillance System study [7]. *Candida albicans* is responsible for 60% of candidal infections [2,9], but non-*albicans* species are emerging increasingly as significant ICU pathogens [10,11]. In one study on candidaemia in the ICU, non-*albicans* strains were responsible for 15% of infections in 1991 and 56% in 1994 [2].

This report describes a prospective study in critically ill patients to compare the morbidity and mortality rates in patients infected with *Candida* spp. with those in patients with bacterial infections, with the hypothesis that patients infected with *Candida* spp. would have a higher magnitude of organ failure and a worse outcome. The factors that predicted candidal infection and mortality were also assessed.

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PATIENTS AND METHODS

The study was conducted prospectively in three distinct periods (April to June 1999, October to November 1999, June to September 2000) in a 31-bed medical-surgical intensive care department of a tertiary care hospital. Patients who stayed in the ICU for < 24 h were excluded. Data recorded included age, gender, cause of ICU admission (medical or surgical), previous hospital stay, total length of ICU stay, length of ICU stay after diagnosis of infection, use and duration of mechanical ventilation, haemodialysis or haemofiltration, previous antibiotic use, previous immunosuppressive therapy, APACHE (Acute Physiologic and Chronic Health Evaluation) II score [12], SOFA (Sequential Organ Failure Assessment) score [13] at admission ($SOFA_0$), maximum SOFA score during ICU stay ($SOFA_m$), SOFA score on the day of diagnosis of infection ($SOFA_{inf}$), daily blood C-reactive protein concentrations, number of medical devices (including endotracheal tube, arterial line, peripheral and central venous catheters, pulmonary artery catheter, Foley catheter, surgical drains), administration of parenteral nutrition, antifungal treatment and outcome. Procalcitonin levels were measured in 157 patients as part of the routine monitoring in these patients at the time of the study.

Patients were divided retrospectively into two groups according to the absence (group A) or presence (group B) of candidal infection. Candidaemia was defined as: (1) one blood culture that grew *Candida* spp. and either histologically documented invasive candidiasis or ophthalmic examination consistent with candidal endophthalmitis; (2) at least two blood cultures obtained at different times from a peripheral vein that grew the same *Candida* sp.; or (3) one blood culture obtained peripherally and one blood culture obtained through an indwelling central line, both of which grew an identical *Candida* sp. [4]. Patients with one positive blood culture drawn through an intravenous line and a positive semi-quantitative catheter tip culture were not considered infected unless they satisfied one of the other criteria. Severe non-bloodstream candidal infections were defined as *Candida* spp. isolated from a normally sterile body site, and the presence of at least one of the following: fever (≥ 38.5 °C), or hypothermia (< 36 °C); unexplained prolonged arterial hypotension (systolic blood pressure of < 90 mmHg for at least 2 h, unresponsive to volume challenge); or absence of response to adequate antibiotic treatment for a suspected bacterial infection [4]. Infections were defined according to the Centers for Disease Control guidelines [14].

Yeast isolates were identified by the API ID 32C system (bioMérieux, Marcy-l'Etoile, France) and growth on CHROMagar Candida medium (CHROMagar, Paris, France). Antifungal susceptibility testing for fluconazole, itraconazole, 5-flucytosine, ketoconazole and amphotericin B was performed by Sensititre YeastOne (Trek Diagnostic Systems, Westlake, OH, USA) according to the manufacturer's recommendations. Susceptibility breakpoints for fluconazole, itraconazole and 5-flucytosine were those recommended by the National Committee for Clinical Laboratory Standards [15]. For amphotericin, a susceptibility breakpoint has not yet been defined, but for this study, susceptibility was defined as an MIC of ≤ 1 mg/L, based on the literature [16]. MICs were expressed as susceptible, susceptible but dose-dependent, or resistant, according to the National Committee for Clinical Laboratory Standards recommendations [15].

Statistical analysis

Student's *t*-test was used to compare continuous variables and a chi-square test to compare categorical data. Results are expressed as mean values ± SD. Univariate and multivariate logistic regression analyses (STATISTIX 3.1 software; Analytical Software, Tallahassee, FL, USA) were performed to identify variables associated with high-risk factors. For all statistical analyses, $p < 0.05$ was considered to be statistically significant.

RESULTS

Of 949 patients who stayed in the ICU for > 24 h, 280 (29%) had, or developed, an infection. Of those, 249 (89%) had a bacterial infection (group B) and 31 (11%) met the criteria for candidal infection (group A). Hence, the proportion of ICU patients with candidal infection was 3%. The mean time of onset of candidal infection was 9 ± 3 days after ICU admission. The characteristics of the infected patients are presented in Table 1. *C. albicans* was identified in 18 (58%) patients, and non-*albicans* species in 13 (42%; Fig. 1).

The main site of infection was the bloodstream, including catheter-related infections, followed by lung, abdomen and urinary tract (Table 2). There were no significant differences regarding the site of infection between *C. albicans* and non-*albicans* species.

Infection with *Candida* spp. in all cases followed a bacterial infection (mean 5 ± 2 days after the onset of bacterial infection). Bacterial pathogens included resistant organisms (58%), notably methicillin-resistant *Staphylococcus aureus* (11 patients), *Enterobacter aerogenes* (three patients), *Klebsiella pneumoniae* (two patients) and *Acinetobacter baumannii* (two patients), and susceptible strains (42%), notably *Pseudomonas aeruginosa* (seven patients), *E. aerogenes* (three patients), methicillin-sensitive *S. aureus* (five patients), *K. pneumoniae* (two patients) and *Enterococcus faecalis* (four patients).

There was no difference between the two groups in age, gender or type of patient (medical/surgical). There was also no difference between the two groups in the degree of morbidity, as assessed by both the APACHE II and SOFA scores, except that the degree of organ failure on the day the infection was diagnosed ($SOFA_{inf}$) was higher in the patients with candidal infection (9.8 ± 1.3 vs. 7.0 ± 3.0; p 0.03). Patients with candidal infection had a longer total length of

Table 1. Characteristics of infected patients

	Infection with *Candida* spp. (group A) *n* = 31	Bacterial infection alone (group B) *n* = 249	p value
Age (range) in years	64 (24–81)	58 (18–81)	NS
Medical:surgical patients	16:15	162:87	NS
APACHE II	18.4 ± 6.0	17.0 ± 7.0	NS
$SOFA_0$	8.4 ± 1.6	7.0 ± 3.0	NS
$SOFA_m$	10.4 ± 1.3	9.0 ± 4.0	NS
$SOFA_{inf}$	9.8 ± 1.3	7.0 ± 3.0	0.03
Hospital stay before ICU admission (days)	4.6 ± 5.6	3.0 ± 3.3	NS
Total length of ICU stay (days)	18 (12–36)[b]	9 (2–68)	0.02
Length of ICU stay after diagnosis of infection (days)	10 (8–22)[b]	5 (3–11)	0.03
Duration of mechanical ventilation (days)	10.9 ± 4.1[b]	4.0 ± 4.7	0.03
Duration of haemodialysis (days)	1.7 ± 2.2[b]	0.6 ± 2.3	0.03
Immunosuppression	10/31 (32%)	74/249 (30%)	NS
Parenteral nutrition	9/31 (29%)	66/249 (26%)	NS
AB therapy			
Number/day	3.6 ± 1.4[b]	1.6 ± 2.0	0.02
Total number of days	14.4 ± 4.4[b]	5.2 ± 6.1	0.01
Previous AB days[a]	11 ± 3	–	
Previous AB number/day[a]	2.1 ± 3.2	–	
Number of medical devices	2.6 ± 1.5	2.6 ± 1.5	NS
Blood levels of CRP	16.3 ± 6.0	13.4 ± 8.8	NS
Blood levels of PCT	4.4 ± 4.6	4.1 ± 3.7	NS
Mortality	15 (48%)	92 (37%)	0.09

ICU, intensive care unit; AB, antibiotic; CRP, C-reactive protein; PCT, procalcitonin; APACHE II, Acute Physiologic and Chronic Health Evaluation II score; SOFA, Sequential Organ Failure Assessment score; NS, not significant.
[a]Before *Candida* spp. infection.
[b]Group A vs. group B.

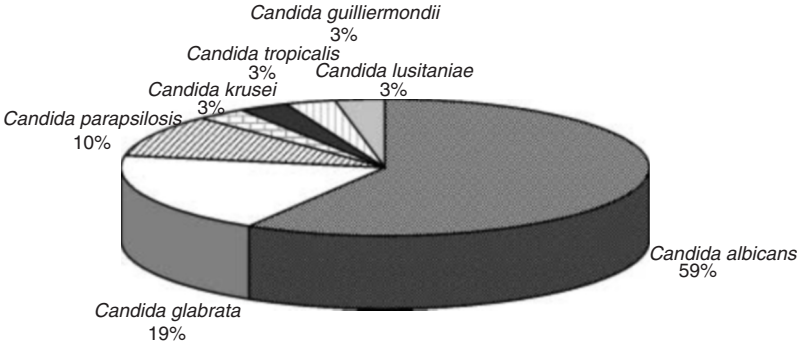

Fig. 1. Distribution of *Candida* spp. isolated from the 31 infected patients.

Table 2. Source of infections in patients with *Candida* spp.

Source of infection	*Candida* spp. infections *n* = 31	*Candida albicans* *n* = 18	*Candida* non-*albicans* *n* = 13	Positive blood culture	*Candida* endophthalmitis
Blood[a]	14	8	6	14	8
Lung	8	4	4	8	4
Abdomen	6	4	2	6	4
Urine	3	2	1	3	2

[a]Including catheter-related infections.

stay (p 0.02), a longer length of stay after diagnosis of infection (p 0.03), and a greater application and duration of mechanical ventilation (p 0.04 and p 0.03, respectively) and of haemodialysis (p 0.03) than patients with bacterial infection. Mortality was also higher in patients infected with *Candida* spp., although this difference was not statistically significant (48% vs. 37%; p 0.09). Mortality was similar in patients infected with *albicans* and non-*albicans* species (47% vs. 50%). By univariate logistic regression, the degree of morbidity and the duration of mechanical ventilation, were independent predictive factors for death, but infection with *Candida* spp. was not.

There were no differences regarding the degree of immunosuppression or the administration of

parenteral nutrition between the two groups of patients. There were no significant differences in blood levels of C-reactive protein or procalcitonin between the two groups on the day that infection was diagnosed.

Patients with *Candida* spp. infection received more antibiotics, with a significant difference in the total use of antibiotics in days (14.4 ± 4.4 vs. 5.2 ± 6.1 days; p 0.01) and in the number of antibiotics/day (3.6 ± 1.4 vs. 1.6 ± 2.0; p 0.02).

Univariate logistic regression revealed the degree of morbidity (p 0.01), the length of ICU stay (p 0.03), previous antibiotic use (p 0.03), the use of mechanical ventilation (p 0.03) and the number of medical devices (p 0.04) as independent factors associated with *Candida* spp. infection compared to bacterial infection. Multivariate logistic regression revealed only the ICU length of stay as an independent predictor for candidal infection (p 0.03).

Among the 31 infected patients, 20 were treated effectively with fluconazole, and eight with amphotericin B; three patients who were unresponsive to fluconazole were switched to amphotericin B. The MICs for the antifungal agents tested are presented in Fig. 2.

DISCUSSION

The incidence of *Candida* spp. infections is increasing [1], along with a shift towards non-*albicans* spp. [10]. In the present study, an infection with *Candida* spp. was diagnosed in 3% of patients admitted for >24 h to the ICU, representing 11% of all infections. This result is in agreement with data from the EPIC study [3], showing that 17.1% of infected patients had a fungal infection. Importantly, the incidence of *Candida* spp. infections is highly dependent on the patient population. The ICU department investigated in the study was mixed medical-surgical, but did not include haematology patients; therefore, the results cannot be generalised to ICUs that include neutropenic patients.

Non-*albicans* species were found in 42% of patients infected with *Candida* spp. In a retrospective study, Blot *et al*. [17] found that, of 57 cases of candidaemia, 41 (72%) were caused by *C. albicans* and 16 (28%) by non-*albicans* species, while Nucci *et al*. [18] reported 37% *C. albicans* and 63% non-*albicans* in a series of 145 patients with candidaemia. According to the National Nosocomial

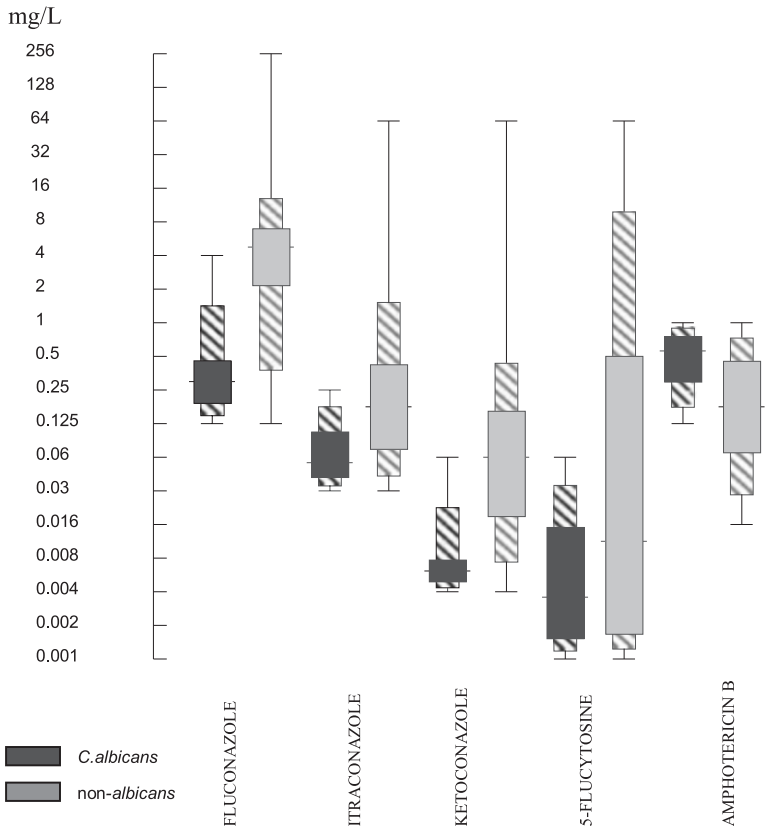

Fig. 2. Distribution of the MICs (interquartile with 10–90% range) of antifungal agents for the *C. albicans* and non-*albicans* isolates from the 31 patients infected with *Candida* spp.

Infections Surveillance System [19], *C. albicans* was responsible for 76%, and non-*albicans* species for 10%, of nosocomial fungal infections between 1980 and 1990. The differences between the percentages of *Candida* spp. found in the different studies can be attributed largely to variations in local microflora.

Infections involving *Candida* spp. have high fatality rates in modern critical care settings. Because of great variabilities in demographic characteristics, severity of disease and definitions of *Candida* spp. infections, outcome comparisons are difficult to perform. The crude mortality rate in this study was 48% for patients with *Candida* spp., compared to 37% in patients with bacterial infection. In a well-matched case control study of candidaemia in ICU patients, Wey *et al.* [20] reported a crude mortality rate of 57%, while Petri *et al.* [21] observed a mortality rate of 31% in a series of 251 patients with at least one positive *Candida* spp. culture.

Serial blood levels of C-reactive protein and procalcitonin have been proposed as markers of fungal infections [22,23]. In the present study, there was no difference between the levels of these markers in patients infected with *Candida* spp. and in those who had a bacterial infection, but since all *Candida* spp. infections were associated with a bacterial infection, any direct association with fungal infection is difficult to assess.

Many risk factors for infections with *Candida* spp. have been identified, including *Candida* colonisation [24], candiduria [25], use of antibiotics [20,26], severity of underlying disease [4,26], alterations of immune response [27,28], central venous catheters [29], total parenteral nutrition [29], major surgical operations [29], states of altered tissue perfusion [30], malnutrition [30], diabetes [30], trauma [30], cancer [30], chemotherapy [30] and acute renal failure [29]. In our series, univariate logistic regression revealed the degree of morbidity, the total length of ICU stay, previous antibiotic use, the use of mechanical ventilation and the number of medical devices as independent factors associated with *Candida* spp. infection compared to bacterial infection, but a multiple logistic model found that only the ICU length of stay was an independent predictor for *Candida* spp. infection. Interestingly, although described increasingly in ICU patients [31–34], antifungal resistance was not a problem in the patients studied. This finding may be explained by the small number of patients included, or perhaps also by the strict policy for antifungal administration in our department.

It was concluded that infections with *Candida* spp. in critically ill patients were associated with the presence of other infections, and particularly with resistant bacterial strains. A longer length of ICU stay is predictive of infection with *Candida* spp.

REFERENCES

1. Beck-Sague C, Jarvis WR. Secular trends in the epidemiology of nosocomial fungal infections in the United States, 1980–1990. National Nosocomial Infections Surveillance System. *J Infect Dis* 1993; **167**: 1247–1251.
2. Voss A, le Noble JL, Verduyn LF, Foudraine NA, Meis JF. Candidemia in intensive care unit patients: risk factors for mortality. *Infection* 1997; **25**: 8–11.
3. Vincent JL, Bihari D, Suter PM *et al.* The prevalence of nosocomial infection in intensive care units in Europe—the results of the EPIC study. *JAMA* 1995; **274**: 639–644.
4. Pittet D, Monod M, Suter PM, Frenk E, Auckenthaler R. *Candida* colonization and subsequent infections in critically ill surgical patients. *Ann Surg* 1994; **220**: 751–758.
5. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients. Excess length of stay, extra costs, and attributable mortality. *JAMA* 1994; **271**: 1598–1601.
6. Pittet D, Garbino J. Fungal infections in the critically ill. *Curr Opin Crit Care* 1995; **1**: 369–380.
7. Richards MJ, Edwards JR, Culver DH, Gaynes RP. Nosocomial infections in medical intensive care units in the United States. National Nosocomial Infections Surveillance System. *Crit Care Med* 1999; **27**: 887–892.
8. Flanagan PG, Barnes RA. Fungal infection in the intensive care unit. *J Hosp Infect* 1998; **38**: 163–177.
9. Nolla-Salas J, Sitges-Serra A, Leon-Gil C *et al.* Candidemia in non-neutropenic critically ill patients: analysis of prognostic factors and assessment of systemic antifungal therapy. Study Group of Fungal Infection in the ICU. *Intens Care Med* 1997; **23**: 23–30.
10. Nguyen MH, Peacock JE, Morris AJ *et al.* The changing face of candidemia: emergence of non-*Candida albicans* species and antifungal resistance. *Am J Med* 1996; **100**: 617–623.
11. Pfaller MA, Jones RN, Messer SA, Edmond MB, Wenzel RP. National surveillance of nosocomial blood stream infection due to *Candida albicans*: frequency of occurrence and antifungal susceptibility in the SCOPE Program. *Diagn Microbiol Infect Dis* 1998; **31**: 327–332.
12. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; **13**: 818–829.
13. Vincent JL, Moreno R, Takala J *et al.* The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intens Care Med* 1996; **22**: 707–710.
14. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control* 1988; **16**: 128–140.

15. National Committee for Clinical Laboratory Standards. *Reference method for broth dilution antifungal susceptibility testing of yeasts*. Wayne, PA: NCCLS, 1997.
16. Nguyen MH, Clancy CJ, Yu VL *et al*. Do in vitro susceptibility data predict the microbiologic response to amphotericin B? Results of a prospective study of patients with *Candida* fungemia. *J Infect Dis* 1998; **177**: 425–430.
17. Blot S, Vandewoude K, Hoste E, Poelaert J, Colardyn F. Outcome in critically ill patients with candidal fungaemia: *Candida albicans* vs. *Candida glabrata*. *J Hosp Infect* 2001; **47**: 308–313.
18. Nucci M, Colombo AL, Silveira F *et al*. Risk factors for death in patients with candidemia. *Infect Control Hosp Epidemiol* 1998; **19**: 846–850.
19. Jarvis WR. Epidemiology of nosocomial fungal infections, with emphasis on *Candida* species. *Clin Infect Dis* 1995; **20**: 1526–1530.
20. Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP. Risk factors for hospital-acquired candidemia: a matched case-control study. *Arch Intern Med* 1989; **149**: 2349–2353.
21. Petri MG, Konig J, Moecke HP *et al*. Epidemiology of invasive mycosis in ICU patients: a prospective multicenter study in 435 non-neutropenic patients. Paul-Ehrlich Society for Chemotherapy, Divisions of Mycology and Pneumonia Research. *Intens Care Med* 1997; **23**: 317–325.
22. Young B, Gleeson M, Cripps AW. C-reactive protein: a critical review. *Pathology* 1991; **23**: 118–124.
23. Cooper D, Sharples L, Cornelissen J, Wallwork J, Alexander G, Trull A. Comparison between procalcitonin, serum amyloid A, and C-reactive protein as markers of serious bacterial and fungal infections after solid organ transplantation. *Transplant Proc* 2001; **33**: 1808–1810.
24. Krause W, Matheis H, Wulf K. Fungemia and funguria after oral administration of *Candida albicans*. *Lancet* 1969; **i**: 598–599.
25. Kauffman CA, Vazquez JA, Sobel JD *et al*. Prospective multicenter surveillance study of funguria in hospitalized patients. The National Institute for Allergy and Infectious Diseases (NIAID) Mycoses Study Group. *Clin Infect Dis* 2000; **30**: 14–18.
26. 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**: 414–421.
27. Diamond RD. Immune response to fungal infection. *Rev Infect Dis* 1989; **11**(suppl 7): S1600–S1604.
28. Sobel JD. *Candida* infections in the intensive care unit. *Crit Care Clin* 1988; **4**: 325–344.
29. Blumberg HM, Jarvis WR, Soucie JM *et al*. Risk factors for candidal bloodstream infections in surgical intensive care unit patients: the NEMIS prospective multicenter study. The National Epidemiology of Mycosis Survey. *Clin Infect Dis* 2001; **33**: 177–186.
30. Komshian SV, Uwaydah AK, Sobel JD, Crane LR. Fungemia caused by *Candida* species and *Torulopsis glabrata* in the hospitalized patient: frequency, characteristics, and evaluation of factors influencing outcome. *Rev Infect Dis* 1989; **11**: 379–390.
31. Rocco TR, Reinert SE, Simms HH. Effects of fluconazole administration in critically ill patients: analysis of bacterial and fungal resistance. *Arch Surg* 2000; **135**: 160–165.
32. Gleason TG, May AK, Caparelli D, Farr BM, Sawyer RG. Emerging evidence of selection of fluconazole-tolerant fungi in surgical intensive care units. *Arch Surg* 1997; **132**: 1197–1201.
33. Kam LW, Lin JD. Management of systemic candidal infections in the intensive care unit. *Am J Health Syst Pharmacol* 2002; **59**: 33–41.
34. Rex JH, Sobel JD. Prophylactic antifungal therapy in the intensive care unit. *Clin Infect Dis* 2001; **32**: 1191–1200.