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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

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Abstract *Objective:* Infections caused by *Candida* spp. are a major cause of morbidity and mortality in critically ill patients and usually develop from endogenous colonization. We assessed the effectiveness of adding fluconazole to a selective digestive decontamination regimen to prevent candidal infections. *Design and setting:* We performed a prospective, randomized, double-blind, placebo-controlled trial among medical and surgical intensive care unit patients at a large university hospital. *Patients:* All adult patients mechanically ventilated for at least 48 h with an expectation to remain so for at least an additional 72 h, and receiving selective decontamination of the digestive tract. *Interventions:* Patients were randomly assigned fluconazole 100 mg daily (n=103) or placebo (n=101). *Measurements and results: Candida* infections occurred less frequently in the fluconazole group (5.8%) than in the placebo group (16%; rate ratio 0.35; Cl_{95} 0.11–0.94). Some 90% of candidemia episodes occurred in the placebo group (rate ratio for fluconazole use 0.10; Cl_{95} 0.02–0.74). The rate of treatment failure, development of candidal infection, or increased colonization, was 32% in the fluconazole group and 67% in the placebo group (P<0.001). Crude in-hospital mortality was similar in the two groups (39% fluconazole vs. 41% placebo). *Conclusions:* Prophylactic use of fluconazole in a selected group of mechanically ventilated patients at high risk for infection reduces the incidence of *Candida* infections, in particular candidemia.

Keywords Critically ill · Intensive care unit · Fungal infections · *Candida* · Randomized trial · Selective digestive decontamination

Introduction

The challenge posed by nosocomial fungal infections in critically ill patients has become increasingly apparent over the past 20 years [1]. *Candida* spp. are now among the leading pathogens in intensive care units (ICUs) both in Europe and the United States, with reported rates ranging from 2.1 to 20.0 per 1000 admissions [1, 2, 3, 4, 5, 6, 7, 8, 9, 10]. The incidence of nosocomial candidemia is increasing dramatically [2, 11] and is associated with high overall (35–80%) and attributable (30–40%) mortality [5, 6, 7, 9, 12, 13].

Candida spp. live as commensals in the gut lumen and on mucocutaneous surfaces, but it has not yet been clearly determined as to how they enter into the bloodstream. Translocation across the gut mucosal barrier oc-

curs in animal experiments, but some form of mucosal disruption is required. In critically ill patients colonization with *Candida* spp. precedes and leads to infection [14, 15, 16, 17]. If multiple body sites are colonized, there is an increased risk of severe infection in high-risk patients, and the chance of invasion can be predicted by the extent of preexisting colonization [14, 15, 18].

Selective digestive decontamination (SDD) decreases the incidence of bacterial ICU-acquired infections, particularly ventilator-associated pneumonia [19, 20, 21, 22]. The rationale for this approach is the well documented observation that colonization of the oropharyngeal and gastrointestinal tract by Gram-negative bacilli frequently occurs before the onset of infection [1, 23, 24, 25]. This study assessed the efficacy of primary antifungal prophylaxis with fluconazole in SDD-treated, mechanically ventilated ICU patients at high risk for candidal infections.

Patients and methods

A total of 5241 patients were recruited over a 30-month period in the 22-bed medical and 25-bed surgical ICUs of the University of Geneva Hospitals. All patients aged over 18 years admitted to these ICUs, mechanically ventilated for at least 48 h, and expected to remain so for at least an additional 72 h were eligible and received SDD at time of randomization. The inclusion criteria were fulfilled by 220. Exclusion criteria were life expectancy less than 7 days after randomization, history of systemic fungal infection, allergy to azoles, treatment with an antifungal agent 7 days before randomization, blood culture positive for *Candida* spp. at study entry, acquired immunodeficiency syndrome, persistence of a prothrombin time less than 50% after 24 h of administration of vitamin K (20 mg), neutropenia, pregnancy, anticipated duration of mechanical ventilation less than 72 h at study entry, and refusal to give informed consent. Of those originally included in the study, 16 were subsequently excluded for the following reasons: protocol violation (n=6), early death (n=3), early discharge to another hospital (n=1), mechanical ventilation for less than 72 h after study entry (n=4), diagnosis of candidemia (n=2, one in each study group; blood cultures positive for *Candida* spp. at time of randomization but results only available later). Finally, 204 patients were subject to the present analysis (Fig. 1). The study was approved by the institutional review boards.

Study design and variables

Variables included patient's demographics and comorbidities [26], admission diagnosis, medical history, surgical procedures, medical treatment, devices, microbiological, biochemical, and hematological data, Acute Physiology and Chronic Health Evaluation II (APACHE II) score [27] at admission to the ICU and at study entry, acute organ system failure [28, 29] at ICU admission, at study entry, and during the study period, and outcome. Bacteriological samples were taken at time of study entry from endotracheal aspirates, gastric fluid, urine, stool/rectal swab, wound, and skin insertion site(s) of medical devices, as well as two sets of blood cultures from distinct puncture sites, and all were repeated once to three times weekly [15]. Follow-up continued until death or discharge from the hospital.

Randomization and treatment regimens

The SDD regimen used was a nonabsorbable syrup consisting of a mixture of polymyxin B (150 mg), neomycin (1000 mg), and vancomycin (1000 mg), in a 60 ml solution (PNV syrup) administered in 15 ml doses 6 times daily [30]. Patients were randomly assigned to receive PNV plus intravenous fluconazole (100 mg in 50 ml NaCl 0.9%; n=103) or PNV plus placebo (50 ml NaCl 0.9%; n=101) according to a list blinded to the study investigators and physicians in charge. The two groups did not differ according to the following characteristics (age, gender, underlying disease, comorbidities, reason for admission, severity of illness on ICU admission, APACHE II score, exposure to stress ulcer prophylaxis, steroids, length of ICU stay, duration of ventilatory support at study entry, or exposure to additional risk factors for *Candida* infection, or duration of exposure to invasive medical devices, exposure to antibiotics, parenteral nutrition prior to study entry; Table 1). Almost all patients (202/204) had at least one central venous catheter inserted, and 201 of 204 patients had an arterial line. Prophylaxis was continued until a fungal infection developed, withdrawal from mechanical ventilation, or suspicion of a serious adverse event.

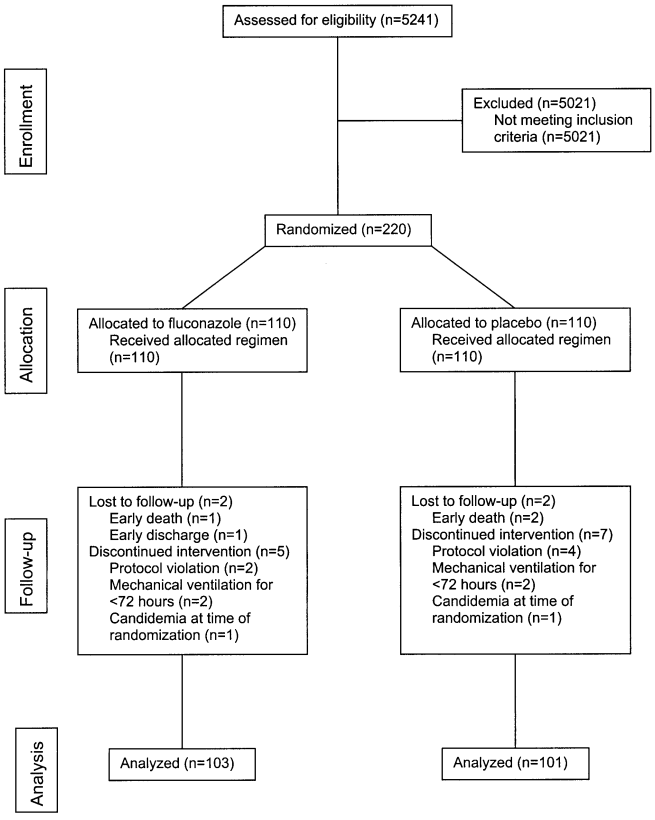

Fig. 1 Flowchart of participants through each stage of the study

Definitions and bacteriological assessment

Colonization was defined as the isolation of the same species of *Candida* from at least two consecutive surveillance samples at any concentration. Intensity was assessed using previously described *Candida* spp. colonization indexes determined daily for each patient enrolled in the study [15]. Candidemia was defined as: (a) one blood culture that grew *Candida* spp. and either histologically documented, invasive candidiasis or an ophthalmic examination consistent with candidal endophthalmitis; or (b) at least two blood cultures obtained at different times from a peripheral vein

Table 1 Baseline characteristics of 204 participants by treatment arm

	Fluconazole (*n*=103)	Placebo (*n*=101)	*p*
Age (years)	52.9±19	55.9±18	0.25
Sex: M/F	70/33	70/31	0.84
Underlying disease/comorbidities			
Diabetes	12	13	
Chronic pulmonary obstructive disease	7	7	
Respiratory disorder	17	15	
Chronic liver dysfunction	2	5	
Cancer	19	12	
Cardiac disease	37	42	
Neurological disorder	12	12	
Renal disorder	10	6	
Reason for admission to the ICU			
Trauma/multiple trauma	34	26	0.86
Heart failure	18	26	0.72
Neurological failure	9	7	0.99
Respiratory failure	23	25	0.99
Peritonitis	10	8	0.99
Mediastinitis	4	1	0.75
Pancreatitis	3	5	0.96
Other	2	3	0.95
Type of surgery			0.66
Abdominal surgery	17	23	
Cardiac/vascular surgery	21	22	
Neurosurgery	9	6	
Orthopedic surgery	7	6	
Other	5	6	
APACHE II score			
At ICU admission	19.5±7.5	19.3±8.5	0.89
At study entry	20.9±6.7	21.3±6.5	0.64
Exposure to antibiotics before study entry[a]	35	45	0.66
Steroids	1	1	1.00
Prophylaxis for stress ulcer[b]	96	99	0.96
Sucralfate	55	49	
Ranitidine	76	69	
Omeprazole	9	20	
Parenteral nutrition	28	30	0.99
Length of ICU stay before study entry (days)	4.34±3.7	4.13±3.4	0.82
Duration of medical device use at study entry (days)			
Orotracheal intubation	3.38±2.6	3.70±3.1	0.44
Central venous line	12.83±8.7	13.63±12.2	0.59
Peripheral venous line	10.81±8.0	10.15±8.3	0.56
Arterial line	11.41±7.7	12.20±7.2	0.44

[a] Exposure to antibiotics for at least 5 days within the 2 weeks before study entry (surgical prophylaxis was excluded)
[b] Some patients received more than one compound

that grew *Candida* spp.; or (c) one blood culture obtained peripherally and one blood culture obtained through an indwelling central line, both of which grew identical *Candida* spp. Severe non-bloodstream candidal infection was defined as *Candida* spp. isolated from a normally sterile body site with at least one of the following: fever (≥38.5°C) or hypothermia (<36°C); unexplained, prolonged hypotension (systolic blood pressure <80 mmHg for more than 2 h, unresponsive to volume challenge); or absence of response to adequate antibiotic treatment for a suspected bacterial infection. *Candida* spp. pneumonia required the recovery of more than 10^4 cfu/ml *Candida* spp. in the absence of another pathogen in bronchoalveolar lavage, in addition to the appearance of a new infiltrate on the chest radiograph [31, 32, 33]. Mucocutaneous candidal infection was diagnosed on the basis of a compatible clinical syndrome and microscopic evidence of candidal infection (positive potassium hydroxide preparation). Superficial wound infection, lower urinary tract infection, and mucocutaneous infection were not considered as severe candidal infection.

Clinical diagnosis of bacterial pneumonia was defined by the presence of all of the following criteria [32, 33, 34]: new or progressive pulmonary radiological infiltrate, purulent tracheal secretions, fever (>38.5°C), and leukocytosis or leukopenia (white blood-cell count $\geq 12\times10^9$/l or $\leq 4\times10^9$/l). Diagnosis of pneumonia was regarded as microbiologically confirmed by the isolation of a potentially pathogenic micro-organism in bronchoalveolar lavage in concentrations of 10^5 cfu/ml or more. Early-onset pneumonia was diagnosed when the infection developed within the first 4 days of mechanical ventilation in a patient requiring intubation within the first 48 h following hospital admission [35]. Late onset pneumonia was defined as an infection which developed after the fourth day of mechanical ventilation. Other nosocomial infections were defined and reported according to standard definitions [34, 36].

Table 2 *Candida* spp. colonization and infection

	Fluconazole	Placebo	*p*
No. of patients colonized at study entry	48 (47%)	50 (49%)	0.78
Mean *Candida* spp. colonization index at study entry[a]	0.56±0.25	0.53±0.21	0.47
Mean *Candida* spp. corrected colonization index at study entry[a]	0.14±0.20	0.13±0.18	0.81
Patients newly colonized with *Candida* spp. after study entry	29/55 (53%)	40/51 (78%)	0.01
Severe infections			
Candidemia	1	9	–
Peritonitis	1	1	–
Pneumonia	2	0	–
Nonsevere infections			
Urinary tract infection	2	2	–
Skin/mucocutaneous infection	0	4	–

[a] Mean values of colonization indexes at study entry are indicated for colonized patients only; values for the entire study population averaged 0.26±30 vs. 0.26±33 (*Candida* spp. colonization index) and 0.15±0.21 vs. 0.13±0.18 (for corrected *Candida* spp. colonization index) in patients in the fluconazole and in the placebo group, respectively

Outcome measures

The primary endpoint was the development of a severe *Candida* spp. infection (candidemia, peritonitis, pneumonia, deep tissue abscess, wound infection, upper urinary tract infection). Secondary endpoints included adverse events, the time from study entry to the development of severe candidal infection, and *Candida* spp. colonization [15]. Clinical efficacy was defined as either the absence of *Candida* infection or the absence of increased *Candida* colonization.

Statistical analyses

A total of 176 patients were required to detect a 50% reduction in the rate of severe candidal infection, assuming an infection rate of 10% in the placebo group, with an α error of 0.05 and a power of 85%. The analysis was made on an intention-to-treat basis. Frequency of infection was summarized by the incidence density, defined as the number of episodes of infection divided by the total number of patient-days in the study [36, 37]. Categorical variables were compared by χ^2 or Fisher's exact tests, and continuous variables by Student's *t* test or nonparametric tests. Rates and rate ratios are displayed with exact confidence limits. Survival analysis was performed using a Kaplan-Meier plot and difference in survival tested by use of the log-rank test. All tests of significance were two-tailed. A *p* of 0.05 or less was considered to indicate statistical significance.

Results

Bacterial infections and outcome

Length of ICU stay after study entry averaged 8.5 days in the fluconazole group and 8.4 days in the placebo group, for a total of 906 and 842 days at risk, respectively. Antimicrobial therapy was administered after study entry in 75% of patients (153/204) because of persistent bacterial infection or ICU-acquired infection (fluconazole 76, placebo 77). There were a total of 108 episodes of ICU-acquired bacteremia among 47% (95/204) of patients, for an overall incidence of 61.8 episodes per 1000 patient-days. Both the incidence and incidence density of bacteremia were similar in the two study groups: 57 episodes among 45 patients in the fluconazole group (62.9 episodes per 1000 patient-days) vs. 51 episodes among 40 patients in the placebo group (60.6 episodes per 1000 patient-days). The most common pathogens were coagulase-negative staphylococci (*n*=52), Enterobacteriaceae (*n*=23), *Staphylococcus aureus* (*n*=11), and *Enterococcus faecalis* (*n*=7); 16 infections were polymicrobial.

Twenty patients (9.8%) acquired ventilator-associated pneumonia after study entry (fluconazole 9, placebo 11) for an overall rate of 11.4 episodes per 1000 ventilator-days. The incidence density of pneumonia was comparable in the two study groups (9.9 vs. 13.1 episodes per 1000 ventilator-days in the fluconazole and the placebo group, respectively). There were 12 episodes of early onset pneumonia (6 in each study group), mostly in patients with multiple trauma (10/12). Pathogens identified were: *S. aureus* (*n*=7), *Streptococcus pneumoniae* (*n*=4), *Haemophilus influenzae* (*n*=3), *Escherichia coli* (*n*=2), *Klebsiella pneumoniae*, and *Enterobacter cloacae*; 7 of 12 infections were polymicrobial. There were only eight episodes of late onset pneumonia (4.6 episodes per 1000 ventilator-days), and the majority (six) were polymicrobial infections. Pathogens identified were: *Pseudomonas aeruginosa* (*n*=4), *Stenotrophomonas maltophilia* (*n*=4), *E. coli* (*n*=2), *E. cloacae* (*n*=2), and *Proteus mirabilis*, *H. influenzae*, *S. aureus*, and *Serratia marcescens*.

Overall mortality during the stay in the ICU was 40% (81/204), with 40 deaths in the fluconazole group and 41 in the placebo group. Apart from one, all occurred within 30 days after study entry.

Candida colonization and infection

Ninety-eight patients enrolled in the study (48%) were colonized with *Candida* spp. at study entry (fluconazole 48, placebo 50, *P*=0.78). The intensity of *Candida* colonization was similar in the two groups (Table 2). *Candida* colonization developed in 53% (29/55) of patients free of colonization at study entry in the fluconazole group vs. 78% (40/51) of patients in the placebo group (*p*=0.01). *Candida* spp. colonization increased with time in patients

Table 3 Distribution of *Candida* spp in the two treatment arms (*n* total number of patients/number of patients in whom *Candida* species isolates were recovered)

	Colonization at study entry				Newly acquired *Candida* spp.				*Candida* infection			
	Fluconazole (*n*=51/49)		Placebo (*n*=56/53)		Fluconazole (*n*=24/24)		Placebo (*n*=31/30)		Fluconazole (*n*=6/6)		Placebo (*n*=16/16)	
C. albicans	41	80%	44	79%	15	62%	27	87%	5	83%	13	81%
C. tropicalis	–	–	2	3.6%	–	–	–	–	–	–	1	6.2%
C. krusei	2	3.9%	1	1.8%	1	4.2%	–	–	–	–	–	–
C. glabrata	2	3.9%	4	7.1%	2	8.3%	2	6.5%	1	17%	–	–
C. lusitaniae	–	–	1	1.8%	1	4.2%	–	–	–	–	1	6.2%
C. parapsilosis	1	2%	–	–	1	4.2%	–	–	–	–	1	6.2%
Saccharomyces cervisiae	1	2%	1	1.8%	1	4.2%	1	3.2%				
Unidentified *Candida* spp.	4	7.8%	3	5.4%	3	12%	1	3.2%	–	–	–	–

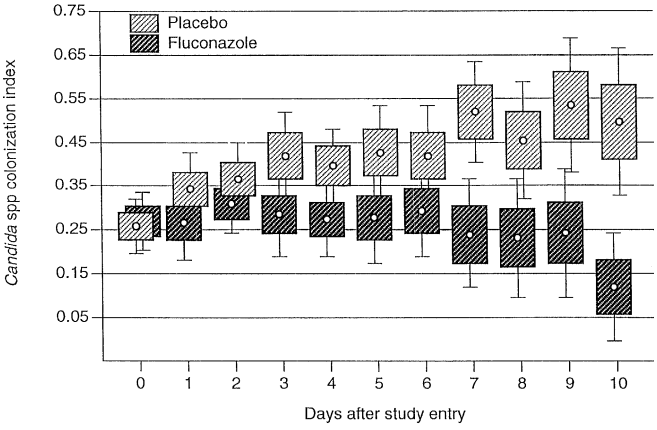

Fig. 2 Dynamics of *Candida* colonization in patients assigned fluconazole prophylaxis or placebo. *Candida* spp. colonization index was measured daily in the fluconazole- and placebo-treated patients. Illustrated are the daily median values (*empty circles*), the 25th and 75th percentiles, i.e., the interquartile range (*borders of the box*), and the range of values (*vertical lines*)

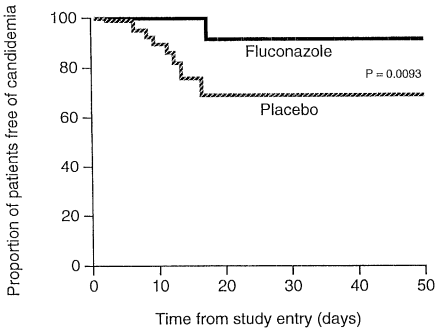

Fig. 3 Kaplan-Meier estimates of the percentages of fluconazole- and placebo-treated patients who remained free of candidemia. The difference in survival free of candidemia was statistically significant (p=0.0093, log-rank test)

in the placebo group but decreased in patients who received fluconazole (Fig. 2).

Severe *Candida* infections developed in four patients assigned to fluconazole and in ten assigned to placebo (Table 2). Of the candidemia episodes, 90% (9/10) developed in patients in the placebo group (rate ratio for fluconazole use 0.10, 95% CI 0.02–0.74, p=0.008). Time of survival free of candidemia is shown in Fig. 3. All candidemic patients were heavily colonized with *Candida* spp. before infection developed; the average colonization index was 0.89±0.17 (range 0.55–1.0). Crude mortality was 60% (6/10) in patients with candidemia. In the placebo group five of nine patients with candidemia died; four deaths were attributable to candidemia. In the fluconazole group, one patient had candidemia and death resulted from the infection. Overall, five of six deaths among candidemic patients were attributable to the infection. Minor candidal infections included lower urinary tract, wound, and mucocutaneous infections (Table 2). The overall incidence of *Candida* infection was significantly lower in patients treated with fluconazole (6.6 episodes per 1000 patient-days) than in those who received placebo (19 per 1000 patient-days; rate ratio for fluconazole use 0.35, 95% CI 0.11–0.94, p=0.022).

Treatment failure, defined as the development of candidal infection or increased *Candida* colonization during the study period, was observed in 33 patients (32%) in the fluconazole group and in 68 patients (67%) in the placebo group (p<0.001). Treatment was stopped in 18 patients (fluconazole 5, placebo 13) because of suspected or confirmed fungal infection; in these cases, intravenous amphotericin B was chosen as antifungal therapy. *Candida* strains recovered from colonized patients at study entry as well as newly acquired *Candida* strains and those causing infections among patients in the two groups are shown in Table 3.

Adverse events

The two treatment groups were similar with respect to the rate of occurrence of abnormalities in laboratory

Table 4 Rate of severe abnormalities in laboratory measurements during antifungal prophylaxis (*ULN* upper limit of normal)

	Fluconazole (*n*=103)	Placebo (*n*=101)
Hematological		
Hemoglobin <8 g/dl	53	47
Granulocytes <750/mm^3	0	0
Platelet count <50,000/mm^3	12	21
Hepatic		
Serum aspartate aminotransferase >5× ULN	21	20
Serum alanine aminotransferase >5× ULN	13	12
Alkaline phosphatase >5times ULN	1	2
Bilirubin >5× ULN	11	12

measurements (Table 4). Treatment was stopped in eight patients (four in each study group) because of probable or possible drug-related side effects. In particular, concern about hepatotoxicity resulted in the discontinuation of treatment in five patients (fluconazole 2, placebo 3). The overall incidence of severe abnormalities in the results of liver-function tests was similar in the two groups. No major event related to the drug was noted in the study population.

Discussion

Candida infection generally arises from endogenous colonization [15, 16, 17, 18]. Our previous study in a comparable patient population found that *Candida* colonization always preceded infection with a genotypically identical strain [38], with *Candida* colonization indexes reaching threshold values [15] before infection developed. The present study confirms those findings. Although the intensity of *Candida* colonization was similar in the two groups at study entry, a significantly higher proportion of patients in the placebo group (p=0.01) became colonized with *Candida* spp., and the intensity of colonization increased with its duration (Fig. 2). Severe infection developed only in patients heavily colonized with *Candida* spp., and fluconazole prophylaxis was associated with a 90% reduction in the risk for candidemia.

Patients in this cohort were at extremely high risk for nosocomial, ICU-acquired infection [1]. As expected, the incidence of nosocomial bacteremia was high (61.8 episodes per 1000 patient-days), a figure among the highest ever reported [4] but similar to the figure which we previously observed in a comparable study population [15]. In contrast, the overall incidence of ventilator-associated pneumonia was remarkably low [36, 39] and did not differ between the two study groups. Although the SDD regimen used in the present study reduced the incidence of late-onset ventilator-associated pneumonia in a previous randomized trial at our institution [30], whether it was responsible for the particularly low observed rates (4.6 episodes per 1000 ventilator-days) in the current study remains speculative. Prevention of ventilator-associated pneumonia by modulating oropharyngeal colonization and preserving the endogenous gut flora using topical SDD only can be attractive for selected groups of high-risk critically ill patients [40, 41].

The objective of this trial was to assess the efficacy of adding fluconazole to the SDD regimen in use in our ICUs to prevent candidal infections. Most SDD regimens have included topical antifungal agents [19, 20, 21, 22, 41]. Invasive *Candida* infections in high-risk bone marrow and liver transplant recipients can be prevented by the use of fluconazole or an amphotericin B preparation [42, 43, 44]. Eggimann and colleagues [45] recently reported the benefit of fluconazole prophylaxis in preventing intra-abdominal candidiasis in high-risk surgical patients with anastomotic leakages or recurrent gastrointestinal perforations. Recently, Pelz and colleagues [46] showed the benefit of antifungal prophylaxis in critically ill surgical patients who remained for at least 72 h in the ICU. In these studies [45, 46], as in the current trial, the proportion of patients colonized with *Candida* spp. at study entry was high, ranging from 48% to 87%. We observed a reduced incidence of *Candida* colonization and candidemia in patients treated with fluconazole. The incidence of candidemia was particularly low in fluconazole-treated patients (1.24 episodes per 1000 patient-days at risk), while within the range of previously published series [2, 4, 5] for the placebo group (11.93 episodes per 1000 patient-days at risk). Our results also confirm the observation of a relationship between increasing endogenous colonization and increased risk for subsequent severe infection [14, 15, 18].

Prophylaxis consisted of 100 mg fluconazole administered once daily intravenously. At the time of study design it was unclear as to what would be the most appropriate dose considering the risk of adverse events among critically ill patients suffering from organ failure and receiving multiple other drugs. This was also the dosage used in several prophylactic studies ongoing or already published among neutropenic cancer patients [47, 48, 49]. Similarly, considering the uncertainty of optimal absorption of oral fluconazole in critically ill patients with impaired digestive function, we decided to use intravenous fluconazole in all patients included. As reported in

other studies in critically ill patients [45, 46, 50], fluconazole was well tolerated in our trial.

The overall proportion of ICU patients included in the current study was low, similar to two [45, 46] of the three other prophylactic studies recently published in nonneutropenic critically ill patients. Pelz et al. [46] randomized 21% of the patients admitted in a surgical ICU over 12 months. Eggimann et al. [45] included only 43 patients over a 3-year period in two surgical ICUs of tertiary university hospitals. These low proportions result from the very strict inclusion criteria applied to restrict the target population to those in whom the expected risk of developing severe *Candida* infection would be greater than 10% [51]. Consistent with the use of strict entry criteria, the proportion of patients with significant *Candida* colonization at randomization was high (48–87%) in studies in which prophylaxis reduced infection rates, illustrating the importance of careful selection of study groups at high risk of infection. In contrast, the proportion of patients colonized at study entry in the report by Sandven et al. [50] was only 30%, with a very low rate of documented fungal infections, which may explain the negative results of the tested prophylactic regimen in the latter study.

Crude mortality rate in the two groups of patients treated with fluconazole or placebo was similar, but was 60% in patients with candidemia. Five of six deaths were attributable to the infection, occurring an average of 9 days (range 4–12) after the first blood culture grew *Candida*. Assuming an attributable mortality of 38% [13] (22 deaths directly attributed to candidemia for every 100 cases), we calculated that a total of at least 348 patients (174 in each group) should have been included in the study to demonstrate a possible impact of fluconazole prophylaxis on overall mortality. Thus no conclusion can be derived from our results as to the possible impact of such a strategy on overall ICU mortality.

The use of antimicrobial prophylaxis in the clinical setting raises concerns about antibacterial and antifungal resistance [1, 52, 53, 54, 55]. We failed to identify any patient colonized with vancomycin-resistant enterococci among those hospitalized in our ICUs during the study period. Importantly, however, these organisms are not endemic in our institution and were identified in a total of only 21 patients between 1994 and 2001 despite regular screening [56], in particular during the course of the current study. Nevertheless, oral vancomycin is currently no longer used as prophylaxis at our institution, and the oral SDD regimen presently administered contains only polymyxin B and neomycin.

Fluconazole resistance has been widely reported and has generally resulted from the prolonged use of new azole compounds in chronically infected, immunosuppressed patients [53, 57, 58]. Whether short-term use in critically ill patients, for whom it is the first exposure, could result in resistance acquisition remains to be studied on a larger scale; no resistance developed under the conditions of fluconazole use in this series (data not shown). Although the proportion of *Candida* species other than *C. albicans* has increased in some centers over the past decade [52, 59, 60], this trend has not been observed at others [42, 45, 61, 62, 63]. We did not observe a shift in the distribution of *Candida* strains from *C. albicans* toward other species following fluconazole use over the study period (Table 3), and the latter represented only 5% (68/1302) of *Candida* strains identified in our series. As previously observed [45, 46], restricting the use of prophylactic fluconazole to carefully selected groups of patients at high risk for severe *Candida* infection may have contributed to the absence of emergence of resistant strains among *Candida* spp., as well as the absence of a shift from *C. albicans* to other *Candida* strains with natural or acquired resistance to fluconazole.

The generalizability of our findings must be discussed. In particular, although a significant proportion (25–49%) of patients mechanically ventilated for at least 72 h developed *Candida* colonization [1, 3, 35], subsequent severe infection remained relatively uncommon. Because of the concern of emerging resistance and possible change in the distribution of *Candida* spp. toward less sensitive organisms, the use of new azole antifungal agents should be restricted to patients at a higher risk for infection [45, 46, 51]. Fluconazole has proven efficacy in invasive candidiasis [64], and selection of resistant isolates and species may well occur when used broadly and injudiciously. Our results suggest that fluconazole prophylaxis could at least be restricted to patients colonized with *Candida*. However, further studies are needed to better define in this population those who would benefit from this therapy; furthermore, it remains to be tested in patient populations not treated with SDD. Indeed, a large majority of critically ill patients receive antibiotics for prophylactic or therapeutic purposes [1, 3, 41] and, whether secondary to SDD or broad-spectrum antimicrobial pressure, yeast colonization develops and increases the risk for subsequent infection. If prophylaxis may be proposed for patients with significant risk factors for developing severe fungal infection, the determination of the colonization index may help to identify subgroups of patients susceptible to benefit from early preemptive antifungal treatment. One very recent study showed the benefit of determining the colonization index once a week [65]. The current policy at our institution is to measure this index twice a week in high-risk patients and to start preemptive therapy with azoles once it is greater than 0.5. Such strategies need, however, further evaluation in controlled studies. Finally, as previously recognized, only a small proportion of our ICU population was included in the current trial, limiting its generalizability among the critically ill.

In conclusion, our results demonstrate that fluconazole prophylaxis in selected, high-risk critically ill patients decreases the incidence of *Candida* infection, in

particular, candidemia. Despite this efficacy further prospective studies are needed to assess the value of preemptive antifungal therapy [66] in high-risk critically ill patients presenting with risk factors for infection that cannot be controlled. Finally, in all circumstances we recommend close surveillance for the emergence of antifungal resistance.

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