SUPPLEMENT ARTICLE

Clinical Trials of Antifungal Prophylaxis among Patients Undergoing Surgery

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Invasive mycoses have emerged as a major cause of morbidity and mortality. Epidemiological studies have shown that surgery services have the highest rate of *Candida* infections in the hospital. In addition to classical risk factors, heavy *Candida* colonization, recurrent gastrointestinal perforations, and acute pancreatitis are frequently associated with invasive candidiasis. Because prompt initiation of antifungal therapy is critical for cure but difficult to accomplish, prevention of fungal infections may play an important role in this clinical setting; however, few prophylactic or preemptive studies have been done to date. The choice, route of administration, and dose of the antifungal and comparator regimens and the use of clinically relevant and robust study end points are critical for the trial design. Various criteria have been used to identify patients at risk of candidiasis: surgical condition, presence of multiple risk factors, colonization indexes, or expected length of stay in the intensive care unit. Some are not selective enough, and others are time consuming and expensive. Rigorous selection of high-risk patients is crucial to optimize the risk-benefit ratio of preventive antifungal strategies. The aim is to maximize chances of reducing morbidity and mortality while minimizing treatment costs, exposure of low-risk patients to adverse events, and emergence of resistant fungal strains.

Fungi have emerged worldwide as increasingly frequent causes of nosocomial infections [1–4]. *Candida* and *Aspergillus* are the most common causes of invasive mycoses. First observed in immunocompromised patients, primarily in patients with cancer or those undergoing transplantation, opportunistic fungal pathogens have now been recognized as a frequent cause of infections in critically ill and debilitated surgery patients. In a recent survey conducted by the Fungal Infection Network of Switzerland in Swiss tertiary care hospitals, intensive care units (ICUs) and surgical wards accounted for about two-thirds of all episodes of candidemia [5]. The incidence of candidemia was 5–10 times higher in ICUs than in other wards. In these clinical settings, *Candida* is a predominant pathogen, accounting for 5%–15% of nosocomial infections and ranking among the 5–10 most frequent bloodstream pathogens [1].

The most frequent clinical manifestations of invasive candidiasis in surgery and ICU patients include candidemia, intra-abdominal candidiasis, candidal urinary-tract infections, and disseminated candidiasis. Other manifestations, such as *Candida* endophthalmitis, pulmonary candidiasis, and *Candida* endocarditis, occur less frequently.

Invasive candidiasis is associated with substantial morbidity, high crude and attributable mortality (40%–60% and 30%–40%, respectively), prolonged hospital stay, and increased health care costs [6–8]. Prompt initiation of antifungal therapy is essential for the control of infection and a favorable outcome. However, early diagnosis of invasive candidiasis remains a major challenge. Conventional microbiological tests, including blood cultures, lack sensitivity (only 40%–60% among patients with proven invasive candidiasis). Radiological manifestations lack specificity, and novel serological and molecular diagnostic tools still need to be validated on a large scale. Because invasive candidiasis is a late-onset and highly lethal nosocomial infection [6, 9, 10], recent clinical studies have examined the impact of

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prophylactic and preemptive treatment strategies. Here, we review the results of clinical studies of antifungal prophylactic and preemptive therapies in surgery patients at risk of *Candida* infections. We also discuss issues related to the design of future clinical trials in this clinical setting.

RISK FACTORS FOR INVASIVE CANDIDIASIS

In primarily immunocompetent patients, 2 conditions predispose to *Candida* infection: the colonization of skin and mucous membranes by *Candida* and alteration of natural host barriers (i.e., by wounds, surgery, and insertion of indwelling intravascular and urinary catheters). The gastrointestinal tract and skin are the most frequent portals for *Candida*. Risk factors for the development of fungal infections have been identified [11, 12]. Prolonged treatment with multiple broad-spectrum antibiotics is known to cause a profound alteration of the endogenous flora, which promotes the growth of *Candida* species. Debilitating underlying diseases, critically ill status as indicated by a high APACHE II score, premature birth, acute renal failure and hemodialysis, intravascular access devices, antacids, total parenteral nutrition, and mechanical ventilation have also been frequently associated with invasive candidiasis [11]. Unfortunately, few of these predisposing factors are sufficiently discriminant. Indeed, they also are frequently present in patients in whom candidiasis will not occur. However, because the onset of invasive candidiasis is typically preceded by the progressive accumulation of multiple risk factors over days or weeks, their recognition may assist clinicians deciding when to implement preventive measures for a given patient.

Candida colonization was found to play a key role in the pathogenesis of invasive candidiasis in studies that performed frequent surveillance cultures at multiple body sites (e.g., oropharynx, gastrointestinal tract, urinary tract, respiratory tract, skin, drains from surgical sites, surgical wounds, and insertion sites of intravascular access devices) [11, 13–15]. Semiquantitative cultures (i.e., plating of biological specimens by means of the clock-streak technique and a calibrated loop) are often used to estimate the degree of colonization, and results are expressed as light (growth on the first of the 3 inoculation quadrants), moderate (growth on the first and second of the 3 inoculation quadrants), and heavy growth (growth on all 3 inoculation quadrants) [16]. Pittet et al. [14] have studied the role of *Candida* colonization as a predictor of infection in critically ill surgery patients. Colonization was defined by the presence of *Candida* in $\geqslant 3$ samples from either the same or different body sites on at least 2 consecutive screening days. Over a 6-month period, 29 (4.5%) of 650 ICU patients found to be colonized at multiple body sites were followed prospectively—18 patients (62%) remained colonized, and 11 (38%) developed invasive candidiasis. In the group with invasive candidiasis, the mean APACHE II score at ICU admission was higher (28 ± 6 vs. 17 ± 4 in colonized controls; $P < .01$), the mean duration of antibiotic therapy and ICU stay were longer (35 ± 14 vs. 16 ± 13 days [$P < .01$] and 27.7 vs. 17.5 days [$P = .12$], respectively), and the 30-day all-cause mortality was higher (55% vs. 11%; $P = .03$). The median duration of *Candida* colonization was similar in the 2 groups (29 days [range, 5–140 days] vs. 25 days [range, 6–70 days]). However, heavy or increasing quantities of *Candida* in serial surveillance cultures occurred in patients with invasive candidiasis more often than in control patients (91% vs. 44%; $P = .02$). A colonization index was calculated by dividing the number of colonized sites by the number of cultured sites. The mean colonization index in patients who developed invasive candidiasis was significantly higher than that in controls (0.70 ± 0.17 vs. 0.47 ± 0.17; $P < .01$), yet colonization index values overlap between the 2 groups. A colonization index threshold of 0.5 was reached at a median of 6 days (range, 2–21 days) before a diagnosis of invasive candidiasis was made in all patients.

As shown in table 1, the proposed colonization index had a sensitivity and negative predictive value of 100% to distinguish patients who will develop invasive candidiasis from those who are merely colonized. The specificity of the colonization index was 69%, and the positive predictive value was 66%. Sensitivity, specificity, positive predictive value, and negative predictive value all reached 100% when a corrected colonization index

Table 1. Sensitivity, specificity, and positive and negative predictive values of various colonization criteria for prediction of invasive candidiasis in surgery intensive care unit patients.

Criterion	Sensitivity	Specificity	Positive predictive value	Negative predictive value
No. of sites colonized by *Candida*				
$\geqslant 2$	100	22	44	100
$\geqslant 3$	45	72	50	68
Colonization index $\geqslant 0.5$	100	69	66	100
Corrected colonization index $\geqslant 0.4$	100	100	100	100

NOTE. Data are %. Adapted from [14].

with a threshold of 0.4 was used. The corrected colonization index was calculated by multiplying the colonization index by the ratio of the number of heavily colonized sites (based on semiquantitative cultures) to the total number of colonized sites. For example, in a patient in whom 6 sites had been screened for colonization (e.g., oropharynx, urine, stool, tracheal aspirate, central venous catheter insertion site, and surgical wound) and 4 of them had been found to be colonized by *Candida* (e.g., heavily in oropharynx, tracheal aspirate, and stool and moderately in urine), the colonization index was 0.67 (4 colonized sites/6 cultured sites) and the corrected colonization index was 0.5 (0.67×3 heavily colonized sites/4 colonized sites). Genotyping of *Candida* strains confirmed that colonization and fungal invasion are sequential events, because identical colonizing and invasive *Candida* genotypes were found in every patient who later developed invasive candidiasis. If patients are be colonized concomitantly with pathogenic and nonpathogenic strains of *Candida,* then the challenge will be to distinguish these 2 types of strains. Molecular typing may help to identify patients who are colonized by invasive versus noninvasive *Candida* strains. At present, these sophisticated, time-consuming, and expensive diagnostic tests remain purely investigational tools.

Preventive treatment strategies are "double-edged swords" associated with potential toxicity that promote the emergence of resistant microorganisms. It is therefore critical to limit their use to a selected group of patients at high risk of infection.

CANDIDA INFECTIONS AFTER ABDOMINAL SURGERY

The gastrointestinal tract is a major reservoir of *Candida* species and an important portal for intra-abdominal and disseminated candidiasis. As a commensal of the digestive tract, *Candida* may leak into the peritoneal cavity after perforation of a hollow viscus or surgical section of the intestinal wall. However, under most circumstances, *Candida* will be cleared quickly from the peritoneum. Nevertheless, in some patients, peritoneal seeding will result in the development of an intra-abdominal *Candida* infection, with a risk of dissemination to the bloodstream and to extra-abdominal tissues and organs [13, 16–21].

In a study of candidemia in nonneutropenic patients, abdominal surgery was found to be a risk factor in one-third of the patients [22]. However, clinicians have expressed different views about the clinical significance of *Candida* isolated from the peritoneum. Whereas some thought that *Candida* played a pathogenic role in patients with intraperitoneal infections and recommended antifungal therapy [13, 18, 20], others considered *Candida* an "innocent bystander" for which no specific therapy was needed [23, 24]. To help reconcile these apparently conflicting findings, we prospectively analyzed the clinical courses of 49 surgery patients with culture of peritoneal fluid positive for *Candida* species [16]. The results of this primarily prospective study are summarized in table 2. Intra-abdominal candidiasis occurred in 19 cases (39%), whereas *Candida* was eliminated spontaneously in 30 patients (61%). Recurrent gastrointestinal perforation (47% vs. 10%; $P = .005$) requiring multiple surgical interventions and acute pancreatitis (47% vs. 3%; $P < .001$) were more frequent in patients with intra-abdominal candidiasis than in patients without it. Furthermore, the presence of a high initial growth (i.e., moderate or heavy, as defined above) or an increasing (i.e., from light to moderate or heavy or from moderate to heavy) amount of *Candida* in serial semiquantitative cultures obtained at surgery or from abdominal drains was found to be an early indicator of infection. Indeed, positive results of culture for *Candida* at surgery (79% vs. 43%; $P = .02$), moderate or heavy initial colonization by *Candida* (53% vs. 13%; $P = .008$), and an increasing quantity of *Candida* in surveillance cultures (79% vs. 7%; $P < .001$) occurred more frequently in patients who subsequently developed intra-abdominal candidiasis. Thus, sustained seeding of the peritoneal cavity with *Candida* in the context of recurrent gastrointestinal leakages is a major risk factor for candidiasis in patients after abdominal surgery. Of note, abdominal candidiasis is associated with high mortality rates (27%–77%) [13, 19, 24–26], which strongly argues in favor of antifungal prophylactic or preemptive treatment approaches in such a high-risk group.

DESIGN OF CLINICAL TRIALS FOR THE PREVENTION OF INVASIVE CANDIDIASIS IN SURGERY PATIENTS

Several issues should be considered when designing clinical trials of antifungal prophylactic and preemptive treatment strategies (figure 1); these are relevant not only for surgery and ICU patients but also for several other types of patients. These issues are the identification of a group of high-risk patients who may benefit from such interventions, the calculation of the sample size needed to test the study hypothesis, the use of clear-cut primary and secondary study end points, and the choice of a control treatment group that respects the principle of equipoise (i.e., the existence of credible doubt about the relative merits of the proposed medical interventions). These and several others issues have been reviewed recently [27] and here will be reviewed only in the context of the surgery patient.

Patient selection. Selection of an appropriate patient population to test the study hypothesis is essential. The goal should be to give prophylaxis or preemptive antifungal therapy to patients at high risk of candidiasis and to exclude patients who are unlikely to benefit from therapy but may be unnecessarily exposed to adverse events, such as drug toxicity and colonization by resistant *Candida* strains. Given the excellent efficacy and safety profiles of azoles, it would be very tempting to use

Table 2. Clinical characteristics, microbiological data, and outcome for surgery patients with intra-abdominal candidiasis or with colonization of the peritoneal fluid but no evidence of invasive disease.

Characteristic	Candidiasis (n = 19)	Candida colonization (n = 30)	P
Underlying surgical conditions			
Gastrointestinal perforation	9 (47)	19 (63)	NS
Recurrent gastrointestinal perforation	9 (47)	3 (10)	.005
Acute pancreatitis	9 (47)	1 (3)	<.001
Other abdominal conditions	2 (11)	10 (33)	.09
Emergency surgery	15 (79)	26 (87)	NS
Microbiological data[a]			
Candida growth in peritoneal fluid			
At surgery	15 (79)	13 (43)	.02
From drains	4 (21)	17 (57)	.02
Light vs. moderate or heavy growth on first culture	9 (47) vs. 10 (53)	26 (87) vs. 4 (13)	.008
Increasing in subsequent cultures	15 (79)	2 (7)	<.001
Outcome			
Failure of surgical drainage without antifungal treatment	16 (84)	0	<.001
Candida peritonitis	11 (58)	NA	
Intra-abdominal *Candida* abscess	5 (26)	NA	
Success with reintervention and antifungal therapy	9 (47)	NA	
Mortality			
Overall	12 (63)	3 (10)	<.001
Death due to infection	8 (42)	1 (3)	.001
Death due to fungal infection	7 (37)	NA	

NOTE. Data are no. of patients (%). NA, not applicable; NS, not significant. Adapted from [16].

[a] Based on semiquantitative cultures, as described in the text.

them as prophylactic agents on a large scale. However, any abuse of these agents could lead to the emergence of dose-dependent susceptible *(Candida glabrata)* or resistant *(Candida krusei)* species, which would result in a decreased efficacy of this remarkable class of antifungal agents. This phenomenon has been reported in neutropenic patients with cancer who received fluconazole prophylaxis and has been associated with an increased mortality [28, 29]. Other authors have made similar observations in general hospital wards and ICUs [30, 31]. In contrast, in the 10-year survey conducted by the Fungal Infection Network of Switzerland [5], *Candida albicans* has remained the predominant species (65%–70% of all bloodstream isolates), and the proportions of *C. glabrata* and *C. krusei* infections remained stable (15% and 2%, respectively), despite a significant increase in fluconazole consumption. Although the impact of azole consumption on recent changes in the epidemiology of *Candida* infections remains debatable [32], caution about any indiscriminate use of these agents is warranted. Selection of high-risk patients will also reduce trial expenses and future treatment costs, which in today's economic environment are nontrivial issues for study sponsors and partners of the public and private sectors of the health care system.

Few studies have examined the impact of antifungal prophylaxis or preemptive therapy in surgery, trauma, or ICU patients. As reviewed recently [27], several of these studies were underpowered to demonstrate an impact of antifungal prophylaxis, if it existed. Savino et al. [33] compared oral clotrimazole, ketoconazole, and nystatin with placebo for patients expected to stay for $\geqslant$48 h in a surgical ICU. Candidiasis occurred in only 2% of placebo recipients, and no benefit of prophylaxis was demonstrated. Slotman and Burchard [34] compared ketoconazole prophylaxis with placebo in 57 surgical ICU patients who were selected on the basis of the presence of $\geqslant$3 risk factors at baseline. *Candida* colonization occurred in 8 (30%) of 27 ketoconazole-treated patients and in 18 (60%) of 30 controls ($P = .03$). Invasive *Candida* infections developed in 5 (17%) of 30 placebo patients but in none of the patients treated with ketoconazole ($P = .05$). These results suggest that 6 patients should be treated with ketoconazole to prevent one episode of invasive candidiasis. Of note, in that study, the frequency of invasive candidiasis in the placebo group (17%) was also 8 times higher than that observed in the study by Savino et al. [33], suggesting that the presence of multiple risk factors may help to predict a higher incidence of invasive candidiasis. However, this requires a laborious and continuous screening of numerous parameters. More recently, Pelz et al. [35] ran-

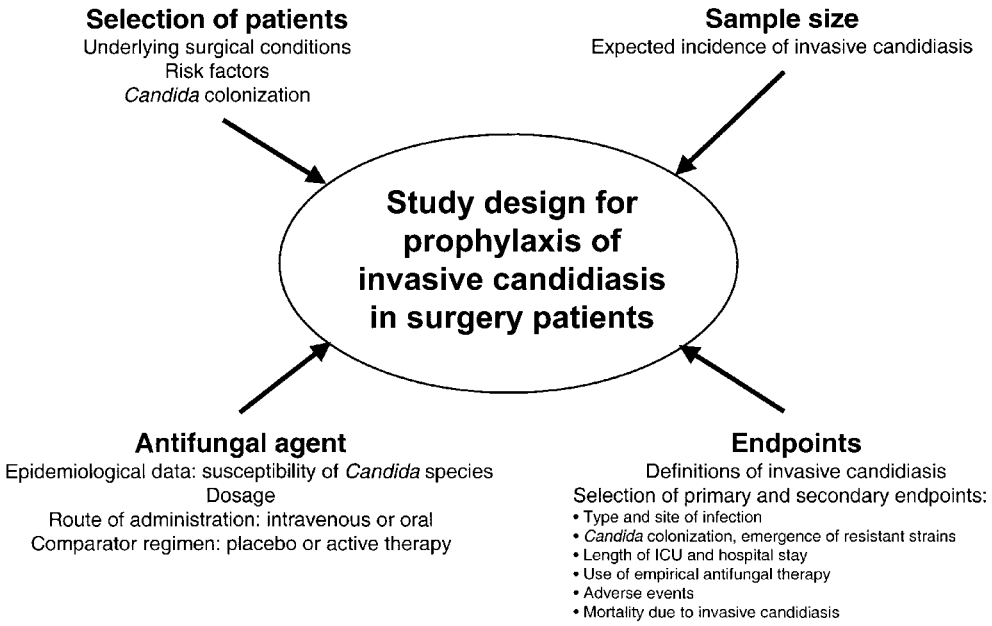

Figure 1. Issues to be considered in the design of clinical trials of antifungal prophylactic and preemptive treatment strategies. ICU, intensive care unit.

domized 260 surgery patients, expected to stay in the ICU for >3 days, to receive oral fluconazole prophylaxis (800 mg first dose, followed by 400 mg/day) or placebo. In the intention-to-treat analysis, 11 fungal infections (9%) occurred in the fluconazole group versus 20 (16%) in the placebo group ($P <$ .05). The number of patients who needed treatment to prevent one episode of *Candida* infection was 15. Mortality was similar in the 2 treatment groups.

Following up on our previous observation that at least one-third of patients with recurrent gastrointestinal perforation develop *Candida* peritonitis, we performed a randomized, double-blind, placebo-controlled study among high-risk surgery patients with recurrent gastrointestinal perforations or anastomotic leakages (table 3) [36]. Patients were selected on the basis of a simple and broadly applicable criterion, namely, a clinically suspected or surgically confirmed recurrent gastrointestinal perforation or anastomotic suture leakage. Patients received either fluconazole (400 mg/day iv, $n = 23$) or placebo ($n = 20$). Patients' characteristics—including classical risk factors for *Candida* infections, number of previous surgical interventions, APACHE II score, and growth of *Candida* in the intra-abdominal fluid—and the number of reinterventions during the study were similar in the 2 groups. At study entry, 60% of the patients were not colonized with *Candida* and thus may have benefited from a true antifungal prophylaxis. In the other patients (40%), treatment was probably more preemptive than truly prophylactic, because they were already colonized with *Candida* at enrollment. However, experts' opinions diverge about definitions of prophylaxis and preemptive therapies. Among patients who were not colonized at study entry, *Candida* was isolated from surveillance cultures during prophylaxis from 62% of the placebo group and 15% of the fluconazole group ($P = .04$). Intra-abdominal candidiasis developed in 1 fluconazole-treated patient (4%) and in 7 placebo-treated patients (35%; $P = .02$). No death attributed to candidiasis occurred in the fluconazole group, but 4 patients (20%) died from intra-abdominal candidiasis in the placebo group ($P = .04$). The reduction of the incidence of candidiasis with fluconazole was substantial (8-fold), and the number of patients who needed to be treated to prevent one episode of intra-abdominal candidiasis was only 3. Data on the reduction of mortality should be interpreted with great caution because of the small numbers of patients enrolled and the impact of possible confounding variables on a patient's outcome. Overall, this study indicates that it is possible to identify, by means of straightforward clinical criteria, a subgroup of post–abdominal surgery patients at high risk of *Candida* infections who would benefit from antifungal preventive therapies.

Alternatively, patients could be selected for a preventive intervention when they become heavily colonized with *Candida* in surveillance cultures. In our initial study, 19 (39%) of 49 patients with *Candida* isolated from postsurgical surveillance cultures of the peritoneal fluid developed intra-abdominal candidiasis [16]. Both the presence of colonization at baseline and the persistence or emergence of colonization in follow-up cultures have been found to be associated with subsequent invasive candidiasis. These results suggested that specimens obtained at surgery and thereafter may help to predict who will or will not

Table 3. Summary of the results of a clinical trial comparing fluconazole with placebo for prophylaxis of invasive candidiasis in surgery patients with recurrent gastrointestinal perforation or anastomotic leak.

Factor	Fluconazole, 400 mg daily iv (n = 23)	Placebo (n = 20)	P
Clinical characteristics			
No. of surgical interventions at study entry, median (range)	2 (1–7)	2 (2–4)	NS
APACHE II score at baseline, median (range)	13 (4–24)	13 (6–24)	NS
Reintervention during study	8 (35)	7 (35)	NS
Microbiological data			
Candida in peritoneal fluid			
At study entry	10 (43)	7 (35)	NS
During study	7 (30)	14 (70)	.01
Persistence	5/10 (50)	6/7 (86)	NS
Emergence	2/13 (15)	8/13 (62)	.04
End points			
Intra-abdominal candidiasis	1 (4)	7 (35)	.02
Candida only	1 (4)	1 (5)	NS
Candida and bacteria	0	6 (30)	.04
Candidiasis secondary to peritonitis	0	2 (10)	NS
Overall mortality	7 (30)	10 (50)	NS
Death due to intra-abdominal candidiasis	0	4 (20)	.04

NOTE. If not indicated otherwise, data are no. (%) or no./total (%). NS, not significant. Adapted from [36].

develop invasive candidiasis. Pittet et al. [14] also performed routine surveillance cultures among 650 surgical ICU patients and found that 4.5% were heavily colonized with *Candida*. The incidence of invasive candidiasis in colonized patients was very high (11 [38%] of 29 patients). Moreover, the authors found a correlation between 2 colonization indexes and the occurrence of invasive candidiasis. The incidence of invasive candidiasis in these 2 studies (39% and 38%) was 20–40 times higher than that of a general ICU population (1%–2%). If a 2% incidence in the surgical ICU population (n = 650) studied by Pittet et al. [14] is assumed, 13 invasive candidiasis episodes would have been anticipated during the period of observation, and 11 episodes of candidiasis occurred among 29 heavily colonized patients (38%). The extrapolated sensitivity, specificity, and positive and negative predictive values of colonization for prediction of invasive candidiasis would be 85%, 97%, 38%, and 100%, respectively. Therefore, this colonization index was associated with high sensitivity, specificity, and negative predictive value (consistent with the well-known observation that colonization precedes infection), but a low positive predictive value. One limitation of the colonization index is that it is fairly labor-intensive and expensive when used on a large scale. A summary of the pros and cons of the screening methods most frequently used to identify surgery patients at risk of invasive candidiasis is shown in table 4.

End points, sample size, and choice of antifungal agents. Development of invasive candidiasis should be the primary end point of any prophylactic or preemptive antifungal therapy trial. For example, intra-abdominal candidiasis would be a relevant end point in post–abdominal surgery patients, whereas candidemia would be preferred as an end point in a more heterogeneous group of ICU patients. Several secondary end points might be considered, including the emergence or the persistence of *Candida* colonization, appearance of resistant *Candida* strains, time to development of *Candida* infection, use of empirical antifungal therapy, adverse events, morbidity, mortality, and length of ICU and hospital stay. To facilitate comparisons of outcome among studies, investigators should, whenever possible, use either consensus or widely accepted definitions of invasive candidiasis. The diagnostic criteria for opportunistic invasive fungal infections in immunocompromised hosts published by the European Organization for Research on Treatment of Cancer Invasive Fungal Infection Group and the Mycoses Study Group of the National Institute of Allergy and Infectious Diseases [37] are an example of such definitions that have contributed to major progress in clinical research of invasive mycoses in patients with cancer or hematologic malignancies.

As in any other clinical investigations, the sample size should be calculated on the basis of the anticipated incidence of the primary study end point in the control population. The number

Table 4. Comparison of different screening methods for the identification of surgery patients at risk of invasive candidiasis.

Factor	Screening method			
	Anticipated duration of ICU stay	Presence of multiple risk factors	Specific surgical conditions	*Candida* colonization
Basis for selection of patients	Clinical evaluation at ICU admission	Medical history and clinical, laboratory, and radiological findings	Surgical evaluation	Routine surveillance cultures
No. of parameters required for evaluation	1	>10	1	1
Practical feasibility	Straightforward, but difficult to predict	Need for continuous follow-up	Straightforward	Time-consuming and expensive
Expected incidence of invasive candidiasis	~2%–15%	~10%–20%	~30%–40%	~30%–40%
No. needed to treat to prevent one episode of invasive *Candida* infection	15–50	5–10	2–5	2–5

NOTE. ICU, intensive care unit. Derived from [14, 33–36].

needed to treat to prevent one episode of primary and secondary end points could be calculated on the basis of the expected reduction of the rate of invasive candidiasis within the experimental treatment arm. Examples of number needed to treat derived from previous clinical trials are shown in table 4.

The choice of the antifungal agent, route of administration (intravenous vs. oral), and dosage should be based on epidemiological, microbiological, pharmacological (i.e., pharmacokinetics, pharmacodynamics, bioavailability), preclinical, and clinical data. Systemic and tissue concentrations of antifungal agents should be high enough to prevent bloodstream and tissue invasion. Nonabsorbable oral antifungal agents, such as the polyenes (amphotericin B or nystatin), act topically in the gastrointestinal tract. These agents have had a limited impact in reducing the incidence of invasive candidiasis in neutropenic and nonneutropenic (i.e., surgery and ICU) patients [27, 33, 38, 39]. Antifungal agents for whom both an intravenous and an oral formulation are available are the most attractive for prevention of *Candida* infections in surgery patients, because they allow a change from iv to oral therapy as soon as gastrointestinal motility and function are restored. Among the existing drugs, fluconazole fulfills all of these prerequisites and, on the basis of the available data, would be the drug of first choice. Inconsistent oral bioavailability would be a limitation for the use of other azoles (such as itraconazole and posaconazole) in the postsurgical patient. Moreover, the administration of azoles might be problematic in centers with a high incidence of fluconazole-resistant *Candida* species and the possibility of cross resistance. Caspofungin, an echinocandin, has been shown to be efficacious for the treatment of invasive candidiasis due to azole-susceptible and azole-resistant *Candida* species. This class of antifungal agents might also be considered for prophylaxis but can be given intravenously only. Treatment cost is another factor to be taken into account in the design of prophylactic trials. Finally, given that azole prophylaxis has been shown in several studies to reduce the incidence of fungal infections, it may become difficult to justify the use of placebo as control therapy in certain populations of surgery and ICU patients at high risk.

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