Intensive Care Med (2005) 31:1466–1468
DOI 10.1007/s00134-005-2806-y

EDITORIAL

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# Oral nystatin as antifungal prophylaxis in critically ill patients: an old SDD tool to be renewed?

Received: 17 August 2005
Accepted: 29 August 2005
Published online: 30 September 2005


This editorial refers to the article available at: http://dx.doi.org/10.1007/s00134-005-2807-x

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Invasive candidiasis remains a dreadful complication in hospitalized patients, generally associated with poor prognosis [1, 2]. Except in the case of candidemia, it is difficult to diagnose. In contrast to *Aspergillus* spp., biological tools have not been developed to diagnose candidiasis [3], and using the current clinical and microbiological criteria the threshold between colonization and infection may be difficult to distinguish [4]. Risk factors including colonization predispose to the development of invasive candidiasis in both immunocompromised and nonimmunocompromised patients [5, 6, 7]. However, as a majority of them are directly linked to an underlying disease or its treatments, it is almost impossible to target them for prevention. The high proportion of bone marrow transplant recipients developing candidiasis has stimulated clinical research which has established the value of antifungal prophylaxis. Azole-based prophylaxis has progressively imposed as a standard of care for severely neutropenic patients [8] and in most solid-organ transplant recipients [9]. However, antifungal prophylaxis has been repeatedly implicated in the increasing proportion of non-*albicans Candida* isolated in many cancer centers [10, 11]. This has generated a considerable debate, and guidelines have been modified accordingly [12].

This is not the case in nonimmunocompromised critically ill patients, in whom international surveillance programs have shown that *C. albicans* remains the predominant strain in most countries [13]. Moreover, this is also the case in almost all recent series on candidiasis in ICU patients [14, 15, 16, 17]. Several characteristics of these patients may have a strong impact on this ecology. ICU patients present many risk factors for invasive candidiasis. In particular, a high proportion of them become colonized with *Candida* spp., but only a minority develop invasive candidiasis. However, related to its poor prognosis, the difficulty in identifying subgroups of patients that could benefit from prophylaxis, and to the good security profile of azoles, it may be tempting to treat systematically all colonized patients. According to the experience acquired with immunocompromised patents, this should be avoided.

Colonization by *Candida* spp. is an independent risk factor for candidiasis. As assessed by the colonization index proposed by Pittet and confirmed by others [14, 15, 16], increasing growth of *Candida* spp. from multiple body sites is predictive of subsequent invasive candidiasis. Despite several studies in critically ill nonimmunosuppressed patients [14, 15, 16, 17] antifungal prophylaxis has been insufficiently validated and is currently not included in most published guidelines. However, a systematic review and meta-analysis of these studies just published in *Intensive Care Medicine* Journal shows a significantly reduced rate of candidiasis, overall mortality, and cases attributable to candidiasis [18]. This con-

firms the proposal of some experts to consider prophylaxis in these patients. All these authors recommend strictly restricting them to high-risk patients [14, 15, 16, 17, 18]. However, such patients are difficult to identify. Identifying them relies on sophisticated and nonvalidated clinical approaches combining the presence of nonspecific risk factors and on the dynamic of colonization by *Candida* [4].

The study performed by Normand et al. [19] now published in *Intensive Care Medicine* suggests a novel way in which to prevent invasive candidiasis in critically ill patients. The open-label study randomized 98 patients mechanically ventilated for more than 48 h to receive oral prophylaxis by nystatin or a placebo. No invasive candidiasis developed, but prophylaxis significantly reduced the colonization index and prevented colonization. The absence of invasive candidiasis was due to the selection of patients at low risk of developing such complication. The severity score at study entry, proportion of patients colonized at entry, and mean value of the colonization index were lower than in other prophylactic studies [14, 15, 16, 17]. This confirms that low-risk patients are characterized by a low proportion of colonization and by a persistent low value of the colonization index over time. Moreover, persistently low values of the colonization index strongly suggested that prophylaxis interferes with the dynamic of colonization by *Candida* spp. in patients receiving nystatin.

Nystatin, as with amphotericin B, is a nonabsorbable polyene with a wide antifungal activity, especially against *Candida* spp., including *C. glabrata* and *C. krusei*. Prophylaxis with nystatin has often been disappointing in immmunocompromised patients, and a meta-analysis found no differences to placebo in colonization or mortality [20]. However, the dose of nystatin and method of administration differed across studies, precluding comparisons of efficacy.

A nonabsorbable drug may present an elegant alternative to the complex and difficult selection of patients at high risk who could benefit from antifungal prophylaxis. The results reported by Normand et al. are the first suggesting a potential efficacy of nystatin prophylaxis in nonimmunocompromised ICU patients. However, it should be remembered that selective decontamination of the digestive tract (SDD) is aimed to prevent nosocomial infection in ICU patients, including those caused by fungi. Nonabsorbable polyenes are integrated in most SDD regimens, and a recent meta-analysis showed that they significantly reduce fungal carriage and overall fungal infections, but without impact on fungemia. However, only few trials were available for analysis of fungal carriage and the definitions of fungal infections were heterogeneous [21].

In critically nonimmunocompromised patients several advantages may favor the use of nystatin instead of azoles as a prophylactic antifungal regimen. First, a nonabsorbable molecule, different from other drugs available for treatment, is an attractive concept. As indicated above, although most species of *Candida* isolated in ICU patients remain susceptible to azoles, indiscriminate use of such drugs may lead to the spread of *C. krusei* and *C. glabrata*, intrinsically resistant and dose-dependent sensitive to azoles, respectively. In contrast, primary resistance to polyenes among *Candida* spp. is limited to *C. lusitaniae* and to some strains of *C. guillermondii*, and resistance seldom develops during treatment. Therefore polyene prophylaxis is less likely to promote the emergence of resistant strains of *Candida*. Second, Normand et al. did not observe adverse effects of nystatin. Azoles are generally well tolerated, but side effects such as hepatic dysfunction are possible. These risks, even if low, could be more difficult to accept in the setting of prophylaxis in critically ill patients. The third advantage of oral nystatin is its low cost, making this strategy potentially highly cost effective—if it works!

Accordingly, as suggested by the authors, these preliminary data should stimulate the medical community to explore the usefulness of oral nystatin prophylaxis in other groups of critically ill patients at higher risk. If confirmed, such approach may contribute to solve ongoing controversies in the field of prevention of invasive candidiasis in nonimmunocompromised critically ill patients.

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