Clinical Trials of Antifungal Prophylaxis among Patients in Surgical Intensive Care Units: Concepts and Considerations

Pamela A. Lipsett
Departments of Surgery, Anesthesiology, and Critical Care Medicine, Nursing, Johns Hopkins University School of Medicine, Baltimore, Maryland

Background. Fungal infections are important clinical infections in patients in surgical intensive care units. In some institutions, antifungal prophylaxis has become commonplace, and increasing resistance has been reported. However, trials of antifungal prophylaxis are hampered by difficulties in trial design, and the findings may not be generalizable.

Methods. Issues in clinical trial design are reviewed from existing and theoretical perspectives.

Results. Identification of a primary hypothesis with a sound epidemiological basis is essential. The study must include institutions where fungal infections have a high and well-studied incidence. A high-risk patient population should be identified and enrolled. The agent selected should have an appropriate spectrum, be easily delivered to the population selected, and be cost effective with few adverse events. At present, fluconazole appears to be the best agent for targeted prophylaxis. The primary end point of the study should be based on an easily measured outcome, for example, days free from fungal infection rather than death due to fungal infection.

Conclusions. Trials of antifungal prophylaxis for patients in surgical intensive care units have had problems in design, and several issues in the conceptual basis of future clinical trials must be addressed.

Nosocomial infections continue to cause morbidity and mortality in surgery patients [1]. Among these infections, fungal infections have been identified with increasing frequency—the National Nosocomial Infection Surveillance data indicated that fungal species are the fourth most common isolate from blood in the surgical intensive care unit (ICU) [2, 3]. Some institutions have documented substantial use of antifungal agents in the treatment of surgical ICU patients without documented infections; in fact, many patients did not even have samples obtained for culture [4]. One of these institutions has also noted an increase in the frequency of isolation of Canada glabrata, a relatively triazole-resistant species [4]. This change in clinical practice has occurred without general agreement about the strength or quality of the evidence from randomized clinical trials of universal prophylaxis for patients in surgical ICUs [5]. Because of fundamental problems in the design and conduct of clinical trials in this area, several issues in the conceptual basis of future clinical trials must be addressed. Here, I do not review the specifics of the published trials among patients in surgical ICUs [6–10]. Instead, I rely substantially on previously published studies by my group to discuss the issues and concepts that must be considered in the development of future studies of antifungal prophylaxis [6, 11–13].

**SELECTION OF THE QUESTION**

The primary question to be answered in a clinical trial of antifungal prophylaxis is, “Should antifungal agents be used to treat patients in surgical ICUs and, if so, which patients?” Although this question may be simplified and is not in the form required for the ultimate clinical trial, we can examine the necessary background information required to answer it.

Before beginning such a trial, one should have a good understanding of the magnitude of the problem. Specifically, one should have information about the incidence of the disease, both inter- and intra-institutional (necessary for a power calculation), and about the population at risk for the disease. Information must be available concerning the following: what fungal species
are present, what the plan is for those species that we desire to prevent clinically (agent selection), and whether fungal infections have a sufficient impact on morbidity, mortality, or economics to warrant implementation of prophylaxis as a public health and patient safety measure [13–17].

Sufficient epidemiological data must be available in the care units considered for study to successfully plan and conduct the clinical trial. To aid in the planning of the clinical trial of antifungal prophylaxis by Pelz and colleagues [12, 13], we conducted a 3-month pilot study of patients in the surgical ICU, medical ICU, and oncology ward. We were specifically interested in identifying the natural incidence in the surgical and medical ICUs and where antifungal prophylaxis was not used and then comparing this with the incidence and species present among patients on the hematology-oncology service, where fluconazole prophylaxis had been implemented for nearly a decade. We also assessed clinical and economic outcomes, risk factors, and a possible strategy for patient enrollment [13]. Using the selection strategy we planned to use in the clinical trial, we identified a 12% incidence of fungal infections and substantial mortality (50%), morbidity, and costs associated with fungal infections [13]. The median ICU costs for patients with a Candida infection was $41,832, with a median ICU stay of 15 days and a median hospital stay of 31 days, whereas patients who were not infected by Candida had a median ICU cost of $19,252, median ICU stay of 7 days, and median hospital stay of 18 days [13]. When this cost was distributed over the entire cohort planned for trial entry, we concluded that any form of prophylaxis that cost <$230/day would be cost effective. Although our data reported ICU costs and not total hospital costs, in a 1998 report by Rentz et al. [15], the economic cost of candidemia was associated with a stay of 36 days, versus 15 days for uninfected patients, and a cost of $34,123 for patients on Medicare and $44,536 for privately insured patients, similar to what we would expect for our total incremental hospital costs.

**SELECTION OF SITES**

The decision about where to conduct a clinical trial may affect the success and, certainly, may affect whether the results of the clinical trial will be widely applicable to a broad number of patients at a variety of institutions (generalizable). For the most broadly applicable studies, a randomized multicenter clinical trial is best. However, in using multiple sites to conduct the trial, one must be certain that the sites have enough commonality that the underlying hypothesis can be successfully tested—that is, that the noise-to-signal ratio is not too large and that no single institution dominates in the number of patients entered overall. In practical terms, each institution should be able to provide baseline information about the disease under consideration, for the best estimate of the ability to successfully determine an end point. The investigator should also have a keen understanding of any practice patterns that could inherently bias patients against entry or that would encourage early removal from the trial. If a multicenter trial is not feasible, then a single-institution, multiunit trial would allow broader patient-entry criteria but still may not have a wide enough applicability to warrant broad implementation. The least desirable prospective trial design for generalizable findings would be one that involves a single unit at a single institution. The potential advantage of this design, however, is the practical ability to conduct a trial under uniform conditions. Thus, the investigator must balance the benefits of a homogenous pattern of care and the drawbacks of a patient population that could be fundamentally different from patients at other institutions. If a therapeutic study comparing 2 treatments is desired, prospective observational and retrospective data are generally of less value.

**SELECTION OF PATIENT POPULATION**

One of the most important considerations for both the conduct and ultimate application of the clinical trial is the selection of the patient population to be studied. Thus, it is critically important to identify a patient population that has a quantifiable risk of developing the disease being studied or, alternatively, that is easily identifiable as having the disease. Unfortunately, this is problematic for patients in surgical ICUs on both accounts. Identification of those who have the disease is discussed below. Although many studies have published the epidemiological factors associated with acquisition of a fungal infection, many of these studies are small and demonstrate that there is wide variation in the incidence of fungal infections [3, 18–23]. In a recent study of >4000 patients, Blumberg et al. [3] demonstrated a rate of 8.82 candidal bloodstream infections per 1000 admissions and a rate of 0.98 candidal bloodstream infections per 1000 ICU patient-days, which increased to a rate of 1.42 infections with the presence of a central venous catheter. Additional independent risk factors associated with an increase in candidal bloodstream infections include prior surgery (relative risk [RR], 7.3), acute renal failure (RR, 4.2), receipt of parenteral nutrition (RR, 3.6), and, for those who had surgery, the triple-lumen central venous catheter (RR, 5.4). Receipt of antifungal agents in this study was recorded but uncontrolled and was associated with decreased risk (RR, 0.3) [3]. The selection of risk factors, the number of risk factors, and the positive and negative predictive value of each risk factor is completely theoretical, as far as prospective application of these factors for entry criteria into a clinical trial. We simply do not know how to weigh individual risk factors, nor do we know the incremental benefit of combined factors. Many studies suggest that not all risk factors are created equal.

One risk factor that should be specifically considered is the
presence or absence of fungal colonization. Although surveil-
ance cultures have shown some value, their greatest value is
in their negative predictive value (94%–100%); that is, in the
absence of fungal colonization, fungal infection is rare [12, 19,
20, 23]. However, the positive predictive value of fungal sur-
veillance cultures is in the range of 12%–18%, and, therefore,
the use of these cultures to define an at-risk population is
probably not effective, especially when the problem of the time
it takes for a positive culture result is considered [11]. In the
Cox analysis of our group’s clinical trial [6], we identified both
fungal colonization and days prior to receiving antifungal pro-
phylaxis as risk factors. Because each day prior to treatment
increased risk (38%/day), patients at risk should be identified
as soon as possible, and therapy should be begun [6].

As time passes during a critical illness, the risk of developing
a fungal infection increases. Patients who develop a severe acute
illness but recover quickly are at a much lower risk of develop-
ing a fungal infection than is a patient who begins with a
similar severity of illness but recovers at a much slower rate,
who has repeated setbacks during recovery, or who will ulti-
mately die during the trial [6, 7]. Thus, acquisition of fungal
infection is a time-dependent variable that must be considered
in both the design and the analysis of clinical trials. Not only
the pathogen but also the patient’s host immune response will,
in part, dictate composite risk. Several studies have used time
in the ICU as part of risk assessment [6–8]. This may be to
enable targeted prophylaxis rather than universal prophylaxis
and may result from the inability to clearly identify and artic-
ulate at ICU entry which patients are at risk and would benefit
from immediate antifungal prophylaxis. Whereas a pilot trial
verified that the institutional selection of an at-risk patient
population was possible on the basis of time in the surgical
ICU; a single, double-blind randomized clinical trial has used
the projected ICU duration of stay (>3 days) in determining
sole eligibility for the clinical trial [6]. Because enrollment was
based on the assessment of a single experienced intensivist,
exporting this criteria to another intensive care specialist whose
patients have potentially different demographics does not guar-
antee a similar result in terms of either magnitude or, possibly,
direction. The use of duration of stay by itself as an entry
criterion could vary by unit, type of institution, size of hospital,
academic versus nonacademic hospital, and ICU organizational
structure. Certainly, it is possible that duration of stay could
vary, for example, from a large center that has inadequate ICU
beds and that quickly moves sick patients though the ICU to a
smaller institution that has less severely ill patients in the
ICU for a longer period. In the first theoretical example, pa-
tients who could be at risk for fungal infection are moved out
of the ICU, and, in the second case, a lower-risk patient who
would be in the smaller ICU for a longer period would receive
the therapy but would not be expected to benefit to the same
degree as in the original clinical trial.

What factors could then be used to predict a high-risk patient
population? The APACHE score uses a series of clinical and
physiological variables obtained at the time of ICU admission
to predict the likelihood of ICU and hospital mortality [24,
25]. On the basis of similar-sized institutions, the APACHE
system can demonstrate performance standards of duration of
stay and of ICU and hospital mortality with observed-to-ex-
pected ratios [24, 25]. Although the APACHE score is often
used as a stratification tool in clinical trials, it was not designed
for this use, and its use as a single tool in predicting ultimate
fungal infection has not been verified. The APACHE scoring
system has undergone 3 revisions and modifications to improve
its predictive value in a broader patient population. APACHE
III, although a better predictor of outcome in surgery patients,
is proprietary and expensive to implement [25]. Other scoring
systems are available but have not been prospectively applied.
In deciding to use a risk factor scoring strategy as an enrollment
criterion for an antifungal clinical trial, one is really studying
the reliability of the formula in the prediction of a fungal in-
fec tion (proof of implementation) rather than the proof of
concept as to whether antifungal prophylaxis is effective. In
using a formula that is unreliable or that selects patients at low
risk for the end point in the clinical trial, one may erroneously
conclude that the therapy was ineffective, whereas the correct
conclusion is that the therapy was not proven by means of the
selection criteria. If the trial has been designed with the as-
sumption of a higher rate of end point than was actually pro-
duced by the formula or risk factors, a type II error may pro-
duce a negative or apparently equivocal result, whereas a larger
clinical trial (sample size) or more predicative entry criteria
could have an alternative result [26].

Although randomization should, in a large clinical trial, bal-
cance any potential confounding variables, it is reasonable to
consider known clinically important confounding variables for
stratification. Statistical methods become very complex if >3
variables are selected; however, stratifying for risk-factor bal-
cance and not for subgroup analysis is appropriate. Because of
the method of drug delivery selected in the recent clinical trial
[6] and to ensure balance of potentially disparate clinical
groups, patients with liver transplantation, patients with pan-
creatitis, and those with prolonged ileus were selected as po-
tential confounders for stratification.

How much risk is enough? As discussed above, the de-
cision to proceed with the clinical trial must include consid-
eration of the overall importance of the disease to be studied
in terms of a public health and patient safety. For example,
ischemic myocardial disease is very prevalent, and thus even
small changes in outcome can have a major impact on public
health. On the other hand, fungal infections, although impor-
tant, are much less common but have a higher associated morbidity and mortality [17, 27]. On balance, prevention of the acquisition of these infections has merit. In theory, the closer one comes to perfect identification of the at-risk patients, the higher the rate of infection in the placebo group and the smaller the overall study [6, 7]. In performing this assessment, one should consider the absolute difference in end point rates. An excellent term that allows the physician to understand the magnitude of the effect of the end point in the trial (benefit or harm) is the number needed to treat: 1/(absolute difference in rate of group A—the rate of group B) [28]. For instance, in the recent trial by my group [6], in the intent-to-treat analysis, the number needed to treat to prevent one fungal infection was 15 (15 patients needed to receive therapy to prevent one infection), which dropped to 9.5 if the analysis during therapy was considered. For a preventive therapy, this is a very low number, suggesting that the selection criteria were effective and that the study was powered adequately.

If the number needed to treat is very high, for example, 100, one should consider the consequences of exposing 99 patients to a therapy that would benefit only one patient. This decision would include factors such as the safety of the proposed therapy, its costs, and the consequences of widespread application of this therapy to, for example, 100,000 patients. This is, of course, the point at which the concern for the development of resistance comes into play with prophylactic antimicrobial agents.

In summary, the use of risk factors or a formula in the selection of the patient population has both advantages and disadvantages. The advantage of this approach is that the many identified and variably quantified risk factors that have been prospectively collected should produce a patient population with a certain predicted risk. The total risk of fungal infection should be relatively homogenous across the group of patients with those risk factors. The disadvantages of this approach are several: it is untested, unproven, and complex. Because of the selection process, unless clinicians have absolute equipoise, the potential for treating the highest-risk patients with the therapy under study is a very real concern given the widespread use of antifungal agents for prophylaxis.

Who should not be included? Exclusion criteria in clinical trials depend somewhat on the established safety and known efficacy of the therapy. First, informed consent for a clinical trial among critically ill patients is daunting, complex, and time consuming to obtain [29, 30]. For some indications, such as tests of early resuscitation, consent is impossible, and trials have been conducted with presumed consent [31]. On the other hand, a prophylaxis trial would mandate consent, given that the study is intended to prevent acquisition of disease. Nonetheless, at-risk patients are critically ill and often, if not usually, unable to provide personal consent. Surrogates must be identified through appropriate legal channels to provide consent (this may vary from hospital to hospital as guided by state regulation). Consent for a clinical research trial from a surrogate of a critically ill patient must be obtained in a manner that is noncoercive and that fully discloses the conditions, risks, and benefits attendant to the study. Because patients are critically ill, the surrogates may be especially vulnerable to hope and promises of benefits that are unproven in experimental therapy. The person obtaining consent should not be the provider of direct patient care (conflict of interest) but should be knowledgeable about the patient’s condition so that questions may be appropriately considered and answered. Lack of sensitivity to cultural concerns can bias the consent process and can lead to uneven selection of patients for the study. During the discussion of the study, if the drug has not been approved, it can be clearly emphasized that the drug can be used only as part of this study. On the other hand, if an agent is approved but is being used for an indication that is unproven but is the subject of study and if the use of the drug for this unproven indication is widespread, the investigators will have difficulty recruiting participants and obtaining consent. There must be a realistic examination regarding the presence or absence of clinical equipoise before the study starts.

SELECTION OF THE AGENT, DOSE, AND ROUTE

There are several agents that could be examined in a clinical trial of antifungal prophylaxis. The agents could be divided into non–systemically absorbed versus systemic agents [9]. Fungal disease in surgical ICU patients is primarily a systemic or deeply invasive disease [2, 3, 6, 7]. Unless the site of systemic infection was known and the infection could be completely prevented with a nonsystemic agent, this form of prevention would not be expected to be successful. Thus, nonsystemic therapy will not be considered further. Part of the initial data assessment included identification of the species known to cause infection at a particular institution. In surgical ICUs in the United States, most infections are still caused by Candida species, with Candida albicans accounting for 59% and C. glabrata accounting for 15%–25% [2, 32]. With the assumption that available agents have comparable efficacy, in my view, the agent selected should have the appropriate spectrum of activity, the lowest toxicity, ease of delivery and administration, and the lowest cost. The agent that makes the most sense in a surgical ICU with rates of C. glabrata infection of <25% is fluconazole. Fluconazole is attractive because it has an acceptable spectrum of activity against common surgical ICU pathogens in most institutions, has been widely used with an excellent safety profile and few known drug interactions, is available in both intravenous and oral (suspension and pill) forms, is given once daily, and is quite economical in oral form. Given that fluconazole is also extremely bioavailable, enteral use of fluconazole is especially
Table 1. Definitions of fungal infection.

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>Evidence</th>
</tr>
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<tbody>
<tr>
<td>Proven invasive</td>
<td>Clinical signs and symptoms of an infection, and (1) histopathologic evidence of invasive infection on biopsy or autopsy; or (2) microbiological evidence of infection in tissue culture (e.g., kidney, lung); or (3) positive result of culture for yeast from any single closed, normally sterile body cavity or organ (e.g., intraoperative peritoneal fluid at laparotomy for infection, or percutaneous drainage of intra-abdominal abscess; but positive results of culture from indwelling peritoneal drains or biliary catheters may not be infections)</td>
</tr>
<tr>
<td>Deep tissue</td>
<td>Fungemia, dissemination (1) positive result of blood culture obtained by venipuncture, or (2) endophthalmitis</td>
</tr>
<tr>
<td>Possible (controversial)</td>
<td>Positive result of culture of 2 urine specimens obtained before and after change of a urinary catheter or by straight catheterization</td>
</tr>
<tr>
<td>Suspected</td>
<td>Clinician-determined need for antifungal therapy for suspected fungal infection, signs of end-organ dysfunction, and evidence of fungal colonization (i.e., in sputum, urine, or biliary sample)</td>
</tr>
</tbody>
</table>

NOTE. From [6].

Attractive. In the clinical trial by my group [6], all fluconazole was given via an enteral route, irrespective of the patient’s clinical condition and ability to eat. If this route is selected, the patient must be able to take medication orally (unusual) or must have a nasogastric, nasoduodenal, gastric, or jejunal tube for administration.

In some instances, an agent for prophylaxis has been suggested at less than the therapeutic dose [7]. Although on the surface this may seem to be a prudent way to minimize drug exposure, in circumstances in which the pathogens have a spectrum of susceptibility to the agent, the use of a low dose could theoretically increase the likelihood of resistance, and pathogens that have borderline susceptibility to usual doses may not be susceptible to the lower “prophylactic” dose. In the trial by my group [6], we selected a loading dose of 800 mg fluconazole followed by a daily dose of 400 mg unless the estimated creatinine clearance was <25 mL/min, in which case we gave 200 mg. The dose selection was also based on the possibility that enteral fluconazole might not be as well absorbed by our high-risk patients, and we were aware that higher doses are used clinically without significant side effects for most patients. We also selected the enteral route because to use the intravenous route the patient would need some means of intravenous access. In addition, the intravenous form currently has substantially higher average wholesale cost than does the enteral form. However, in electing to deliver fluconazole via the enteral route to patients whose prior history of absorption was not known, we were testing not only whether fluconazole prevented fungal infections but also whether it would be sufficiently well absorbed in our patient population. Asking more than one question as a primary end point in a clinical trial can lead to failure to find a positive result. Because we were concerned about this possibility, we planned a substudy of the pharmacokinetics of fluconazole, measuring serum levels and the MICs for all infecting species [11].

STUDY END POINTS AND DEFINITIONS

Other remaining difficulties are how the investigator will define infection and how the primary end point of the study will be defined. Unfortunately, there is no consensus among infectious disease physicians, surgeons, intensivists, or other clinicians about what constitutes a definite or even clinically significant infection in surgical ICU patients [5]. In immunocompromised patients, consensus has been developed for what does and does not constitute an infection [33]. Table 1 presents definitions of infection that would be considered by most to represent infection, as well as areas for controversy. Several points merit discussion. Deep-tissue evidence of invasion obtained by biopsy or autopsy would be considered definitive evidence of infection. In the presence of clinical signs and symptoms, both candidemia and isolation of Candida from a normally sterile deep site would also constitute a definite infection. Isolation of Candida from bile or from in situ drains is not a reliable sign of infection and usually represents colonization. However, isolation of Candida from the peritoneal cavity can and often does represent true infection [6, 10, 18, 34]. One of the controversial major areas is how to define a urinary infection versus colonization and what constitutes an upper or lower urinary tract infection [34–38]. In patients in ICUs, there are very few data about the origin and consequence of candiduria. From the experiment by Krause et al. [39], which involved ingestion of Candida organisms (concentration ingested, 10^{12}), we know that even immunologically normal hosts can develop signs and
symptoms of an infectious syndrome, candidemia, and candiduria. Although there is no agreement about this issue, an increase in Candida concentrations in the urine or the new onset of Candida in urine would be a concern. Candida isolated from a vascular catheter is associated with candidemia but probably should not be considered a sign of probable fungal infection [5, 33, 40]. Isolation of Candida from sputum is also problematic. The incidence of Candida involvement in the lungs is based on few small studies, and thus true incidence is difficult to estimate [41, 42–43]. Multisite colonization (>3 sites) is often considered an indication for therapy in a clinically infected patient without a defined bacterial infection who is taking broad-spectrum antibiotics [44]. Colonization cannot define infection.

The end point in a clinical trial should have clearly defined parameters [28]. Unfortunately, fungal infection may be present without positive culture results and identified only at autopsy. Nonetheless, prevention of fungal infection is a reasonable end point. A word of caution should be offered: it is not the absolute proportions of patients with and without infection that should be analyzed (e.g., by χ^2 analysis); because fungal infection is time dependent, a longitudinal method of data analysis is required. Because patients with fungal infections have high mortality, it is also reasonable to consider mortality as an end point in a clinical trial. However, patients with critical illness have many comorbidities and a substantial predicted mortality even in the absence of a clinical infection. Antifungal prophylaxis would have no effect on this baseline mortality and would be predicted to affect only mortality attributable to the fungal infection. Because there is little agreement on who has or does not have a fungal infection, there would be even less agreement on what would constitute a death attributable to fungal infection.

Other established end points that can be objectively measured could include such measures as duration of ICU stay or hospital stay. However, criteria that define eligibility for discharge would have to be objectively applied, preferably by an adjudication panel. Occasionally, in trials in which mortality is substantial, an end point is used that constitutes being free of the study disease or of the major therapeutic modality, such as being ventilator-free in a study of adult respiratory distress syndrome. Fungus-free survival is, therefore, a viable trial end point.

**CONCLUSIONS**

Patients in surgical ICUs are at increased risk of fungal infections. Several clinical trials have suggested that antifungal prophylaxis reduces the rate of fungal infection by 30%–60% in this patient population [6, 7]. However, universal prophylaxis to all surgical ICU patients is not warranted, and the specific patient populations that would benefit most are not clearly defined. Before a multicenter randomized controlled trial is begun, it would be best to identify an enrollment strategy for high-risk patients entering surgical ICUs. This assessment should be done by use of actual institutional natural-history data to calculate the expected placebo rates of infection. From this careful assessment, an appropriate trial size can be determined. Agreement about the primary end point—fungal infection–free survival versus fungal infection—is necessary, as well as clear prestudy definitions of infection, especially those involving urine cultures.

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