Intensive Care Med (2005) 31:1508–1513
DOI 10.1007/s00134-005-2807-x

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Oral nystatin prophylaxis of *Candida* spp. colonization in ventilated critically ill patients

Received: 18 May 2005
Accepted: 29 July 2005
Published online: 30 September 2005

This article is discussed in the editorial available at: http://dx.doi.org/10.1007/s00134-005-2806-y

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Abstract *Objective:* Colonization of multiple body sites is a leading risk factor for *Candida* spp. infection in intensive care unit (ICU) patients. We evaluated whether oral nystatin prophylaxis reduces *Candida* spp. colonization in ventilated ICU patients. *Design and setting:* Prospective, randomized, open-label study with blinded assessment of the objective primary evaluation criterion in the medical-surgical ICU of a teaching hospital. *Patients:* The study included 98 consecutive patients mechanically ventilated for at least 48 h (mean age 58±19 years; mean SAPS II 40±11), assigned to either treatment group (n=51) or control group (n=47). Study groups were comparable for age, SAPS II, reason for admission, and immune status. *Interventions:* Patients were randomized to receive oral nystatin (treatment group; 3×10^6 U per day) or no nystatin (control group). Multiple body sites (trachea, stomach, rectum, urine, groin, and blood) were tested for *Candida* spp. on admission and then every 3 days by mycologists blinded to group assignment, and the colonization index was determined. *Results:* Colonization by *Candida* spp. developed in 25% of controls but in none of the treated patients. In multivariate analysis, the absence of nystatin prophylaxis and ICU length of stay were independently associated with *Candida* spp. colonization. No invasive candidiasis was diagnosed in either study group. *Conclusions:* Oral nystatin prophylaxis efficiently prevented *Candida* spp. colonization in ICU patients at low risk of developing invasive candidiasis. Further studies are needed to determine whether this strategy remains efficient in reducing *Candida* spp. infections in higher risk ICU patients.

Keywords *Candida* · Selective digestive decontamination · Critically ill

Introduction

The incidence of nosocomial fungal infections is steadily increasing, especially in severely ill patients. In the United States, a threefold increase in the incidence of sepsis caused by fungal organisms was observed between 1979 and 2000 [1], and *Candida* spp. was the third most common organism isolated from blood cultures in patients hospitalized in intensive care units (ICUs) from 1995 to 2002 [2]. A European epidemiological study [3] found that invasive candidiasis accounted for 17% of hospital-acquired infections in ICU patients. *Candida* spp. has thus emerged over the past two decades as a source of severe infections not only in immunocompromised hosts but also in critically ill patients requiring aggressive therapy or invasive procedures [4].

Increasing incidence of severe fungal infections in nonimmunosuppressed patients hospitalized in the ICU is presumably related to the predisposing factors for invasive candidiasis (e.g., *Candida* spp. colonization, prolonged wide-spectrum antibiotics, mechanical ventilation, multiple invasive devices) that are frequently encountered

Table 1 Patients characteristics in both study groups (*SAPS* Simplified Acute Physiology Score; *ICU* intensive care unit)

	Treatment group (*n*=51)	Control group (*n*=47)	*p*
Age (years)	59±19	57±19	0.53
Gender: M/F	31/20	34/13	0.23
SAPS II	40±11	39±11	0.76
Reason for admission			
Medical	22 (43%)	23 (49%)	0.56
Surgical	11 (22%)	8 (17%)	0.62
Trauma	18 (35%)	16 (34%)	1.00
Immunocompromised patients	6 (12%)	6 (17%)	0.46
Duration of mechanical ventilation (days)	10.1±9.5	9.8±7.6	0.87
ICU length of stay (days)	12±12	12±13	0.54
ICU mortality	13 (25%)	15 (32%)	0.48

in this population [4]. Colonization originating from the endogenous flora that develops within the gastrointestinal tract is usually a prerequisite for the development of invasive candidiasis [4, 5, 6, 7, 8]. Invasive candidiasis is a late-onset nosocomial infection associated with a high mortality rate, and its diagnosis remains challenging due to few and nonspecific clinical signs. Since *Candida* spp. infections are usually preceded by a period of colonization, oral antifungal prophylaxis has been proposed to prevent invasive candidiasis, particularly in immunocompromised hosts (i.e., patients with neutropenia, cancer, or transplant) [9]. In the ICU setting, antifungal prophylaxis has been evaluated mainly in nonimmunosuppressed surgical patients considered at high risk for candidal infection, and this remains controversial [10, 11, 12]. Nevertheless, only few studies have enrolled medical ICU patients [13, 14] and have used oral nystatin for routine prophylaxis in the ICU setting [15, 16, 17]. In addition, the ability of an early prophylaxis to prevent *Candida* spp. colonization during the ICU stay in consecutive patients admitted for a medical or surgical reason remains to be determined.

We therefore sought to prospectively evaluate the efficacy of a systematic antifungal prophylaxis using oral nystatin, a nonabsorbable antifungal agent, in preventing *Candida* spp. colonization in a cohort of patients admitted to a medical-surgical ICU. Our study hypothesis was that systematic nystatin prophylaxis would decrease the incidence of *Candida* spp. colonization, which usually precedes invasive candidiasis [4, 6, 7, 8] during the ICU stay.

Methods and materials

Our institutional review board approved the study, and the patients or their next-of-kin provided informed consent to participation in the study. This was a randomized, open-label, single-center study with blinded assessment of the objective primary evaluation criterion.

Study population

Patients admitted to our ICU between February and July 2002 were eligible if older than 18 years of age and expected to require invasive mechanical ventilation for more than 48 h. Exclusion criteria were: pregnancy, prophylactic or curative antifungal treatment within the last 2 months, contraindication to oral drug administration, known allergy to nystatin or its derivatives, and prior inclusion in the study. In addition, patients who exhibited at baseline a *Candida* spp. colonization or infection were excluded from the study. Reasons for admission, demographic characteristics, immune status and the Simplified Acute Physiology Score (SAPS) II were recorded on admission. The time to colonization, the duration of mechanical ventilation, the length of stay in the ICU, and ICU mortality were also recorded.

Of the 116 eligible patients 18 were excluded because of the presence of *Candida* spp. colonization at baseline; the study thus included 98 patients (65 men, 33 women; mean age 58±19 years; mean SAPS II: 40±11). The reason for ICU admission was a medical condition in 45 patients (46%), a surgical procedure in 19 patients (19%), and trauma in 34 patients (35%). In 65% of cases, the patient was hospitalized directly from home, 15% from a medical ward, and 20% from a surgical ward. Immunodeficiency was present in only 12 patients (12%), including diabetes mellitus (*n*=6), malignancy (*n*=3), and long-term immunosuppressive therapy (*n*=3; Table 1). All patients had a central venous catheter and 79 of them (81%) received antibiotics during the ICU stay.

A computer-generated randomization list in balanced blocks of unequal sizes was used and patients were allocated to receive either systematic nystatin prophylaxis (3×10^6 U per day in three divided oral doses; *n*=51) or no oral nystatin prophylaxis (*n*=47; Fig. 1). Baseline characteristics of patients in the two study groups were similar (Table 1). Since randomization was performed on admission, patients of the treatment group received the first dose of nystatin within the first 12 h of hospitalization in the ICU. The 18 excluded patients were evenly distributed between the two study groups and had similar demo-

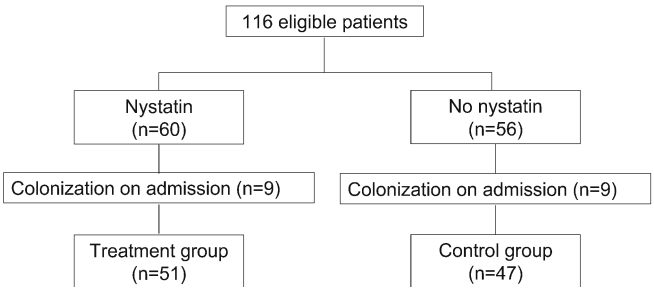

Fig. 1 Trial profile

graphic characteristics as the overall study population, with the exception of a greater proportion of immunocompromised hosts.

Mycological studies and definitions

Multiple-site testing for fungi included: tracheal secretions, stomach contents, rectal swab, groin skin fold swab, urine, and blood. These tests were performed in each patient at ICU admission and subsequently every 3 days throughout the ICU stay. The colonization index was calculated for each multiple-site testing as the ratio between the number of distinct body sites colonized by *Candida* spp. and the total number of sites tested, as previously described [7]. In addition, the need for an antibiotic or corticosteroid therapy, the route of nutrition (i.e., enteral vs. parenteral), and vomiting or the presence of a gastric residual volume greater than 500 ml/24 h were recorded at the time of multiple-site testing. Fungal infections identified during the study period were recorded.

The specimens were placed in a dry medium and taken to the Mycology Laboratory. Group assignment was not indicated on specimens, the mycologists were therefore blinded to treatment allocation. Each specimen was directly microscopically examined and cultured on three media (Chromagar, Sabouraud plus chloramphenicol, and Sabouraud plus actidione). Colonization was assessed for each body site specimen, and yeasts were identified. Fungal colonization was defined as either the presence of the same yeast on two or more of the five distinct body sites tested (blood sample excepted), or on two consecutive specimens from the same body site. Fungal infection was defined as either the presence of a candidemia or the identification of *Candida* spp. in a normally sterile body site associated with a severe sepsis with negative tests for bacteria or other causes [7].

Statistics

Statistical analysis was performed on the intention-to-treat basis using Statview 5.0 software (SAS Institute, Cary, N.C., USA). The primary evaluation criterion was the development of fungal colonization during ICU stay. Secondary evaluation criteria were the course of the colonization index over time and the occurrence of a fungal infection during the ICU stay. The χ^2 test or Fisher's exact test when indicated were used to compare distributions of qualitative variables between the two patient groups. The Mann-Whitney *U* test was used for the between-group comparison of quantitative variables. The proportion of positive gastrointestinal sites (i.e., stomach and rectum) over time was compared between the two study groups using the trend χ^2 test. To identify independent predictors of fungal colonization in the study population, variables for which the *p* value was less than 0.20 in the between-group comparison by univariate analysis were entered into a logistic regression model. For an estimated rate of fungal colonization reaching approx. 60% in ICU patients [18], 49 patients per group should have been enrolled in the study to show a 50% reduction in fungal colonization, with an α error of 5% and β error of 20%. Despite a lower incidence of colonization in our study population, a three-member independent data-monitoring institutional committee decided to interrupt the study based on a significant difference in efficacy between study groups for the occurrence of the primary evaluation criterion after having enrolled 98 patients into the trial.

Results

In the treatment group, no *Candida* spp. colonization occurred whereas 12 patients (25%) from the control group exhibited a fungal colonization ($p<0.001$). In the latter subset of patients, the mean time lag between ICU admission and the diagnosis of fungal colonization was 8.4±5.2 days (range 2–17 days; Fig. 2), and mean number of positive body sites was 2.2 (range 2–4). During hospitalization in the ICU, the mean colonization index was higher in the control group than in the treatment group (0.19±0.20 vs. 0.06±0.13; $p<0.0001$). This difference persisted over time (Fig. 3). In the treatment group, the proportion of positive gastrointestinal sites (i.e., stomach and rectum) tended to decrease during the ICU stay ($p=0.02$), as opposed to the control group ($p=0.20$; data not shown). No *Candida* spp. infection was diagnosed in the two study groups during the ICU stay. The *Candida* species isolated in the 12 patients were: *C. albicans* ($n=9$), *C. tropicalis* ($n=2$) and *C. krusei* ($n=1$). No clinically detectable adverse effect of nystatin therapy was recorded. Specifically, none of the patients from the treatment group suffered from repeated vomiting impeding oral administration of nystatin.

In the univariate analysis, risk factors for fungal colonization included the ICU length of stay, the duration of antibiotic therapy, and the absence of nystatin prophylaxis

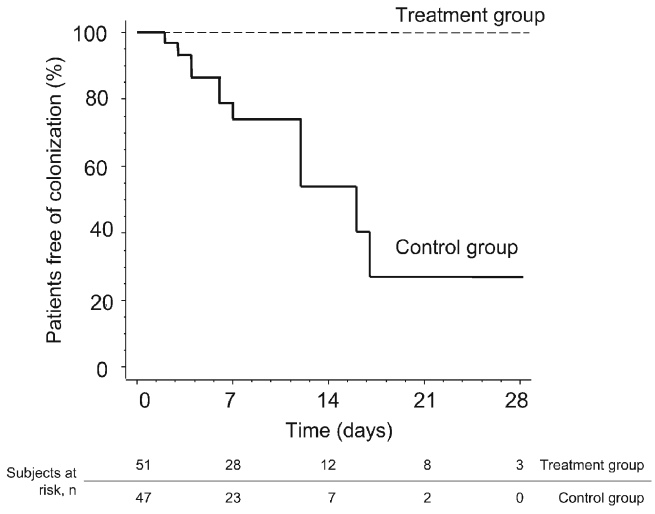

Fig. 2 Course of *Candida* spp. colonization during the ICU stay in the two study groups

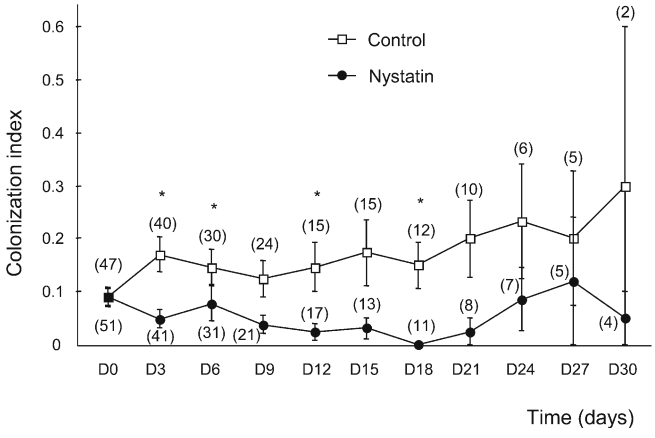

Fig. 3 Course of the colonization index over time in the treatment group (*filled circles*) and controls (*open squares*). Data are expressed as mean ±SD; *parentheses* number of patients in each of the two study groups over time. *$p<0.05$

(Table 2). In the multivariate analysis, both the absence of nystatin prophylaxis (odds ratio not computable) and ICU length of stay (odds ratio 1.05, $p=0.02$, 95% confidence interval 1.01–1.10 per additional day of hospitalization) were independent factors associated with fungal colonization during the ICU stay.

Discussion

The main finding of the present study is that systematic nystatin oral prophylaxis initiated upon admission in patients expected to be mechanically ventilated for more than 48 h efficiently prevents the development of *Candida* spp. colonization without noticeable adverse effects. In our low-risk patients, however, we failed to demonstrate any effect on the occurrence of invasive candidiasis since no case of *Candida* spp. infection was recorded in the two study groups.

The reported incidence of *Candida* spp. colonization in medical-surgical ICUs varies greatly according to study populations. In the current trial, it reached 25% in the absence of nystatin prophylaxis, similar to that reported in a recent multicenter survey [19]. Using similar diagnostic criteria, Garbino et al. [14] found an overall incidence of 65% of fungal colonization during the ICU stay. In this trial, however, the proportion of patients admitted from other wards or having immunodeficiency was substantially larger than that of the current study.

In patients who were admitted to our ICU without fungal colonization, the mean time to colonization was 8 days, ranging from 2 to 17 days (Fig. 2). Similarly, a recent study showed that in the absence of antifungal prophylaxis, *Candida* spp. colonization developed rapidly, within a few days after hospitalization in the ICU [14]. None of the studied variables allowed us to accurately distinguish patients who developed early *Candida* spp. colonization (<5 days) from those who had late positive tests (>8 days) (data not shown).

Table 2 Risk factors for *Candida* spp. colonization in the univariate analysis

	Colonization (n=12)	No colonization (n=86)	p
Nystatin therapy	0	51	<0.0001
Age (years)	59±19	58±19	0.87
Gender: M/W	10/2	31/55	0.18
SAPS II	40±9	40±12	0.71
Reason for admission			
Medical	4 (33%)	41 (48%)	0.54
Surgical	2 (17%)	17 (20%)	1.00
Trauma	6 (50%)	28 (32%)	0.33
Immunocompromised patients	1 (8%)	13 (15%)	0.53
ICU length of stay (days)	24±20	10±10	0.0007
Presence of one positive site for *Candida* spp. upon ICU admission	6 (50%)	33 (38%)	0.44
Antibiotics during ICU stay	12 (100%)	67 (78%)	0.12
Duration of antibiotic therapy[a] (days)	9±8	5±7	0.04

[a] Before fungal colonization, if applicable, or during the hospital stay before ICU discharge

When initiated systematically on the first day of ICU hospitalization, oral nystatin was consistently effective in preventing *Candida* spp. colonization in our ICU patients. Accordingly, the absence of nystatin prophylaxis was an independent predictor of *Candida* spp. colonization, in conjunction with ICU length of stay. This finding was presumably related to the efficacy of nystatin administered orally to significantly reduce the proportion of positive gastrointestinal sites (e.g., stomach and rectum), as shown in the treatment group. Accordingly, the colonization index previously defined by Pittet et al. [7] regularly decreased over time in patients receiving nystatin, whereas it tended to increase in controls (Fig. 3), as recently observed in high-risk medical patients evaluated serially throughout their ICU stay [20].

The present trial found no deep-seated or systemic fungal infections in either of the two study groups during the ICU stay, whereas Garbino et al. [14] previously reported a 16% rate of *Candida* spp. infection in ICU patients who did not receive an antifungal prophylaxis. Jacobs et al. [13] observed the development of a local fungal infection in 5% of patients and a systemic candidiasis in 1% of patients admitted in the ICU for septic shock in the absence of antifungal prophylaxis. Charles et al. [20] reported one case of disseminated candidiasis in 92 nonneutropenic ICU patients hospitalized for more than 7 days. Interestingly, the mean colonization index in our colonized patients (n=12; none of them receiving nystatin prophylaxis) was 0.31±0.13, markedly lower than that reported by Garbino et al. [14] and Charles et al. [20]. This discrepancy is due to our recruiting patients at low risk for invasive candidiasis; 65% of them were hospitalized directly from home and only 12% were immunocompromised. Despite the presence of other risk factors for *Candida* spp. infection in our study population (e.g., central venous catheter, severity of illness, prior abdominal surgery) [4, 19], the clinical relevance of routine antifungal prophylaxis in our patients was retrospectively questionable with regard to the absence of documented *Candida* spp. infection in the control group. Recent guidelines for antifungal prophylaxis either do not include nonimmunocompromised patients [9] or fail to recommend routine oral prophylaxis in ICU patients [21] due to the absence of published studies with sufficient statistical power to demonstrate the benefit of this approach on large groups of critically ill patients [11, 12]. In addition, fluconazole, the most frequently used agent for antifungal prophylaxis, may lead to selection of resistant organisms and substantial cost [11]. In contrast, minimally absorbed agents from the gastrointestinal tract such as nystatin may prevent the emergence of resistant fungal strains, and has the advantages of its low cost (approx. €1 per day) and absence of side effects, as shown in the present study. Although questioned in immunocompromised patients [22], the efficacy of nystatin prophylaxis to reduce *Candida* spp. infection rate has been shown in burned patients and in surgical ICU settings [15, 16].

To determine the efficacy of routine nystatin prophylaxis in preventing *Candida* spp. colonization in our medical-surgical ICU, we purposely excluded from the current study all patients who presented with positive sites for *Candida* spp. on admission. This presumably selected a subgroup of patients at low risk for invasive candidiasis, as reflected by the absence of *Candida* spp. infection in the control group and did not allow us to evaluate the efficacy of nystatin to decrease the number of positive sites over time in colonized patients. Since the present study was not designed to evaluate the ability of nystatin prophylaxis to significantly decrease candidal infection rate, the positive results obtained to prevent *Candida* spp. colonization in our patients cannot be extrapolated to the prevention of fungal infection. Further studies are needed to evaluate the ability of oral nystatin to reduce *Candida* spp. infection rate in ICU patients at higher risk of sustaining deep-seated fungal infections or candidemia (e.g., higher colonization index), as recently emphasized [10, 12]. The present results underline the utmost importance of inclusion criteria in future clinical trials to carefully select ICU patients who are at high risk of developing *Candida* spp. infection.

Conclusions

In the present study *Candida* spp. colonization was efficiently and safely prevented in a selected group of low-risk critically ill patients by a low-cost systematic nystatin prophylaxis initiated upon admission to the ICU. Although our patients were not heavily colonized, they had other significant risk factors for *Candida* spp. infection and were representative of the population routinely admitted to a medical-surgical ICU. As far as we know, this is the first trial that demonstrates that early nystatin prophylaxis efficiently prevents the occurrence of *Candida* spp. colonization in critically ill, yet nonimmunocompromised patients during the ICU stay. Further studies are needed to determine whether this strategy is efficient in reducing the rate of invasive candidiasis in patients at higher risk for *Candida* spp. infection who are admitted to medical-surgical ICUs.

Acknowledgements We gratefully thank Pr. Didier Pittet for his expertise and constructive critique of this manuscript.

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