Antifungal prophylaxis with azoles in high-risk, surgical intensive care unit patients: A meta-analysis of randomized, placebo-controlled trials*

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Objective: **The use of antifungal prophylaxis remains controversial in most populations including surgical intensive care unit patients. A meta-analysis of randomized controlled trials was performed to evaluate the safety and effectiveness of azoles as antifungal prophylaxis in high-risk patients receiving treatment in the surgical intensive care unit.**

Data Source: **Data were obtained from PubMed, Current Contents, Cochrane central register of controlled trials, and references from relevant articles.**

Study Selection: **Randomized controlled trials using azoles as antifungal prophylaxis vs. placebo were included in the study.**

Data Extraction: **Two independent reviewers extracted data concerning the development of fungal infections (superficial or invasive), adverse effects, and mortality.**

Synthesis: **Six randomized controlled trials were included in the main analysis. Publication bias and statistically significant heterogeneity were not observed among the analyzed studies. Patients receiving antifungal prophylaxis developed fewer episodes of candidemia (odds ratio [OR] = 0.28, 95% confidence interval [CI] 0.09–0.86), nonbloodstream invasive fungal infections (OR = 0.26, 95% CI 0.12–0.53), and noninvasive (superficial) fungal infections (OR = 0.22, 95% CI 0.11–0.43), respectively. No reduction in mortality was observed among patients who received azole prophylaxis (OR = 0.74, 95% CI 0.52–1.05). There was no significant difference in reported adverse effects (OR = 1.28, 95% CI 0.82–1.98).**

Conclusions: **Despite its limitations, our meta-analysis suggests that the prophylactic use of azoles in high-risk surgical intensive care unit patients is associated with a reduction of fungal infections but not in all-cause mortality. However, although not noted in the analyzed randomized controlled trials, there is concern about the use of azoles due to possible shift toward non-*albicans* species and development of resistance to azoles. (Crit Care Med 2006; 34:1216–1224)**

KEY WORDS: azole; amphotericin B; fluconazole; itraconazole; ketoconazole; prevention; polyene; surgery; transplantation

Candida species are part of the normal human skin and mucous membrane microflora. However, these yeasts may also represent important pathogens causing opportunistic infections of increasing frequency in specific populations. According to the Hospital Infection Program released from the Centers for Disease Control and Prevention, the incidence of fungal infections increased between 1980 and 1990 from 2.0 to 3.8 infections per 1,000 discharges, including a significant increase of candidemia (1). *Candida* species are more commonly isolated from patients of burn or trauma intensive care units (ICUs) and patients with abdominal surgery, hematologic malignancies, and solid organ and bone marrow transplantation (1). More specifically, *Candida* spp are the fourth more common pathogen isolated from blood in surgical intensive care unit (SICU) patients (2). Furthermore, the development of such infections is associated with increased overall and attributable mortality (ranging in different studies from 20% to 85% and from 30% to 60%) and with morbidity, which lengthens the duration of ICU stay and increases the cost of hospitalization (2).

Many risk factors contributing to the development of fungal infections in SICU and other high-risk patients have been identified (3); however, their predictive value remains unclear. Among them, prior colonization with *Candida* spp appears to be of special importance, since the colonizing and the offending fungus are identical in 84–94% of cases (4, 5), and the probability of *Candida* spp infection in the absence of previous colonization is very low (negative predictive value 94–100%). In addition, the symptoms and signs of fungal infections are nonspecific, and the available microbiological (including blood cultures) and imaging tests for early diagnosis usually do not provide a definite diagnosis (6, 7).

Prophylaxis with antifungal regimens has been proposed as an effective (and probably cost-effective) approach to prevent such infections in high-risk patients (8). Azoles and polyenes were used in a number of randomized controlled trials to assess their effectiveness as prophylactic regimens. Azoles are associated with fewer adverse effects compared with polyenes and can be administered orally. On the other hand, azoles are suspected of

***See also p. 1286.**

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contributing to selection of resistant *Candida* isolates and a shift toward wild non-*albicans* species (1, 9). In most studies, the use of a prophylactic regimen led to a decrease of opportunistic fungal infections, whereas the effect on mortality was not resolved. We performed a meta-analysis of randomized controlled trials (RCTs) in a defined patient population, namely SICU patients, to reassess their safety and effectiveness on a bigger scale and clarify the issue of mortality.

METHODS

Data Sources

Relevant RCTs were identified through a search of PubMed (until February 2005), Current Contents, Cochrane central register of RCTs, and references from relevant articles, including review papers. Search terms included *prophylaxis*, *prevention*, *antifungal*, *azoles*, *fluconazole*, *ketoconazole*, *itraconazole*, *miconazole*, *clotrimazole*, *polyenes*, *amphotericin B*, *nystatin*, *surgical*, *transplantation*, and *intensive care unit*.

Selection of Randomized Controlled Trials

Two independent reviewers performed a literature search and examined the identified RCTs for further evaluation of data on safety, effectiveness, and mortality. A study was considered eligible if a) it was a randomized, placebo-controlled clinical trial; b) it focused on the role of azole antifungal regimens as prophylaxis against fungal infections (mainly against *Candida*), in high-risk, surgical ICU patients; and c) it assessed the effectiveness and/or toxicity of triazoles as well as mortality. No restriction in language was set. Both blind and nonblind RCTs were included in the analysis. RCTs focusing on pharmacokinetic and/or pharmacodynamic variables were excluded. RCTs studying the effect of azole derivatives on adrenal hormone production and RCTs in which the azoles were used for preemptive or early empirical therapy were also excluded. RCTs using antifungal prophylaxis with amphotericin B and/or nystatin (liposomal or not, alone or in combination with other antifungal agents, systemic or topical, or as part of a regimen for selective bowel decontamination) or comparing a polyene with an azole antifungal agent were considered ineligible for the present meta-analysis.

Definitions

Fungal Infections. The definitions of the various types of fungal infections (candidemia, nonbloodstream invasive fungal infections, and superficial fungal infections [skin or mucosal]) were based on the definitions provided in the reported RCTs. In brief, candidemia was defined as the isolation of a *Candida* species in at least one blood culture. An invasive fungal infection diagnosis required positive histologic findings from deep tissues, with or without clinical symptoms, signs, or radiologic lesions suggestive of this type of infection. The isolation of *Candida* species from a biopsy specimen from the peritoneal cavity or the peritoneal fluid and clinical evidence of infection were necessary for the diagnosis of intra-abdominal candidiasis. Noninvasive (superficial) fungal infections were defined as infections with clinical symptoms and/or signs of oral, esophageal (without histologic proof for invasive candidiasis), superficial wound, lower urinary tract, and vaginal candidiasis, with positive cultures of specimens from the site of infection.

High- and Low-Risk Patients. Medical or surgical patients having three or more risk factors associated with fungal infections were considered high risk for the development of such an infection, whereas those with two or fewer risk factors were considered low-risk patients. Patients undergoing transplantation were considered high risk for the development of fungal infections if they were expected to stay in the ICU for >5 days following the operation.

Adverse Effects. No specific definitions were reported for various types of drug toxicity, including nephrotoxicity and hepatoxicity, in most of the analyzed RCTs, although numerical data about drug toxicity were provided in some of them. Hepatotoxicity was defined as elevation of liver function tests more than five times than the upper normal limit in one of the RCTs.

Data Extraction

The following data were extracted from each study: year of publication, clinical setting, patient population, numbers of patients, antifungal agents and doses used, clinical and microbiological outcomes, toxicity, statements of the authors concerning the development of resistant *Candida* species or a shift toward colonization or infection from non-*albicans* species, and mortality. Data were extracted by two independent reviewers. Any disagreement between the two reviewers was resolved by consensus meetings of the authors.

Outcomes

The development of fungal infections, all-cause mortality, and adverse effects due to study regimens were considered as primary outcome measures for the present meta-analysis. Development of fungal infections was further analyzed using four different outcome measures as defined previously: candidemia, nonbloodstream invasive fungal infections, and noninvasive (superficial) fungal infections. Mortality was also analyzed in the subset of studies that included exactly the same study azole and the same patient population. All-cause mortality was analyzed based on the reported data for mortality during the study period.

Data Analysis

Statistical analyses were performed using the Meta-analyst software (Joseph Lau, Tufts University School of Medicine, Boston, MA). The heterogeneity between RCTs was assessed by using a chi-square test; $p < .10$ was defined to note statistical significance in the analysis of heterogeneity. Publication bias was assessed by the funnel plot method using Egger's test. Pooled odds ratios (OR) and 95% confidence intervals (CI) for all primary and secondary outcomes were calculated, using both the Mantel-Haenszel fixed effects and the DerSimonian-Laird random effects models. Results from the fixed effects model are presented only when no heterogeneity between RCTs was observed; otherwise results from the random effects model are presented.

RESULTS

Randomized Controlled Trials

We identified 45 published RCTs, performed on medical and surgical ICU patients at risk of fungal infections. Of those RCTs, 18 were excluded because amphotericin B or nystatin was used as part of a selective bowel decontamination regimen (10–27), six because amphotericin B or nystatin alone or in combination with other antifungal agents was compared with various antifungal agents including azoles or the lipid forms of amphotericin B (28–33), three because amphotericin B or nystatin was compared with placebo or no drug (34–36), three because they compared the effectiveness of azole derivatives against placebo in nonsurgical, non-ICU patients (37–39), and three because they compared azoles with placebo in preterm, low-weight infants (40–42). In addition, one RCT was excluded because one perioperative dose of fluconazole was used as prophylaxis (43), one because the primary outcome was the *Candida* colonization and/or infection of prosthetic devices in postlaryngectomy patients under prophylaxis with fluconazole (44), one because it compared the effectiveness of prophylactic itraconazole vs. fluconazole (45), one because it was conducted in a mixed low- and high-risk patient population and it was not placebo controlled (46), and one because it was performed in low-risk surgical patients (47).

In Figure 1, we present a flow diagram describing the selection process applied to identify the pool of RCTs used in the final analysis. An RCT that studied the value of antifungal prophylaxis in surgical ICU patients with septic shock due to bacterial pathogens (48) was used only in the secondary analysis, together with the other six RCTs of the main analysis (49–54), since septic shock represents a special condition. This is mainly because the patients enrolled in this RCT already had an established serious bacterial infection leading to septic shock, whereas the patients enrolled in the other RCTs that were included in our meta-analysis had several risk factors for fungal infections but septic shock was not an inclusion criterion. Two of the included RCTs reported results of both medical and surgical patients: Garbino et al. (50) with 62% surgical patients and Pelz et al. (51) with 92% surgical patients.

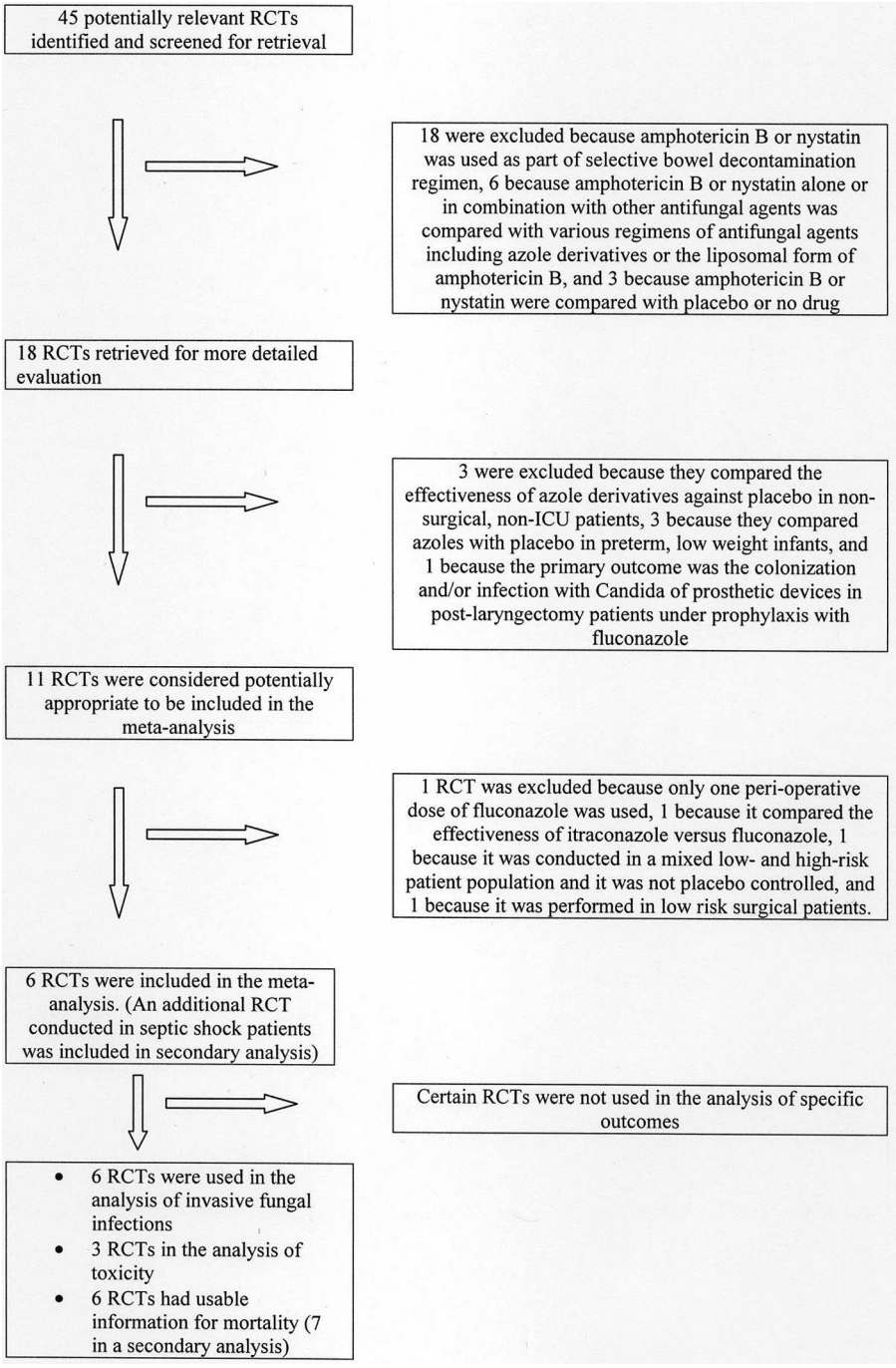

Figure 1. Flow diagram of reviewed randomized controlled trials (*RCTs*). *ICU*, intensive care unit.

The main characteristics of all RCTs used in the meta-analysis are shown in Table 1. Risk factors for fungal infections that were commonly present in patients enrolled in the RCTs that were included in our meta-analysis were fungal colonization before enrollment, diabetes, solid tumors, abdominal surgery, presence of central and peripheral venous catheters for >3 days, exposure to antibiotics, and intubation or mechanical ventilation. The duration of hospitalization and ICU stay varied in the different RCTs; however, there was no imbalance between the compared treatment groups in the individual RCTs. There was also no difference in the severity of the underlying disease between patients in the prophylaxis or the placebo group, based on the reported data, including Acute Physiology and Chronic Health Evaluation II and III scores. No publication bias was found by the funnel plot method using Egger's test.

Administration of Study Drugs

Azoles as antifungal prophylaxis were administered either intravenously or orally. Fluconazole was administered intravenously in two RCTs and orally in one RCT, whereas in one RCT it was administered intravenously before the operation and switched to oral administration at a later stage. The dosages of the administered drugs are shown in Table 1. The duration of administration of antifungal prophylaxis or placebo varied in different RCTs, but there was no statistical difference in duration of therapy between the compared treatment groups in the individual RCTs. When itraconazole (49) or ketoconazole (54) was administered, plasma levels were measured to verify the absorption of the prophylactic medications; effective plasma levels were achieved (>0.25 mg/L for itraconazole and >5 mg/L for ketoconazole) in most of the patients.

Development of Fungal Infections

Outcome data from the selected RCTs are presented in Table 2. Data on the development of fungal infections were reported in all RCTs. Antifungal prophylaxis with azoles, compared with placebo, was significantly associated with fewer fungal infections (816 patients, fixed effects model, OR = 0.20, 95% CI 0.13–0.32). Odds ratios for the development of invasive fungal infections and candidemia in individual RCTs as well as the pooled odds ratio are presented in Figure 2. The

Table 1. Characteristics of the randomized controlled trials included in the meta-analysis

Study	Year of Publication	Study Type	Population	Antifungal Prophylaxis	Duration of Antifungal Prophylaxis	Other Medication	ITT (total)	APACHE Score[a]	Fungal Colonization on Enrollment, %
Jacobs et al. (48)	2003	DB placebo-controlled RCT	Adults, bacterial septic shock	Fluonazole IV 200 mg every 24 hrs itraconazole PO, 5 mg/kg preoperatively, then 2.5 mg/kg every 12 hrs	NA	Antibiotics, noradrenaline, insulin	71	19 vs. 18	ND
Sharpe et al. (49)	2003	DB placebo-controlled RCT	Adults, liver transplantation		6 wks	Corticosteroids, cyclosporine, azathioprine	71	ND	52.1 vs. 36.8
Garbino et al. (50)	2002	DB placebo-controlled RCT	Adults, ICU and surgical ICU	Fluconazole IV 100 mg every 24 hrs	8 days	Gut decontamination every 4 hrs (vancomycin 1 g, polymyxin B 150 mg, neomycin 1 g)	204	21 vs. 21	46.6 vs. 49.5
Pelz et al. (51)	2001	Placebo-controlled RCT	Adults, surgical ICU	Fluconazole PO, loading dose 800 mg, then 400 mg every 24 hrs and adjusted to renal function	NA	Immunosuppresive drugs, antibiotics	260	63 vs. 65	73.1 vs. 80.8
Winston et al. (52)	1999	DB placebo-controlled RCT	>16 yrs, liver transplantation	Fluconazole 400 mg every 24 hrs adjusted to renal function, IV preoperatively, PO postoperatively	10 wks	Corticosteroids, cyclosporine, azathioprine, OKT3	212	ND	68.5 vs. 59.5
Eggimann et al. (53)	1999	DB placebo-controlled RCT	>12 yrs, surgical patients with GI diseases	Fluconazole IV, 400 mg every 24 hrs	15–17 days	Antibiotics, corticosteroids	49	13 vs. 13	43.5 vs 35
Slotman and Burchard (54)	1987	DB placebo-controlled RCT	Adults, surgical ICU	Ketoconazole PO 200 mg every 24 hrs	21 days or till discharge from ICU	Antibiotics, corticosteroids	74	ND	17 patients, all excluded from the analysis

ITT, intention to treat; APACHE, Acute Physiology and Chronic Health Evaluation; DB, double blind; RCT, randomized controlled trial; IV, intravenously; NA: not applicable; ND, not described; PO, orally; ICU, intensive care unit; GI, gastrointestinal.

[a]APACHE II for all except APACHE III for the study by Pelz et al.

use of azoles as antifungal prophylaxis was significantly associated with fewer episodes of candidemia (604 patients, fixed effects model, OR = 0.28, 95% CI 0.09–0.86), fewer nonbloodstream invasive fungal infections (604 patients, fixed effects model, OR = 0.26, 95% CI 0.12–0.53), and noninvasive (superficial) fungal infections (816 patients, fixed effects model, OR = 0.22, 95% CI 0.11–0.43).

Mortality

All-cause mortality during the whole study period (based on the reported data) was available in four RCTs. In two additional RCTs, only the deaths occurring during the ICU stay were reported. In Figure 3 we present data from individual RCTs as well as pooled data on mortality. Mortality in high-risk patients receiving azoles as anti-fungal prophylaxis was not lower compared with placebo recipients (847 patients, fixed effects model, OR = 0.74, 95% CI 0.52–1.05). The same result was also observed in subgroup analyses, in which fluconazole was used as antifungal prophylaxis (50–53) (719 patients, fixed effects model, OR = 0.81, 95% CI 0.56–1.18), and for RCTs not conducted in transplant recipients (50, 51, 53, 54) (564 patients, fixed effects model, OR = 0.80, 95% CI 0.54–1.19). A subset analysis conducted on RCTs using only surgical patients (49, 51–54) also showed that azole prophylaxis was not associated with a reduction in mortality (643 patients, fixed effects model, OR = 0.64, 95% CI 0.41–1.01). Finally, a meta-analysis after incorporating one RCT with prophylactic use of fluconazole in ICU patients with septic shock due to bacteria (48) showed that azole prophylaxis was associated with a statistically significant reduction in overall mortality (918 patients, fixed effects model, OR = 0.68, 95% CI 0.49–0.95).

Adverse Effects—Development of Resistance

Numerical data regarding adverse effects were reported in three RCTs (49, 52, 53). The use of antifungal prophylaxis with azoles was associated with more adverse effects; however, this finding was

Table 2. Outcome data from the selected randomized controlled trials used in the meta-analysis

Study	Fungal Colonization After Treatment, %	Mortality Rate, %	Fungal Infections, %				Adverse Effects, %	Changes in Susceptibility of *Candida* Species	Shift Toward Non-*Candida Albicans* Species
			Candidemia	Non-bloodstream Invasive	Noninvasive	Total[a]			
Jacobs et al. (48)	ND	34.4 vs. 59	0 vs. 0	0 vs. 0	3 vs. 5.1	3 vs. 5.1	NA	ND	ND
Sharpe et al. (49)	ND	3 vs. 15.8	0 vs. 0	4 vs. 16.2	0 vs. 8.1	4 vs. 24.3	30.3 vs. 28.9	ND	ND
Garbino et al. (50)	74.8 vs. 89.1	38.8 vs. 40.6	1 vs. 8.9	2.9 vs. 1	1.9 vs. 5.9	3.9 vs. 15.9	NA	No resistance	no
Pelz et al. (51)	ND	10.8 vs. 12.3	0 vs. 2.5	3.4 vs. 13.2	2.6 vs. 3.3	6 vs. 16.5	NA	No changes in MICs	No association with prophylaxis
Winston et al. (52)	34.1 vs. 78.3	11.1 vs. 14.4	ND	ND	3.7 vs. 27.9	9.3 vs. 43.3	39.8 vs. 26.9	ND	No association with prophylaxis
Eggiman et al. (53)	52.2 vs. 75	30.4 vs. 50	4.3 vs. 0	4.3 vs. 35	0 vs. 0	8.7 vs. 35	30.4 vs. 50	Likely to be low	ND
Slotman and Burchard (54)	29.6 vs. 60	25.9 vs. 36.7	0 vs. 0	0 vs. 16.7	0 vs. 0	0 vs. 16.7	NA	ND	ND

ND, not described; NA, not applicable.

[a]Some patients may develop both superficial and invasive fungal infections; thus the total fungal infections do not represent the sum of them. Outcomes for the azole vs. the placebo group are reported.

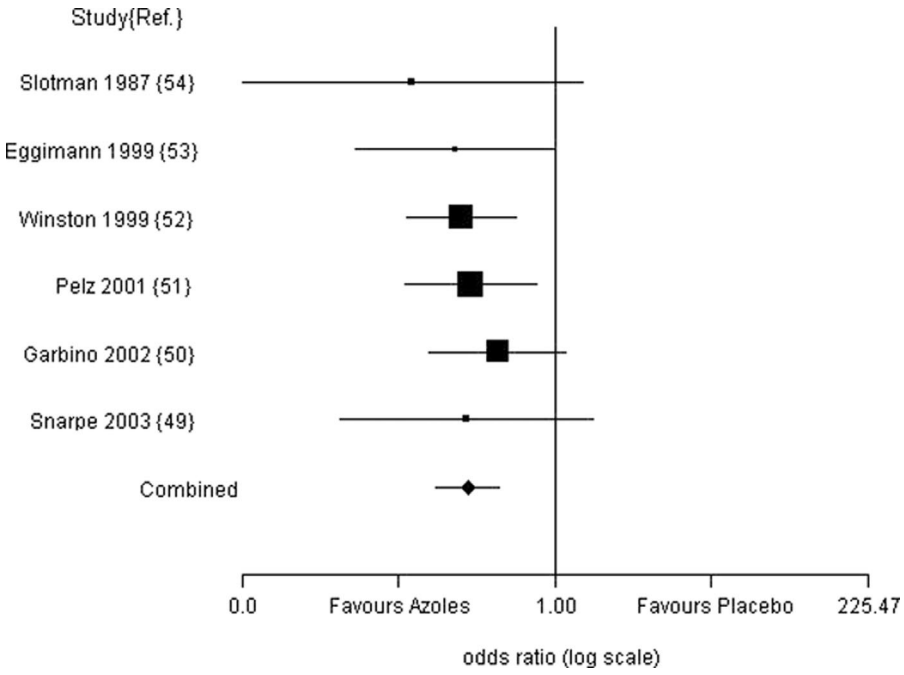

Figure 2. Odds ratios for the development of candidemia and nonbloodstream invasive fungal infections in individual randomized controlled trials and the pooled analysis. The vertical line represents the "no difference" point in invasive fungal infections between the two regimens. Squares denote the odds ratios of individual trials; the size of each square represents the proportion of information contributed by each trial. The diamond indicates the pooled odds ratio. The horizontal lines represent the 95% confidence intervals.

not statistically significant (499 patients, fixed effects model, OR = 1.36, 95% CI 0.86–2.15). The adverse effects more commonly observed were nausea, vomiting, and diarrhea. Hepatotoxicity was the reason for discontinuation of the studied drugs in only five patients. Data regarding development of resistance were also reported in four RCTs (50–53). There was no development of resistance among the fungal isolates. In addition, no shift from *Candida albicans* toward non-*albicans* species was noted.

Sensitivity Analyses

An additional analysis was conducted excluding the RCTs conducted on transplant recipients and patients with recurrent gastrointestinal perforations or anastomotic leakages. Three RCTs were included in this subset analysis; a reduction in fungal infections was observed after the administration of azoles as prophylaxis (499 patients, random effects model, OR = 0.30, 95% CI 0.16–0.58). No statistically significant differences were found regarding invasive fungal infections (499 patients, fixed effects model, OR = 0.38, 95% CI 0.10–1.41) and mortality (521 patients, fixed effects model, OR = 0.86, 95% CI 0.56–1.30).

A second sensitivity analysis was conducted after the exclusion of the RCT by Garbino et al. (50), in which selective bowel decontamination was also administered. The administration of antifungal prophylaxis was associated with a statistically significant reduction in the development of fungal infections (612 patients, random effects model, OR = 0.18, 95% CI 0.10–0.33) and severe fungal infections (612 patients, random effects model, OR = 0.18, 95% CI 0.11–0.31).

DISCUSSION

The results of our meta-analysis suggest that the use of azoles as antifungal prophylaxis in high-risk patients in the SICU is associated with fewer fungal infections but appears not to be associated with lower overall mortality rate. Our study provides clinically useful information, since the results include point estimates of the effect of antifungal prophylaxis on several outcomes, including mortality, with narrower confidence intervals compared with the results of the individual studies. All outcomes related to the occurrence of fungal infections

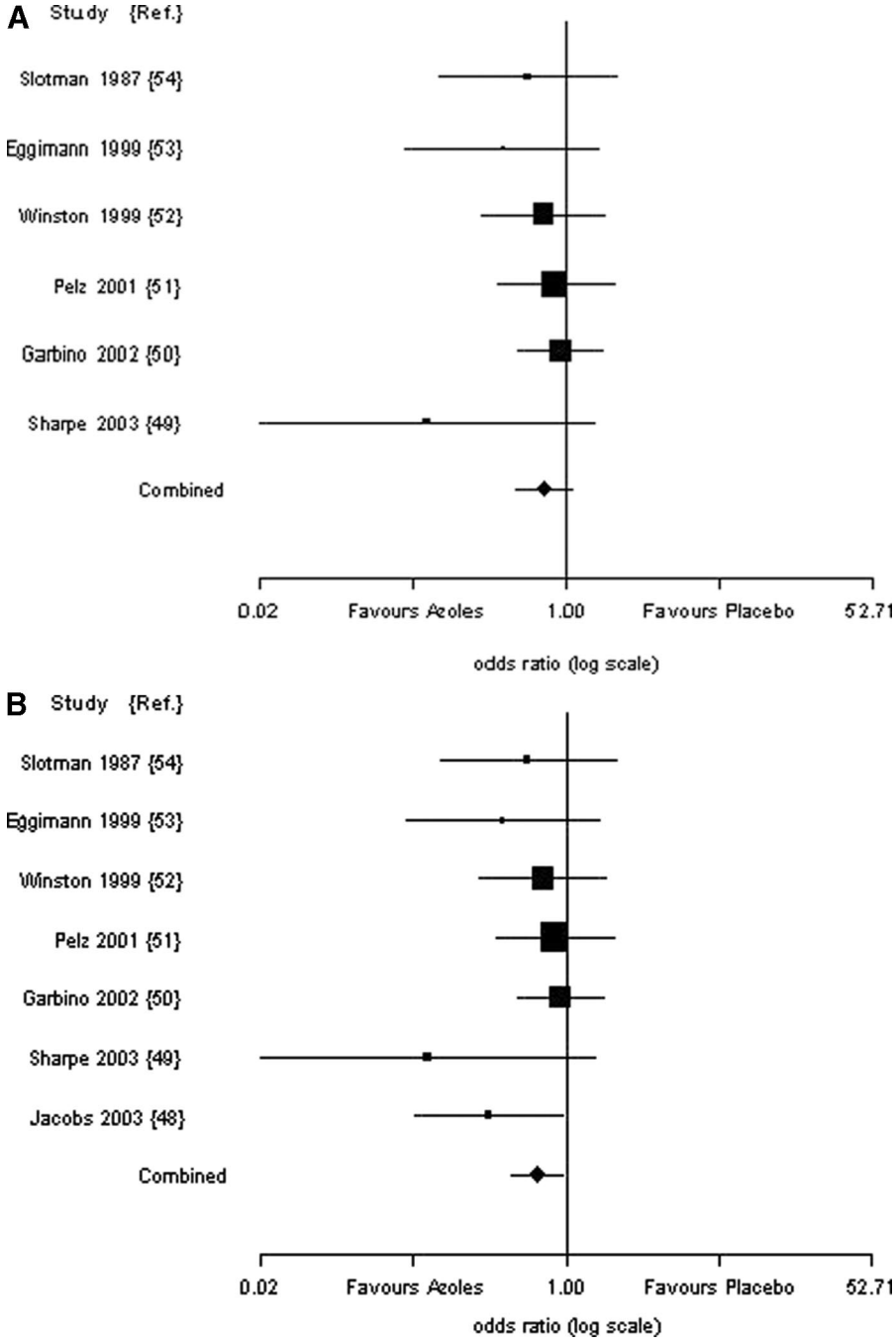

Figure 3. Odds ratios in individual randomized controlled trials (RCTs) and the pooled analysis on mortality. *Top*, mortality in the main analysis. *Bottom*, mortality after the inclusion of an RCT with bacterial septic shock patients. The vertical line represents the "no difference" point in all-cause mortality between the two regimens. Squares denote the odds ratios of each trial; the size of each square represents the proportion of information contributed by each trial. The diamond indicates the pooled odds ratio. Horizontal lines represent 95% confidence intervals.

were fewer among patients receiving azole prophylaxis. Specifically, candidemia, nonbloodstream invasive fungal infections, superficial fungal infections, and total fungal infections (invasive and superficial) were all lower among patients receiving antifungal prophylaxis. A similar result was also observed in the sensitivity analyses (after the exclusion of transplant recipients and patients with gastrointestinal perforations or after the exclusion of nonsurgical patients). Of importance, mortality rate was not reduced in our primary analysis as well as in secondary analyses when using RCTs performed on patients receiving fluconazole prophylaxis, RCTs excluding transplant patients, and/or RCTs using selective bowel decontamination. However, the addition of one RCT with bacterial septic shock patients showed that azole prophylaxis appeared to be associated with better survival rate ($p = .02$). Also, a reduction of fungal colonization was observed with the use of antifungal prophylaxis.

We acknowledge that our meta-analysis is not without limitations. First, the RCTs used in our meta-analysis were conducted during a prolonged period of time (1987–2003). Subsequently, the management of the underlying diseases and the susceptibility of the isolated *Candida* strains as well as the mixture of different fungal species may have undergone several changes during this period. Second, the patient populations included are not homogeneous, since both transplant and nontransplant patients were incorporated in the analysis. In addition, a small proportion of the enrolled patients in two of the six RCTs used had not undergone any operation. However, separate analyses after the exclusion of RCTs that enrolled transplant recipients or nonsurgical patients did not substantially alter the results. Third, the azole used was not the same in all RCTs. Fluconazole, itraconazole, and ketoconazole were used as the prophylactic regimen in different RCTs. In addition, the daily dosage and the route of administration of fluconazole were not identical. The dose of fluconazole varied from 100 to 400 mg daily, and it was given orally or intravenously. Unfortunately, the available data do not provide enough conclusive evidence regarding the minimum dosage of various antifungal agents, including azoles, that is sufficient for prophylaxis. Fourth, there was a variation in the duration of antifungal prophylaxis used in different RCTs.

Also, we acknowledge that the RCTs included in our meta-analysis were not designed to specifically identify risk factors for the development of fungal infections among SICU patients. However, we selected only those RCTs that included patients with several risk factors (as identified by other investigators) for the development of fungal infections. In addition, the definitions of fungal infections in the RCTs included in our meta-analysis were not in accordance with the definitions of the European Organization for Research and Treatment of Cancer (55), because all of them were designed before the introduction of these definitions to the literature in 2002. More spe-

cifically, none of the RCTs provided data specifically for proven, probable, and possible fungal infections; data regarding invasive and superficial fungal infections were provided in all included studies, whereas data on proven and suspected fungal infections were provided in the studies by Sharpe et al. (49) and Pelz et al. (51). Therefore, we could not differentiate between proven, probable and possible fungal infections. Of note, data about drug toxicity were reported only in three of seven RCTs, and in these studies no specific definitions of various types of adverse events were reported; the reporting of only limited data regarding drug toxicity is unfortunately common in published papers reporting results of RCTs. Another limitation is that the development of antifungal resistance was not the focus of the analyzed RCTs and, thus, it was not examined systematically in the studies included in our meta-analysis. Finally, although quality assessment of the studies was not performed, all included studies were double-blind, placebo-controlled RCTs (except for one RCT that was not a double-blind study).

The effectiveness of antifungal prophylaxis is debated in most patient populations. A meta-analysis on antifungal prophylaxis for transplant recipients reported that fluconazole was effective in reducing invasive and superficial fungal infections but not mortality (56). Data from RCTs using other azoles as antifungal prophylaxis were not conclusive regarding either invasive fungal infections or mortality (56). When all antifungal regimens (azoles and polyenes) used in RCTs of solid organ transplant recipients were analyzed together, a reduction in invasive and superficial fungal infections was noted, but mortality was not reduced (56). In another meta-analysis, conducted on RCTs with neutropenic patients, it was reported that although prophylaxis contributed to a reduction of fungal infections, mortality remained unaffected, whereas only specific subgroups of patients (patients with prolonged neutropenia or undergoing allogeneic hemopoietic stem cell transplantation or patients receiving high daily doses of antifungal agents for prophylaxis) would benefit (57). Also, in another meta-analysis of RCTs of neutropenic patients it was reported that oral fluconazole prophylaxis was beneficial in reducing invasive fungal infections in patients undergoing bone marrow transplantation but not in patients who were not undergoing bone marrow transplantation (58).

Our meta-analysis was purposely restricted to RCTs that included high-risk surgical patients. This strategy was selected because not all patients undergoing operations or in need for ICU care have the same probability for the development of fungal infections. Many risk factors for the development of such infections among patients treated in the ICU have been identified; however, each factor alone does not contribute significantly to increased mortality (3, 59). On the contrary, the combination of several risk factors predisposes to worse outcomes (3). In addition, the inclusion of RCTs with low-risk patients in the present meta-analysis would increase the heterogeneity of the analyzed patients and therefore the possibility for statistical errors.

Superficial fungal infections, although easy to treat, are a problem that affect quality of life. Invasive fungal infection is a serious and potentially fatal condition, with increasing frequency in high-risk medical and surgical patients. Furthermore, there are important considerations related to the effect of fungal infections on the length of hospitalization and the cost of health care. Although the incidence of invasive fungal infections can be reduced in high-risk medical and surgical patients by prophylactic or preemptive administration of antifungal agents (by both polyenes and azoles), as indicated in a number of RCTs (35, 36, 44, 48, 51–53, 60), the economic aspects of the use of such prophylactic or preemptive antifungal strategies have not been systematically evaluated. Two recent developments are related to the control of fungal infections, namely the decrease in the price of fluconazole since the availability of generic forms of the drug and the introduction of echinocandins that may have a significant impact on financial analyses regarding the prevention and treatment of fungal infections. Subsequently, these interventions deserve further study, including cost-effectiveness analyses in various populations.

Azoles represent a more attractive approach because they are administered orally. However, the possibility of administering azoles by mouth as prophylactic agents against invasive fungal infections is not so important in the population studied in this meta-analysis; it is true that in SICU patients the absorption after oral administration of various medications may be compromised due to bowel edema. In addition, the bioavailability of oral administration of azoles, mainly itraconazole and ketoconazole, is frequently impaired by several comorbidity factors and concomitantly administered medications that may lead to differences in the effect on clinically important outcomes. Subsequently, intravenous administration of antifungal prophylaxis may be a better option in this population.

A recent advance in the field of mycology that may affect clinical practice is the development of several newer molecular diagnostic tests for fungal infections (such as the detection of fungal DNA and antigens like galactomannan and glucan). The widespread use of these tests may change several aspects of the management of fungal infections in various populations including high-risk SICU patients. However, it is unclear how these developments may change the practice of antifungal prophylaxis (61).

Another important and intensely debated issue regarding the use of prophylactic antifungal agents is the development of resistant *Candida* strains or the selection of resistant *Candida* species under antifungal drug pressure. Especially, fluconazole was accused of the selection of such species (mainly *Candida krusei* and *Candida glabrata*) in retrospective studies (62, 63). Only four of the RCTs included in this meta-analysis reported whether an increase in the incidence of resistant species was observed (50–53). Although no specific microbiological data were reported, in these four RCTs there was little evidence that the azole prophylaxis was associated with emergence of resistant fungal strains or a shift toward non-*albicans* species. However, the number of infections as well as the number of isolated fungi in patients in the analyzed RCTs are too small to provide sufficient information on these important issues.

These observations regarding the emergence of resistant *Candida* species are in keeping with the results of three other meta-analyses (in transplant recipients and neutropenic patients), which did not associate the emergence of resistant species to antifungal prophylaxis alone (59, 60, 61). In addition, the fact that *C. krusei* and *C. glabrata* exhibit innate resistance to fluconazole, the azole most widely used for antifungal prophylaxis, supports the previous findings (61, 64, 65). Furthermore, there are other factors that can explain, in part, the shift toward non-*albicans* species that was observed during the last decade, such as the

more intense and aggressive management of the underlying disease (63, 65–67), the neutrophil count of treated patients (63), and the simultaneous prophylactic use of antibiotics (mainly quinolones, as well as other broad-spectrum antibiotics) (63, 68).

CONCLUSIONS

Despite its limitations, we believe that our meta-analysis offers clinically useful information regarding the controversial issue of antifungal prophylaxis in SICU patients. A clinical trial with a very large number of patients is still needed to obtain a definitive answer on the value of antifungal prophylaxis with azoles in high-risk SICU patients, although such a trial is unlikely to be done soon. Subsequently, the results of our meta-analysis may be useful because they help clarify further the effect of azole prophylaxis in this population. Specifically, our data indicate the reduction of fungal infections and subsequently provide support for the use of azoles as antifungal prophylaxis in this defined population, namely high-risk SICU patients. However, the possible benefit of prophylaxis should be weighed against the considerable possible drawbacks such as the emergence of resistance, the selection of non-*albicans* strains, and drug-related toxicity.

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REFERENCES

1. Castagnola E, Machetti M, Bucci B, et al: Antifungal prophylaxis with azole derivatives. *Clin Microbiol Infect* 2004; 10(Suppl 1):86–95
2. Lipsett PA: Clinical trials of antifungal prophylaxis among patients in surgical intensive care units: Concepts and considerations. *Clin Infect Dis* 2004; 39(Suppl 4):S193–S199
3. McKinnon PS, Goff DA, Kern JW, et al: Temporal assessment of Candida risk factors in the surgical intensive care unit. *Arch Surg* 2001; 136:1401–1408
4. Voss A, Hollis RJ, Pfaller MA, et al: Investigation of the sequence of colonization and candidemia in nonneutropenic patients. *J Clin Microbiol* 1994; 32:975–980
5. Reagan DR, Pfaller MA, Hollis RJ, et al: Characterization of the sequence of colonization and nosocomial candidemia using DNA fingerprinting and a DNA probe. *J Clin Microbiol* 1990; 28:2733–2738
6. Calandra T, Marchetti O: Clinical trials of antifungal prophylaxis among patients undergoing surgery. *Clin Infect Dis* 2004; 39(Suppl 4):S185–S192
7. Paya CV: Prevention of fungal infection in transplantation. *Transpl Infect Dis* 2002; 4(Suppl 3):46–51
8. Swoboda SM, Merz WG, Lipsetta PA: Candidemia: The impact of antifungal prophylaxis in a surgical intensive care unit. *Surg Infect (Larchmt)* 2003; 4:345–354
9. 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
10. Zwaveling JH, Maring JK, Klompmaker IJ, et al: Selective decontamination of the digestive tract to prevent postoperative infection: A randomized placebo-controlled trial in liver transplant patients. *Crit Care Med* 2002; 30: 1204–1209
11. Riedl S, Peter B, Geiss HK, et al: Microbiological and clinical effects of selective bowel decontamination in transthoracic resection of carcinoma of the esophagus and cardia. *Chirurg* 2001; 72:1160–1170
12. Barret JP, Jeschke MG, Herndon DN: Selective decontamination of the digestive tract in severely burned pediatric patients. *Burns* 2001; 27:439–445
13. Wijers OB, Levendag PC, Harms ER, et al: Mucositis reduction by selective elimination of oral flora in irradiated cancers of the head and neck: A placebo-controlled double-blind randomised study. *Int J Radiat Oncol Biol Phys* 2001; 50:343–352
14. Lingnau W, Berger J, Javorsky F, et al: Selective intestinal decontamination in multiple trauma patients: Prospective, controlled trial. *J Trauma* 1997; 42:687–694
15. Schardey HM, Joosten U, Finke U, et al: The prevention of anastomotic leakage after total gastrectomy with local decontamination. A prospective, randomized, double-blind, placebo-controlled multicenter trial. *Ann Surg* 1997; 225:172–180
16. Quinio B, Albanese J, Bues-Charbit M, et al: Selective decontamination of the digestive tract in multiple trauma patients. A prospective double-blind, randomized, placebo-controlled study. *Chest* 1996; 109:765–772
17. Hammond JM, Potgieter PD, Saunders GL: Selective decontamination of the digestive tract in multiple trauma patients—Is there a role? Results of a prospective, double-blind, randomised trial. *Crit Care Med* 1994; 22: 33–39
18. Gastinne H, Wolff M, Delatour F, et al: A controlled trial in intensive care units of selective decontamination of the digestive tract with nonabsorbable antibiotics. The French Study Group on Selective Decontamination of the Digestive Tract. *N Engl J Med* 1992; 326:594–599
19. Blair P, Rowlands BJ, Lowry K, et al: Selective decontamination of the digestive tract: A stratified, randomized, prospective study in a mixed intensive care unit. *Surgery* 1991; 110:303–309
20. Kerver AJ, Rommes JH, Mevissen-Verhage EA, et al: Prevention of colonization and infection in critically ill patients: A prospective randomized study. *Crit Care Med* 1988; 16: 1087–1093
21. Ruza F, Alvarado F, Herruzo R, et al: Prevention of nosocomial infection in a pediatric intensive care unit (PICU) through the use of selective digestive decontamination. *Eur J Epidemiol* 1998; 14:719–727
22. Arnow PM, Carandang GC, Zabner R, et al: Randomized controlled trial of selective bowel decontamination for prevention of infections following liver transplantation. *Clin Infect Dis* 1996; 22:997–1003
23. Wiener J, Itokazu G, Nathan C, et al: A randomized, double-blind, placebo-controlled trial of selective digestive decontamination in a medical-surgical intensive care unit. *Clin Infect Dis* 1995; 20:861–867
24. Henrion J, Schapira M, Derue G, et al: Prevention of bacterial infection using selective intestinal decontamination in patients with cirrhosis admitted to intensive care. Controlled study in 120 patients. *Acta Gastroenterol Belg* 1992; 55:333–340
25. Cerra FB, Maddaus MA, Dunn DL, et al: Selective gut decontamination reduces nosocomial infections and length of stay but not mortality or organ failure in surgical intensive care unit patients. *Arch Surg* 1992; 127: 163–167
26. Rimola A, Bory F, Teres J, et al: Oral, nonabsorbable antibiotics prevent infection in cirrhotics with gastrointestinal hemorrhage. *Hepatology* 1985; 5:463–467
27. Lykkegaard Nielsen M, Scheibel JH, Wamberg T: Septic complications in colo-rectal surgery after 24 hours versus 60 hours of preoperative antibiotic bowel preparation. I. Prospective, randomized, double-blind clinical study. *Acta Chir Scand* 1978; 144: 523–526
28. Drew RH, Dodds Ashley E, Benjamin DK Jr, et al: Comparative safety of amphotericin B lipid complex and amphotericin B deoxycholate as aerosolized antifungal prophylaxis in lung-transplant recipients. *Transplantation* 2004; 77:232–237
29. Biancofiore G, Bindi ML, Baldassarri R, et al: Antifungal prophylaxis in liver transplant recipients: A randomised placebo-controlled study. *Transpl Int* 2002; 15:341–347
30. Tortorano AM, Viviani MA, Pagano A, et al: Candida colonization in orthotopic liver transplantation: Fluconazole versus oral amphotericin B. *J Mycologie Medicale* 1995; 5:21–24
31. Lumbreras C, Cuervas-Mons V, Jara P, et al: Randomized trial of fluconazole versus nystatin for the prophylaxis of Candida infection following liver transplantation. *J Infect Dis* 1996; 174:583–588
32. Ruskin JD, Wood RP, Bailey MR, et al: Comparative trial of oral clotrimazole and nystatin for oropharyngeal candidiasis prophylaxis in orthotopic liver transplant patients. *Oral Surg Oral Med Oral Pathol* 1992; 74:567–571

33. Gombert ME, duBouchet L, Aulicino TM, et al: A comparative trial of clotrimazole troches and oral nystatin suspension in recipients of renal transplants. Use in prophylaxis of oropharyngeal candidiasis. *JAMA* 1987; 258:2553–2555
34. Tollemar J, Hockerstedt K, Ericzon BG, et al: Liposomal amphotericin B prevents invasive fungal infections in liver transplant recipients. A randomized, placebo-controlled study. *Transplantation* 1995; 59:45–50
35. Leon A, Toubas D, Renard P, et al: Diagnosis and prevention of candidiasis in intensive care patients. *Agressologie* 1990; 31(8 Spec No):514–518
36. Lo WK, Chan CY, Cheng SW, et al: A prospective randomized control study of oral nystatin prophylaxis for Candida peritonitis complicating continuous ambulatory peritoneal dialysis. *Am J Kidney Dis* 1996; 28: 549–552
37. He YM, Lv XS, Ai ZL, et al: Prevention and therapy of fungal infection in severe acute pancreatitis: A prospective clinical study. *World J Gastroenterol* 2003; 9:2619–2621
38. Gallin JI, Alling DW, Malech HL, et al: Itraconazole to prevent fungal infections in chronic granulomatous disease. *N Engl J Med* 2003; 348:2416–2422
39. Kohl TD, Martin DC, Nemeth R, et al: Fluconazole for the prevention and treatment of tinea gladiatorum. *Pediatr Infect Dis J* 2000; 19:717–722
40. Kaufman D, Boyle R, Hazen KC, et al: Fluconazole prophylaxis against fungal colonization and infection in preterm infants. *N Engl J Med* 2001; 345:1660–1666
41. Kicklighter SD, Springer SC, Cox T, et al: Fluconazole for prophylaxis against candidal rectal colonization in the very low birth weight infant. *Pediatrics* 2001; 107:293–298
42. Wainer S, Cooper PA, Funk E, et al: Prophylactic miconazole oral gel for the prevention of neonatal fungal rectal colonization and systemic infection. *Pediatr Infect Dis J* 1992; 11:713–716
43. Sandven P, Qvist H, Skovlund E, et al: NORGAS Group and the Norwegian Yeast Study Group. Significance of Candida recovered from intraoperative specimens in patients with intra-abdominal perforations. *Crit Care Med* 2002; 30:541–547
44. van Weissenbruch R, Bouckaert S, Remon JP, et al: Chemoprophylaxis of fungal deterioration of the Provox silicone tracheoesophageal prosthesis in postlaryngectomy patients. *Ann Otol Rhinol Laryngol* 1997; 106: 329–337
45. Winston DJ, Busuttil RW: Randomized controlled trial of oral itraconazole solution versus intravenous/oral fluconazole for prevention of fungal infections in liver transplant recipients. *Transplantation* 2002; 74: 688–695
46. Savino JA, Agarwal N, Wry P, et al: Routine prophylactic antifungal agents (clotrimazole, ketoconazole, and nystatin) in nontransplant/nonburned critically ill surgical and trauma patients. *J Trauma* 1994; 36:20–25
47. Ables AZ, Blumer NA, Valainis GT, et al: Fluconazole prophylaxis of severe candida infections in trauma and postsurgical patients: Prospective, double blind, randomised, placebo controlled trial. *Infect Dis Clin Pract* 2000; 9:169–175
48. Jacobs S, Price Evans DA, Tariq M, et al: Fluconazole improves survival in septic shock: A randomized double-blind prospective study. *Crit Care Med* 2003; 31: 1938–1946
49. Sharpe MD, Ghent C, Grant D, et al: Efficacy and safety of itraconazole prophylaxis for fungal infections after orthotopic liver transplantation: A prospective, randomized, double-blind study. *Transplantation* 2003; 76: 977–983
50. Garbino J, Lew DP, Romand JA, et al: Prevention of severe Candida infections in nonneutropenic, high-risk, critically ill patients: A randomized, double-blind, placebo-controlled trial in patients treated by selective digestive decontamination. *Intensive Care Med* 2002; 28:1708–1717
51. Pelz RK, Hendrix CW, Swoboda SM, et al: Double-blind placebo-controlled trial of fluconazole to prevent candidal infections in critically ill surgical patients. *Ann Surg* 2001; 233:542–548
52. Winston DJ, Pakrasi A, Busuttil RW: Prophylactic fluconazole in liver transplant recipients. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1999; 131: 729–737
53. Eggimann P, Francioli P, Bille J, et al: Fluconazole prophylaxis prevents intra-abdominal candidiasis in high-risk surgical patients. *Crit Care Med* 1999; 27:1066–1072
54. Slotman GJ, Burchard KW: Ketoconazole prevents Candida sepsis in critically ill surgical patients. *Arch Surg* 1987; 122(2):147–51
55. Ascioglu S, Rex JH, de Pauw B, et al: Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer; Mycoses Study Group of the National Institute of Allergy and Infectious Diseases. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: An international consensus. *Clin Infect Dis* 2002; 34:7–14
56. Playford EG, Webster AC, Sorell TC, et al: Antifungal agents for preventing fungal infections in solid organ transplant recipients. *Cochrane Database Syst Rev* 2004; (3): CD004291
57. Bow EJ, Laverdiere M, Lussier N, et al: Antifungal prophylaxis for severely neutropenic chemotherapy recipients: A meta analysis of randomized-controlled clinical trials. *Cancer* 2002; 94:3230–3246
58. Kanda Y, Yamamoto R, Chizuka A, et al: Prophylactic action of oral fluconazole against fungal infection in neutropenic patients. A meta-analysis of 16 randomized, controlled trials. *Cancer* 2000; 89:1611–1625
59. Strahilevitz J, Sugar AM, Engelhard D: Fluconazole in transplant recipients: Options and limitations. *Transpl Infect Dis* 2000; 2:62–71
60. Nguyen MH, Peacock JE Jr, 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
61. Jones BL, McLintock LA: Impact of diagnostic markers on early antifungal therapy. *Curr Opin Infect Dis* 2003; 16:521–526
62. Abi-Said D, Anaissie E, Uzun O, et al: The epidemiology of hematogenous candidiasis caused by different Candida species. *Clin Infect Dis* 1997; 24:1122–1128
63. Wingard JR, Merz WG, Rinaldi MG, et al: Increase in Candida krusei infection among patients with bone marrow transplantation and neutropenia treated prophylactically with fluconazole. *N Engl J Med* 1991; 325: 1274–1277
64. Wingard JR: Importance of Candida species other than C. albicans as pathogens in oncology patients. *Clin Infect Dis* 1995; 20: 115–125
65. Safdar A, Chaturvedi V, Koll BS, et al: Prospective, multicenter surveillance study of Candida glabrata: Fluconazole and itraconazole susceptibility profiles in bloodstream, invasive, and colonizing strains and differences between isolates from three urban teaching hospitals in New York City (Candida Susceptibility Trends Study, 1998 to 1999). *Antimicrob Agents Chemother* 2002; 46:3268–3272
66. Viscoli C, Girmenia C, Marinus A, 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; 28:1071–1079
67. Eggimann P, Garbino J, Pittet D: Management of Candida species infections in critically ill patients. *Lancet Infect Dis* 2003; 3:772–785
68. Husain S, Tollemar J, Dominguez EA, et al: Changes in the spectrum and risk factors for invasive candidiasis in liver transplant recipients: Prospective, multicenter, case-controlled study. *Transplantation* 2003; 75: 2023–2029