Prophylactic Antifungal Therapy in the Intensive Care Unit

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Antifungal prophylaxis is regularly used during treatment of patients with some cancers, as subgroups with high rates of invasive fungal infections are readily identified; for these patients, prophylaxis has been shown to be of value. High-risk liver transplant recipients also benefit from antifungal prophylaxis. Although the idea of extending this concept to the prevention of candidal infections in the larger population of critically ill patients who are seen in the intensive care unit (ICU) and who do not have neutropenia is attractive, implementation of this strategy is difficult because of the widely varying characteristics of patients in the ICU. Two studies have shown the benefit of such prophylaxis, but the benefit was shown only in selected groups of patients who had an unusually high risk for invasive candidiasis. Although the concept is sound, broad-scale implementation of antifungal prophylaxis would be premature and costly, both financially and with regard to resistance and toxicity. Investigations are needed to define and prove the utility of predictive tools for the identification of patients in the ICU who would benefit from prophylaxis.

Although there is little doubt that “a stitch in time saves nine,” knowing where and when to place that stitch is another matter. With respect to invasive fungal infections, prophylactic therapy has been extensively studied. Although the use of prophylaxis was long limited by the toxicity of amphotericin B deoxycholate, the steady introduction during the past 20 years of increasingly safe and well-tolerated alternatives has made prophylaxis both feasible and attractive. Although there may remain issues for debate [1–3], antifungal prophylaxis is now regularly used in selected populations of patients with cancer. As nosocomial fungal infections have steadily risen in frequency and have become commonplace in populations without cancer [4, 5], the idea that the success of the use of antifungal prophylaxis in patients with cancer might be extended to patients in the intensive care unit (ICU) who do not have neutropenia is tantalizing and is the subject of this review.

STUDIES OF PATIENTS WITH CANCER PROVIDE VALUABLE LESSONS AND SHOW THAT ANTIFUNGAL PROPHYLAXIS IS POSSIBLE

The outcomes of studies of prophylaxis in patients with cancer offer many valuable insights into the issues of the use of prophylaxis for patients in the ICU who do not have neutropenia. In patients with cancer, the principal fungi of concern are Candida species and the various filamentous fungi, especially Aspergillus species. Because candidal infections have been historically predominant, most investigations done to date have focused on this area. The findings of studies of the use of orally administered but minimally absorbed agents (such as nystatin [6], amphotericin B [7], and clotrimazole [8]) among patients with hematologic malignancies have suggested that these drugs have variable but generally limited efficacy.

The advent of fluconazole, an antifungal agent that has excellent activity against many Candida species, opened the door to a large number of studies that collectively demonstrated that antifungal prophylaxis was entirely possible [1, 3]. However, these studies have also shown the limitations of prophylactic strategies. Clear demonstrations of the utility of antifungal prophylaxis have been limited to patients undergoing bone marrow transplantation. Two placebo-controlled studies of fluconazole,
400 mg/day, given to a total of 656 recipients of bone marrow transplants (two-thirds of the transplants were allogeneic and one-third were autologous) demonstrated that prophylaxis reduced the incidence of proven systemic fungal infections from 17% to 4.5% (a 3.7-fold reduction) [9, 10].

These and related results emphasized the importance of the degree of immunosuppression with regard to the risk for fungal infection [11, 12], and the issue of immunosuppression was emphasized in a recent review of these risks [13]. If the risk of fungal infection is too low, then prophylaxis will not be warranted because of the potential negative aspects of treatment (e.g., selection of resistant isolates, drug reactions, and cost). For example, a placebo-controlled study of fluconazole, 400 mg/day, given to 255 adults who were undergoing chemotherapy for acute leukemia, showed a trend similar to that seen in the 2 bone marrow transplantation studies: fluconazole reduced the rate of proven systemic fungal infection from 8% to 4% [14]. However, this 2-fold reduction in the rate of infection had a $P$ value of only .3; given the lower event rate in the placebo-treated patient group (relative to that seen in patients in the bone marrow transplantation studies), a study ~2.5 times larger would have been required to yield a $P$ value of <.05. Likewise, a study that compared fluconazole therapy, 200 mg/day, with nystatin suspension, 6,000,000 IU/day, among 109 adults with leukemia found that rates of systemic fungal infections among patients who received fluconazole were reduced from 11% to 4%; however, the associated $P$ value in this small study was .15 [15].

The choice of comparison agent is also important. It is presumed that the origin of invasive candidiasis is often in gut colonization [16, 17]. Although nonabsorbed antifungal agents would not be presumed to be effective treatment for a fungal infection, they might reduce the incidence of gut colonization, and, in at least 1 study [7], they have produced a modest effect on the rate of development of invasive candidiasis. Such an effect might have contributed to the findings of Menichetti et al. [18]. Their study compared the effects of fluconazole, 150 mg/day, with those of oral amphotericin B among 820 adults who were undergoing chemotherapy for acute leukemia; proven systemic infections were seen in 2.6% and 2.5% of the fluconazole- and oral amphotericin B–treated patients, respectively. Either the rate of invasive fungal infections among patients in the group treated with oral amphotericin B was unexpectedly low (and, therefore, was not amenable to much further reduction by fluconazole), or oral amphotericin B provided some protection against invasive candidiasis. Either way, these results show that placebo-controlled studies are preferred, at least until the value of prophylaxis is clearly established.

Another concern is the potential for selection induction of resistant isolates. Most studies have focused on the use of azoles—most notably, fluconazole—so it is not surprising that the majority of the reports on this topic have focused on azole resistance [19]. Although mutation of susceptible isolates into resistant isolates appears to be uncommon during the relatively short durations of antifungal therapy given to patients with cancer [20], selection of inherently less susceptible species (such as Candida krusei and Candida glabrata) has been described [21, 22]. Although other factors could be operative [23], prior antifungal therapy has been strongly linked to infection caused by these species [24, 25].

### THE STATISTICAL CHALLENGE

These data show that a firm understanding of statistical principles is critical to establishing the utility of prophylaxis and to determining its subsequent proper use. If the rate of invasive fungal infections is high enough, demonstrating the value of prophylaxis is straightforward. Such a strong and convincing benefit is important when prophylaxis is weighed against the inevitable problems of drug resistance and toxicity. The statistical implications of these ideas are shown in the series of sample-size estimates presented in table 1.

With use of a common set of trial-design specifications, the grid shows typical sample sizes for a variety of possible trial-design scenarios. For example, if the group of placebo-treated patients in a trial were expected to have a 10% infection rate,

<table>
<thead>
<tr>
<th>Treatment arm A event rate</th>
<th>Treatment arm B event rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5%</td>
<td>1%</td>
</tr>
<tr>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>10%</td>
<td>15%</td>
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<tr>
<td>20%</td>
<td>25%</td>
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<td>30%</td>
<td>35%</td>
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<tr>
<td>1%</td>
<td>5065</td>
</tr>
<tr>
<td>2%</td>
<td>989</td>
</tr>
<tr>
<td>5%</td>
<td>249</td>
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<tr>
<td>10%</td>
<td>106</td>
</tr>
<tr>
<td>15%</td>
<td>66</td>
</tr>
<tr>
<td>20%</td>
<td>47</td>
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<tr>
<td>25%</td>
<td>36</td>
</tr>
<tr>
<td>30%</td>
<td>29</td>
</tr>
<tr>
<td>35%</td>
<td>23</td>
</tr>
</tbody>
</table>

Table 1. Sample-size estimates in relation to event rates.

**NOTE.** The table shows approximate sample sizes required per treatment arm of a 2-arm study, in relation to the estimated event rates. The sample size is computed according to the method of Casagrande et al. [26] and uses these commonly selected trial-design specifications: (1) the ultimate statistical test will be a 2-sided test comparison of proportions of success (or failure), (2) the desired statistical significance ($P$ value or $a$ value) will be set at .05, and (3) the desired power will be 80% (corresponding to a $β$ value of 0.20). Note also that these values are the theoretical values for the study design. In actual practice, the values shown in **boldface type** should be further increased so that treatment arm B could have at least 5 events. For example, when going from 5% (treatment arm A) to 0.5% (treatment arm B), the theoretical value is 249 per treatment arm. However, one would then see only 249 x 0.5% = 1.2 events in treatment arm B. In practice, a more robust result would be produced if 1000 patients were enrolled in each treatment arm, thus giving an expected absolute number of 5 events in arm B.
and if the treatment were expected to reduce this rate to 5%, then a study of 948 patients (2 × 474 patients) would be needed to detect this treatment benefit 80% of the time.

Table 1 presents several points. First, therapy should reduce the event rate sharply. Consider comparisons in which the event rate drops by only 5% (e.g., from 20% to 15%): these designs require at least several hundred patients per treatment arm. On the other hand, comparisons in which the rate drops 4-fold to 5-fold (e.g., from 20% to 5%) require much smaller sample sizes. Second, these effects are magnified as the rates approach zero: a 2-fold rate of reduction (from 30% to 15%) requires only 266 patients (2 × 133 patients), whereas a reduction from 1% to 0.5% requires 10,130 patients (2 × 5065 patients).

A third and more profound consequence of the association of large sample sizes with small event rates is that it raises the issue of clinical relevance. There is no reason why we could not do a trial with 10,130 patients and demonstrate that a given therapy in a specific population reduces the rate of invasive fungal functions from 1% to 0.5%. If the study were well done, the result would be scientifically and statistically sound. However, it would be almost irrelevant in a medical sense. Because we would have to treat 200 patients to eliminate 1 infection, the cost of the therapy (measured in dollars and according to side effects and induction of resistance) would almost certainly exceed its value.

Therefore, this statistical analysis defines 2 key criteria for the successful study and use of prophylaxis. A therapy that produces a 4-fold to 5-fold reduction in the rate of infection is highly desirable, both medically and statistically. This therapy should be targeted toward subgroups with a baseline rate of infection of ∼10% or more.

**ANTIFUNGAL PROPHYLAXIS FOR PATIENTS IN THE CRITICAL CARE SETTING WITHOUT NEUTROPENIA: PRINCIPLES**

With the aforementioned concepts as a background, let us now turn to the issues that surround the particular question at hand and try to determine whether antifungal prophylaxis is either possible or relevant in the critical care setting. Note that invasive candidiasis can also be a particular problem for patients who have undergone liver transplantation [27–29] and that effective prophylaxis is possible [30–33]. Likewise, prophylaxis might have value for patients who have undergone pancreas transplantation [34]. However, both of these entities are quite specialized in nature and limited in overall scope. This review focuses on the relevance of prophylaxis to the much larger population of patients in the general ICU. (Although neonatal patients will not be specifically discussed, the concepts for the patient population in the general ICU are applicable to that population as well.)

*If the population is critically ill patients who do not have neutropenia, then the target is Candida species.* Although causative agents other than Candida species may be seen, such fungal infections usually are the cause of a patient’s admission to the ICU (e.g., for rhinocerebral zygomycosis in a patient with diabetes) or are related to neutropenia (e.g., invasive aspergillosis after engraftment in a bone marrow transplant recipient). Otherwise, fungal infections in this setting are limited almost entirely to invasive candidiasis. The subsequent discussion will focus on this fungus.

**Prophylaxis versus empirical (or preemptive) therapy for the febrile patient.** It is important to distinguish prophylactic from empirical therapy. If one is faced with a new febrile illness in a patient with diabetes who has undergone broad-spectrum antibiotic therapy, hemodialysis, multiple intravascular catheterizations, and abdominal surgery during a 3-week ICU stay and who is colonized with Candida albicans at multiple sites, the time for prophylaxis is long past. This patient has multiple well-established risk factors for invasive candidiasis [35, 36] and is a candidate for empirical (also sometimes referred to as “preemptive”) antifungal therapy.

On the other hand, this patient might have been a candidate for antifungal prophylaxis at the start of the ICU stay. The proper, early identification of such patients is the key to establishing the value of this strategy.

**What is the rate of incidence of invasive candidiasis among patients in the critical care setting who do not have neutropenia?** As the statistical discussion above makes clear, this question is fundamental to our ability to apply prophylaxis. To answer the question, we must make some decisions about the forms of candidiasis that we will accept as relevant. Candida species produce diseases that range from trivial (albeit troublesome) mucosal syndromes to acute bloodstream infections without clear evidence of visceral involvement, to focal involvement of any organ. The presence of mucosal disease might necessitate therapy, but use of a systemic agent to reduce the rate of incidence of oral candidiasis does not seem warranted. Therefore, studies of prophylaxis should focus exclusively on invasive forms of candidiasis.

Some general diagnostic criteria for invasive fungal infections have been put forward [37]. Generally speaking, the easiest syndromes to diagnose are those that involve growth of Candida species from a sterile body site. Bloodstream infection is the most common of such presentations. Although one can debate almost endlessly about the meaning of 1 positive blood culture result, in comparison with 3 such results, and about the relevance of whether the culture specimen was obtained by means of peripheral venipuncture or via a pre-existing vascular catheter, it is clear that a report from the microbiology laboratory about the growth of Candida species in a blood culture should...
precipitate investigation and (in the vast majority of instances) therapy [38].

Diagnostic use of the recovery of Candida species from non-sterile sites or from generally sterile sites that have close proximity to a mucosal surface is problematic. Candida isolates in urine samples are the prototype for this problem, and careful investigations (albeit primarily in patients outside of the ICU) have made it clear that asymptomatic candiduria (1) has few clinical consequences and (2) follows a natural history that is only minimally affected by antifungal therapy [39, 40]. Candida isolates in sputum samples are equally problematic. The true rate of candidal pneumonia among patients who do not have cancer is not known [41]. Two small autopsy series that focused primarily on surgical patients revealed that ~20% of patients have at least a minor focus of candidiasis in a lung [42, 43]. Even if present, such lesions appear to be clinically imperceptible; a recent investigation of a series of 435 prospectively followed patients in the ICU who did not have neutropenia failed to yield even a single convincing case of candidal pneumonia [44]. Finally, a detailed study that correlated findings of immediate postmortem bronchoalveolar lavage, transbronchial biopsy, and open-lung biopsy demonstrated an 8% rate of infection with candidal pneumonia [45]. However, quantitative sputum sampling did not reliably predict the presence of underlying pneumonia. Therefore, although the presence of Candida species at these sites may be relevant as a risk factor for invasive candidiasis, it will not be useful as a marker of disease or as an outcome measure.

A third issue is the frequent occurrence of a syndrome that is strongly suggestive of invasive candidiasis but that lacks clear microbiological proof of infection. The aforementioned example of a febrile, antibacterial antibiotic–unresponsive, heavily colonized patient in the ICU is the prototypical scenario. Even with use of the newer technologies, blood cultures have a sensitivity for invasive candidiasis that is no more than 50%–60% [46, 47]. Colonization has clearly been established as a major risk factor (if not the major risk factor) for invasive candidiasis among these patients [48], and many clinicians would feel compelled to initiate empirical antifungal therapy in such a scenario. Although a diagnosis based on colonization is intellectually less satisfying than a diagnosis based on growth in a specimen from a sterile site, prevention of the need for empirical antifungal therapy is a valid clinical outcome measure, and it parallels the findings of prior investigations that have involved patients who did not have neutropenia.

With this background in mind, the literature on rates of incidence of invasive candidiasis can be analyzed. Although nosocomial fungal infection rates of incidence of 7–16 cases per 1000 discharged patients have been reported by the National Nosocomial Infection Surveillance system for patients in a variety of critical care settings [4], such surveillance data are limited by the definitions and processes used to collect the data. Reports that have focused specifically on invasive candidiasis have described case rates that have ranged from 35% (in a series of 111 patients who stayed for ≥4 days in a trauma ICU [49]) to as low as 2% (in a series of 435 patients who were admitted to medical or surgical ICUs [44]).

Differences in diagnostic criteria, along the lines of those discussed in the preceding paragraphs, explain this range of rates. The 35% rate of infection seen in the study of Mahr et al. [49] was reached because the authors had used quite liberal definitions, and at least 75% of the reported infections should have been classified, at best, as “possible” invasive candidiasis. On the other hand, the 2% rate reported in the study of Petri et al. [44] was determined on the basis of stringent criteria that allowed for the diagnosis of only conclusively proven invasive candidiasis. A study by Pittet et al. of 650 patients in surgical or neonatal ICUs used similarly stringent rules and showed a 1.7% rate of invasive candidiasis [48]. Finally, the study by Borzotta and Beardsley [50] of a series of 459 patients who were admitted to a trauma ICU for ≥4 days revealed an overall rate of invasive candidiasis of 4.3% but a fungemia rate of only 1.5%.

Collectively, the data from studies with the more stringent rules are similar to those from the National Nosocomial Infection Surveillance system and suggest that a figure of ~2% is a good baseline rate with regard to the incidence of invasive candidiasis in patients who stay in an ICU for more than a few days. On the other hand, more liberal rules that include presumed forms of invasive candidiasis may yield rates that are 2-fold to 15-fold higher. Although it is hard to deny the need to make an empirical diagnosis at times, the subjective aspects of this process must be carefully addressed. Clinical trials will probably need to use a combination of such rules, but it is likely that most attention would be paid to the subset of cases of proven disease.

**ANTIFUNGAL PROPHYLAXIS IN PATIENTS IN THE CRITICAL CARE SETTING WHO DO NOT HAVE NEUTROPENIA: PRACTICES**

As is evident from the earlier discussion of statistical factors, a baseline rate of incidence of 2% for proven invasive candidiasis makes prophylaxis problematic for several reasons. However, not all patients in the ICU are at equal risk for invasive candidiasis; this figure of 2% is an average, and some subgroups have much higher rates of disease. How, then, can we identify those higher-risk patients? Risk factors for patients both with and without neutropenia have been studied. Unfortunately, the amount of data here is surprisingly limited. Although many investigators have described the characteristics of patients who have invasive candidiasis, the key risk factors can be identified
only by means of comparison with a control group. Studies that have included such an analysis are shown in table 2.

Neutropenia, the one factor that consistently makes prophylaxis of value for patients with cancer, is not at all relevant to patients in the ICU setting. On the other hand, several new factors become important for patients who do not have neutropenia. Among these factors, use of hyperalimentation and issues related to the gut are particularly intriguing. Also of interest is the absence of burn injury as a risk factor in these studies, despite the association of patient admissions to burn units with high rates of invasive fungal infections [66]. Likewise, surgery is probably a risk factor [62], but reports to date have not teased out the impact of different types of surgery.

Studies of the relevance of candidal colonization also have been notably limited. Most reports simply show that colonization is a risk factor; the critical issues of site, extent, and duration of colonization are only beginning to be explored. Some carefully performed studies have found that colonization was not a meaningful independent predictor of invasive disease [62]. Pittet et al. [48] have broken new ground in this subject area with their work that shows that semiquantitative measures of density of colonization could be linked to risk. Further work in this important area is clearly needed. The intriguing issue of the duration of the period when the patient is at risk also has been little studied. Craven et al. [67] showed a median time to onset of nosocomial infection (of any type) of 7–10 days among a large group of patients in the medical and surgical ICUs, and the time at risk might well be relevant with regard to fungal infections.

As an example of the possible use of these types of data, the study by Wey et al. [35] has generated a regression equation by use of logistic regression for 4 predictive factors (number of antibiotics administered, presence of Candida species in a sample other than a blood sample, performance of hemodialysis, and use of a Hickman catheter). Such data could be used to directly compute a risk for invasive candidiasis and, therefore, to permit identification of patients who would be most likely to benefit from prophylactic therapy. However, the data of Wey et al. are not directly applicable to many patients in the ICU, because the case-control selection process included matching with regard to whether the patient underwent a prior major surgical procedure. Therefore, risk factors related to surgery could not have been (and were not) identified by these investigators. Because surgery, especially on the gut, often seems to be relevant, additional data are needed. Furthermore, many patients with neutropenia who had Hickman catheters inserted were included in the dataset, again making this group not directly applicable to patients in the general ICU setting.

Despite these data limitations, 5 attempts [65, 68–71] to apply these concepts in the ICU setting have been made to date (table 3). Savino et al. [68] enrolled 292 patients from surgical and trauma ICUs in 4 different treatment arms (i.e., no therapy, therapy with oral clotrimazole, therapy with oral nystatin, and therapy with oral ketoconazole). The rate of incidence of invasive

Table 2. Reports of studies of risk factors for invasive candidiasis.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Study cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with cancer</td>
</tr>
<tr>
<td>Granulocytopenia, BMT, type/duration of chemotherapy, GVHD, extent of mucositis</td>
<td>[16, 51–56]</td>
</tr>
<tr>
<td>Colonization with Candida species</td>
<td>[17, 51, 55, 57–59]</td>
</tr>
<tr>
<td>Broad-spectrum antibiotics</td>
<td>[51, 54, 59]</td>
</tr>
<tr>
<td>Hemodialysis or azotemia</td>
<td>[35, 60]</td>
</tr>
<tr>
<td>Central vascular catheter</td>
<td>[55]</td>
</tr>
<tr>
<td>Severity of illness</td>
<td>[50, 61–63]</td>
</tr>
<tr>
<td>Hyperalimentation</td>
<td>[64, 65]</td>
</tr>
<tr>
<td>Recurrent or persistent gastrointestinal perforation</td>
<td>[64, 65]</td>
</tr>
<tr>
<td>Prior surgery</td>
<td>[62]</td>
</tr>
<tr>
<td>Neonatal ICU: gestational age, low Apgar score, length of stay, shock, H2 blockers, and intubation</td>
<td>[61]</td>
</tr>
</tbody>
</table>

NOTE. Although many investigators have reported the general characteristics of groups of patients who have developed invasive candidiasis, data from case-control or cohort studies that have assessed the critical risk factors are less abundant. The data in this table are limited to results from such studies (identified via both MEDLINE searches and reviews of bibliographies of articles on this topic), and the reported factors are either those identified by means of logistic regression or, if no logistic regression was performed, those with relatively high ORs in univariate analyses. The studies involved the use of diagnostic criteria that range from the presence of candidemia to inclusion of various forms of localized invasive candidiasis. Other than a study of pediatric patients with leukemia in the group of patients with cancer [56], a study of patients who were in the pediatric ICU that included a group of patients in the ICU without neutropenia [63], and a study of patients who were in the neonatal ICU [61] that included a group of patients in the ICU without neutropenia, all data are from studies of adults. BMT, bone marrow transplantation; GVHD, graft-versus-host disease.
Invasive candidiasis was only 3% (even though the case definition included patients who were merely colonized at multiple sites). The 4 treatment arms made the study underpowered for any given comparison, and (not surprisingly) no differences were seen between the treatment arms. The exclusion of colonized patients may have contributed to the low event rate. In addition, ketoconazole is inconsistently absorbed even in healthier individuals, so the amount of drug delivered in this setting is uncertain.

In the second study, Eggimann et al. [65] followed up on the observation [64] that patients with refractory gastrointestinal perforation had candidal peritonitis at significant rates. These authors then enrolled 43 of these highly selected patients in the surgical ICU, and the trial is thus relevant. These authors then enrolled 43 of these highly selected patients in a randomized, prospective, double-blind, placebo-controlled trial of prophylaxis with fluconazole, 400 mg/day [65]. They observed a rate of peritonitis of 35% among the placebo-treated patients, a rate that fell to 4% among the fluconazole-treated patients (P = .02). This striking result is even more impressive when the sample size is revealed: there were only 23 patients in the fluconazole treatment arm and 20 in the placebo arm.

Despite its small size, the study is sound and convincing. Its success depended on administration of a potent therapy (there was a 10-fold reduction in the rate of infection) to a group of very-high-risk patients, all of which makes it a good example of the aforementioned statistical principles. With that, the outcome seems inevitable, at least in retrospect. However, the strength of this study (the use of carefully selected patients) is also its limitation, because the results do not apply more broadly.

In the third study, Ables et al. [69] enrolled patients in a trauma/surgical ICU who had an anticipated ICU stay of at least 48 h in a randomized, prospective, double-blind, placebo-controlled trial of prophylaxis with fluconazole, 400 mg/day. Prophylaxis was considered a failure if a patient developed documented invasive candidiasis, a syndrome compatible with invasive candidiasis that was believed to require specific treatment, or a systemic inflammatory response syndrome without demonstrable bacterial or other etiologies. With 60 evaluable patients in one treatment arm and 59 in the other, the failure rates were 22% and 24%, respectively. There were slightly more

**Table 3. Data from studies of antifungal prophylaxis in patients in the intensive care unit.**

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Inclusion criteria</th>
<th>Exclusion criteriaa</th>
<th>Invasive candidiasisb</th>
<th>Study arm (evaluable n)</th>
<th>IC rate, % (n)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>[68]</td>
<td>Remaining or expected to remain in an SICU for &gt;48 h</td>
<td>Pregnancy, burn, transplant, yeast colonization</td>
<td>“BC, &quot;peritoneal Cx, or Cx results from &gt;3 sites&quot;</td>
<td>Placebo (59)</td>
<td>19 (11)c</td>
<td>NS</td>
</tr>
<tr>
<td>[65]</td>
<td>Recurrent or refractory GI perforation/leakage</td>
<td>Hemodialysis, peritoneal dialysis</td>
<td>“Peritoneal Cx with symptoms, and increasing amounts of Candida species”</td>
<td>Placebo (20)</td>
<td>35 (7)</td>
<td>.02</td>
</tr>
<tr>
<td>[69]</td>
<td>Expected to remain in an SICU for &gt;48 h plus a risk factord for candidiasis</td>
<td>Pregnancy, life expectancy &lt;3 mo</td>
<td>Documented candidiasis or colonization with fever</td>
<td>Placebo (59)</td>
<td>19 (11)c</td>
<td>NS</td>
</tr>
<tr>
<td>[70]</td>
<td>Expected to remain in an SICU for &gt;72 h plus mechanical ventilation</td>
<td>Not specified in abstract</td>
<td>“Severe Candida species infection”</td>
<td>Placebo (101)</td>
<td>8.9 (9)</td>
<td>.2</td>
</tr>
<tr>
<td>[71]</td>
<td>Expected to remain in an SICU for &gt;72 h plus “acutely critically ill”</td>
<td>Not specified in abstract</td>
<td>“Cx result at autopsy, BC result at biopsy</td>
<td>Placebo (130)</td>
<td>15.3 (20)</td>
<td>.07</td>
</tr>
</tbody>
</table>

**NOTE.** BC, blood culture; Clotr, clotrimazole; Cx, culture; Flu, fluconazole; GI, gastrointestinal; IC rate, rate of incidence of invasive candidiasis; Keto, ketoconazole; Nys, nystatin; p.o., by mouth; Ref., reference; SICU, surgical intensive care unit; “”, positive.

a Exclusions for prior antifungal therapy, preexisting fungal infection, likelihood of death within a few days of enrollment, and significant baseline laboratory abnormalities (e.g., for liver enzyme levels or platelet count) were generally used and are not specifically noted.

b The principal form of invasive candidiasis diagnosed in the study. Other forms may have also been noted, but these forms are the basis for the key results.

c An additional case of candidemia was noted in the fluconazole treatment arm; inclusion in the definition of invasive candidiasis raises the P value to .06.

d Central venous catheter, total parenteral nutrition, mechanical ventilation for >24 h, or broad-spectrum antibiotics.

e Most cases appear to have been diagnosed on the basis of colonization (usually via a sputum culture; see text for discussion).
failures due to candidiasis in the placebo arm (19% vs. 13%), but the case definition confuses the results. None of the cases of candidiasis involved the bloodstream, and the majority of cases were diagnosed on the basis of positive sputum culture results. Critical examination of this study shows that it seems to suffer from both small sample size and lack of use of a stringent case definition. Because the patients were only minimally selected, an event rate of no more than 2% for proven invasive candidiasis might have been expected. With a sample size of 60 patients per study arm, only 1.2 events ($60 \times 0.02$) would be expected in the placebo arm. Application of the Poisson estimation for rare events [72] shows that one would expect to see this one event only 70% of the time in a sample this small. It is therefore hard to draw convincing conclusions from this study.

The final 2 studies come close to providing generally applicable approaches to this problem. The study by Garbino et al. [70] included 220 patients in the medical/surgical ICU who, either on or after their third day in the ICU, were enrolled in a randomized, prospective, double-blind, placebo-controlled trial of prophylaxis with fluconazole, 100 mg/day. All patients in this study were also undergoing mechanical ventilation and selective digestive tract decontamination with nonabsorbed antibacterial agents. The incidence of documented invasive candidal infections was reduced from 8.9% to 3.9% by treatment with fluconazole, but this result did not reach statistical significance ($P = .2$). A significant reduction in the frequency and intensity of candidal colonization was observed, however. The encouraging trend observed in this study thus shows the potential for prophylaxis to be effective, but the low event rate causes the results to be statistically nonsignificant. As suggested by the data in table 1, a sample size of $\sim 500$ patients per study arm (for a total of $\sim 1000$ patients) would have been required to give the study a power of 80%.

Pelz et al. [71] enrolled 260 acutely critically ill patients with predicted durations of stay of at least 3 days in the ICU at The Johns Hopkins University Hospital, Baltimore. The patients were randomized to receive fluconazole, 400 mg/day given enterally, or placebo, starting as soon as possible after ICU admission. With use of a very strict case definition for invasive candidiasis that required microbiological proof of infection (colonization, no matter the extent, was not used), the rate of incidence of proven invasive candidiasis was 15.3% in the placebo arm and only 8.5% in the treatment arm ($P = .07$ by use of the $x^2$ test, but $P < .01$ in a time-to-event analysis). These results are impressive and clearly show the potential for prophylaxis. The use of oral therapy is also intriguing: a companion pharmacokinetic study shows reasonable blood levels [73], and (as discussed above) it is possible that the local effects in the gut added to the systemic effects of this therapy.

However, generalization of these results requires a good understanding of the nature of the enrolled patients, especially in light of the fact that the 15.3% rate of development of invasive candidiasis among the placebo-treated patients is comparable to the 15.8% rate in a previous study of patients who were undergoing bone marrow transplantation [9]. Given that the enrollment criterion for the study (staying or being predicted to stay at least 3 days in the ICU) is so similar to that for studies with much lower rates of invasive candidiasis, are there other factors at play?

Analysis of the available data suggests that this is so. On the basis of comparison with the patients enrolled in the study of Garbino et al. [70] and according to data obtained from the published abstracts and their authors (D. Pittet and P. Lipsett, personal communications), the patients enrolled by Pelz et al. were older (mean age, $\sim 65$ vs. $\sim 55$ years), were more severely ill (mean Acute Physiology and Chronic Health Evaluation version III [APACHE III] score of $\sim 65$ vs. APACHE II score of $\sim 21$), more often had recently undergone surgery ($>90\%$ vs. $\sim 60\%$), more often had diabetes ($\sim 25\%$ vs. $\sim 12\%$), more often had severe liver dysfunction or cirrhosis ($\sim 20\%$ vs. $\sim 2\%$, with many of the patients of Pelz et al. being candidates for liver transplantation), and stayed in the ICU and thus continued receiving the study therapy for a longer duration (mean duration of therapy, $\sim 14$ days vs. $\sim 7$ days).

Duration of study enrollment may be a factor of unappreciated importance—70% of the observed infections in the study by Pelz et al. were seen during or after the second week of therapy. An additional subtle indication of the difference in the ICU populations comes from examination of the relative proportions of the patients in the ICU who were enrolled in the study. Pelz et al. found that 38% of the patients admitted to their ICU were study candidates (and the study enrolled 21% of the admitted patients), whereas Garbino et al. found that $<5\%$ of their admitted patients were eligible for their study. Likewise, the patients studied by Pelz et al. were measurably more ill than were the ICU populations studied by Petri et al. (median APACHE II score, 14; median age, 59 years [44]), Ables et al. (median APACHE II score, $\sim 18$; mean age, $\sim 45$ years [69]), and Borzotta and Beardsley (mean APACHE II score, $\sim 16$; mean age, $\sim 40$ years [50]). The possibility that the observed results are principally due to outcomes in a subset of patients (e.g., the cirrhosis/liver transplantation candidates) also cannot be excluded, and a better understanding of the patient group(s) that drove the end result awaits more complete publication of the data. However, this study makes clear the potential for prophylaxis: if a suitable group can be identified, prophylaxis can and will be of value. With regard to the unusually ill patient population in the ICU studied by Pelz et al., selection appears straightforward. On the other hand, the published experience of other ICUs shows that most other ICU
CONCLUSIONS AND FUTURE DIRECTIONS

As this review emphasizes, antifungal prophylaxis appears beneficial for selected critically ill patients who do not have neutropenia. Antifungal prophylaxis has been shown to be effective and useful for carefully chosen patients with persistent intestinal perforation or who undergo liver transplantation or, possibly, pancreatic transplantation. Additional studies are needed to identify other subpopulations that might benefit. The studies by Garbino et al. [70] and Pelz et al. [73] make it clear that such demonstrations are entirely possible. Consistent with these observations, a multivariate analysis in a multicenter observational study showed that antifungal prophylaxis was independently associated with a decreased risk for fungal infection [62]. However, routine clinical use of antifungal prophylaxis will require thoughtful analysis on the part of the physician.

The patients enrolled by Pelz et al. appear to belong to an unusual risk group that is not typical of other ICU settings, and it may also be that the majority of the benefit was received by a minority of the patients. The patients enrolled by Garbino et al. appear to be closer to representing a typical group of patients in the ICU, but some form of additional patient selection would appear to be needed. Overall, it would appear likely that only a fraction of the patients in any given ICU would be candidates for prophylaxis, and careful patient selection will be required to maximize the benefit of such therapy.

In the recently released guidelines of the Infectious Diseases Society of America–Mycoses Study Group for treatment of fungal infections, we and our coauthors discouraged routine use of antifungal prophylaxis in the general ICU setting [74]. This position is consistent with that previously recommended by the British Society for Antimicrobial Chemotherapy [75] and in a consensus statement of a group of international clinicians [76]. This review illustrates both the strengths and the weaknesses of the data behind these conclusions. The work of Pelz et al. [73], Garbino et al. [70], and Eggiman et al. [65] makes it clear that patient selection is the key.

The existing data regarding risk factors need to be updated in the current practice environment, with a particular focus on understanding the significance of fungal colonization. The relevant regression coefficients would then be used to define truly useful patient selection criteria. Studies to generate such data have recently been completed, and their analysis may answer significant parts of these questions. Studies in the neonatal ICU may be particularly easy to implement, because the uniform presence of the risk factors related to prematurity creates a relatively homogeneous population with a significant rate of disease. Although measurements of colonization rates, including types of sites and extent of colonization, are of value in the determination of the predictive value of colonization when selecting patients at risk for invasive candidiasis, current knowledge does not justify performance of routine surveillance cultures, especially in light of the enormous logistical difficulties and costs attached to such testing.

The principal negative aspects of prophylaxis will be selection of resistant strains and drug-related toxicity. These negative consequences are anything but trivial and should not be underestimated. None of the study reports published to date have addressed such events, but larger-scale use over longer periods of time than in a typical clinical trial would probably be required to observe the true rate of such events. Despite this, both possibilities are more than theoretical and lead to challenging questions about choice of drug and route of therapy for prophylaxis.

All currently available antifungal agents have the potency required to produce a good clinical effect. However, they do differ with regard to the secondary features of toxicity and resistance. The azole antifungal agents are very safe, but selection for resistant species is relatively common. The polyenes have significant risk of toxicity but low rates of clinical resistance. Agents of the echinocandin class (e.g., caspofungin, FK463, and LY303366 [77]) appear quite safe, but the risk for selection of clinically resistant strains is not yet known.

The process of defining the utility of antifungal prophylaxis would also be simplified by the availability of better tools for the diagnosis of invasive candidiasis. Our current techniques (most notably, blood culture) are, at best, blunt instruments with limited sensitivity. Being forced to rely solely on definite cases that have been diagnosed with available tools surely makes the task of assessing the value of prophylaxis more difficult. It is unfortunate that serodiagnostic strategies for candidiasis (e.g., PCR and antigen detection) remain problematic, and a convincing tool has yet to emerge.

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References

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