Empirical Fluconazole versus Placebo for Intensive Care Unit Patients

A Randomized Trial

Mindy G. Schuster, MD; John E. Edwards Jr., MD; Jack D. Sobel, MD; Rabih O. Darouiche, MD; Adolf W. Karchmer, MD; Susan Hadley, MD; Gus Slotman, MD; Helene Panzer, PhD; Pinaki Biswas, PhD; and John H. Rex, MD

Background: Invasive infection with *Candida* species is an important cause of morbidity and mortality in intensive care unit (ICU) patients. Optimal preventive strategies have not been clearly defined.

Objective: To see whether empirical fluconazole improves clinical outcomes more than placebo in adult ICU patients at high risk for invasive candidiasis.

Design: Double-blind, placebo-controlled, randomized trial conducted from 1995 to 2000.

Setting: 26 ICUs in the United States.

Patients: 270 adult ICU patients with fever despite administration of broad-spectrum antibiotics. All had central venous catheters and an Acute Physiology and Chronic Health Evaluation II score greater than 16.

Intervention: Patients were randomly assigned to either intravenous fluconazole, 800 mg daily, or placebo for 2 weeks and were followed for 4 weeks thereafter. Two hundred forty-nine participants were available for outcome assessment.

Measurements: A composite primary outcome that defined success as all 4 of the following: resolution of fever; absence of invasive fungal infection; no discontinuation because of toxicity; and no need for a nonstudy, systemic antifungal medication (as assessed by a blinded oversight committee).

Results: Only 44 of 122 (36%) fluconazole recipients and 48 of 127 (38%) placebo recipients had a successful outcome (relative risk, 0.95 [95% CI, 0.69 to 1.32; $P = 0.78$]). The main reason for failure was lack of resolution of fever (51% for fluconazole and 57% for placebo). Documented invasive candidiasis occurred in 5% of fluconazole recipients and 9% of placebo recipients (relative risk, 0.57 [CI, 0.22 to 1.49]). Seven (5%) fluconazole recipients and 10 (7%) placebo recipients had adverse events resulting in discontinuation of the study drug. Discontinuation because of abnormal liver test results occurred in 3 (2%) fluconazole recipients and 5 (4%) placebo recipients.

Limitations: Twenty-one randomly assigned patients were not included in the analysis because they either did not meet entry criteria or did not have postbaseline assessments. Fewer fungal infections than anticipated occurred in the control group. Confidence bounds were wide and did not exclude potentially important differences in outcomes between groups.

Conclusion: In critically ill adults with risk factors for invasive candidiasis, empirical fluconazole did not clearly improve a composite outcome more than placebo.

At least 1% to 2% of all intensive care unit (ICU) patients develop invasive candidiasis at some point during their stay (1–4). The mortality rate attributable to candidemia and invasive infection with *Candida* species at other normally sterile sites exceeds 30% to 40%, and invasive candidiasis is associated with increased length of ICU stay and health care costs (5–8). Known risk factors for candidemia include prolonged ICU stay, central venous catheterization, prolonged exposure to antibiotics, and recent abdominal surgery; other possible risk factors include colonization with *Candida* species and a high Acute Physiology and Chronic Health Evaluation (APACHE) II score (3–5, 7, 9, 10).

Because the yield of *Candida* species in blood culture is suboptimal even with current culture techniques (11), available data probably underestimate the morbidity and mortality because of invasive candidiasis in the ICU. Small prophylactic trials have studied various ways to decrease morbidity and mortality, with mixed results (12–15). Concerns about prophylactic strategies include the necessity of treating many patients who may not truly be at risk for invasive candidiasis and the potential for emergence of drug-resistant *Candida* species (16–21). In other patient populations, such as febrile, neutropenic patients with cancer, a strategy of empirical (rather than prophylactic) antifungal therapy has been adopted (22, 23). We postulated that a similar strategy in the ICU population could limit unnecessary exposure to antifungal agents and target only those patients at highest risk for invasive candidiasis. Furthermore, a recent decision-analytic model for the cost-effectiveness of empirical anticandidal therapy in high-risk ICU patients showed that empirical fluconazole would be reasonable from a cost perspective if the likelihood of invasive candida is greater than 2.5% (24).

Fluconazole, 400 mg daily, is an accepted treatment for documented candidemia (25, 26). Patients may tolerate doses as high as 800 mg daily (26), and higher doses may

Context

Does empirical fluconazole prevent invasive candidiasis in high-risk, critically ill patients?

Contribution

In this multicenter trial, 270 intensive care unit patients with fever despite use of broad-spectrum antibiotics were randomly assigned to fluconazole, 800 mg/d, or placebo for 2 weeks. About 40% of patients in each group achieved the composite end point: resolution of fever, absence of invasive fungal infection, no therapy discontinuation because of toxicity, and no need for a nonstudy systemic antifungal medication.

Caution

Few fungal infections occurred in either group.

Implication

Empirical antifungal therapy with fluconazole is not proven more beneficial than placebo for high-risk intensive care unit patients.

—*The Editors*

have better activity against some of the non-*albicans Candida* species. With these issues in mind, we conducted a randomized trial that compared fluconazole, 800 mg daily, with placebo in ICU patients at high risk for invasive candidiasis.

METHODS

Design

The study was a randomized, double-blind, placebo-controlled trial of empirical fluconazole, 800 mg daily, for 14 days in febrile ICU patients at high risk for invasive candidiasis. Participants were enrolled at 26 U.S. medical centers. Most were academic medical centers (**Appendix**, available at www.annals.org). The institutional review board for each site approved the protocol. Written informed consent was obtained from each patient or his or her legal guardian. Patients were enrolled from 1995 to 1999. Patient follow-up was completed in 2000.

Setting and Participants

Participating sites regularly screened all ICU patients for eligibility. Entry criteria included the following: age 18 years or older, ICU stay of at least 96 consecutive hours, APACHE II score within 24 hours of randomization of 16 or more, 4 days of fever (defined as temperature >38.3 °C on 3 separate occasions at least 12 hours apart within 72 hours before study entry, with at least 1 temperature spike within 12 hours of study entry), broad-spectrum antibiotics (both gram-positive and gram-negative coverage) for at least 4 of the preceding 6 days, and the presence of a central venous catheter for at least 24 hours before study entry. Patients were excluded from enrollment for serum

aspartate aminotransferase, alanine aminotransferase, or total bilirubin levels greater than 5 times the upper limit of normal; neutropenia (absolute neutrophil count $<1.0 \times 10^9$ cells/L); AIDS or HIV with CD4 count less than 0.5×10^9 cells/L; immunosuppressive treatment for organ or bone marrow transplantation; and ICU admission due to burn injury. Further exclusion criteria were receipt of terfenadine, cisapride, or any investigational drug within 14 days before study enrollment; evidence of an invasive fungal infection within 7 days before study entry; life expectancy of 48 hours or less; or previous enrollment in the study.

Randomization and Interventions

We randomly assigned eligible participants in a 1:1 ratio to receive intravenous fluconazole, 800 mg daily, or placebo for 14 days. Randomization was stratified by site and generated centrally by computer. Study drugs were assigned through a telephone call from the pharmacist to a central interactive voice-response system. Participants received fluconazole, 800 mg, as a solution containing 2 mg/mL, or a matching placebo at a maximum rate of 200 mg per hour. Patients who were receiving other oral medications could receive fluconazole or placebo orally only after the third day. Participants and all members of the study and health care team, except the investigational pharmacist, were blinded to study drug assignment.

Outcomes and Measurements

Whether the primary outcome was achieved was determined 4 days after the last dose of study medication. Four factors made up a composite end point: no temperature greater than 38 °C for 72 hours while the patient was receiving a study drug plus 4 days (that is, resolution of the index fever); no emergent invasive fungal infection identified; no study medication treatment stopped for toxicity; and no use of alternative systemic antifungal medication. If patients met all of these conditions while they received the study medication plus 4 days after the study medication was discontinued, they were coded as a success. The secondary end points included time to discharge from ICU and from the hospital unit, and death at 30 days. Outcomes were coded by the principal investigators at the individual sites by using protocol-defined categories.

In addition, 6 investigators made up a blinded oversight committee that reviewed each case report form for inclusion and exclusion criteria, response to therapy, and documentation of any invasive fungal infection. The primary end point was the assessment of the blinded oversight committee's success; a secondary end point was the assessment of the principal investigator's success.

Clinical assessments were done on all patients daily for the first 7 days and then every 2 to 3 days during study medication treatment. The occurrence of any adverse event was recorded. Hematologic studies and serum chemistries were done twice weekly, and surveillance blood cultures were done at least every 48 hours if the temperature re-

mained greater than 38 °C. At the end of the primary observation period (4 days after discontinuation of study drug), cultures of urine, sputum, and deep wounds for fungus were obtained. To evaluate suspected fungal infection, we required participants to at least have a physical examination and fungal culture of all suspected sites of infection. If no suspected site could be found, culture was obtained from urine and 2 sets of blood cultures from separate sites.

Follow-up Procedures

Participants were followed for 30 days after the study drug was discontinued. Definitions of invasive fungal infections were isolation of *Candida* species from blood or from other normally sterile body sites that prompted discontinuation of the study medication and initiation of systemic antifungal treatment. The sponsor periodically monitored the individual sites by assessing medical records and case report forms for accuracy.

All adverse events, regardless of treatment group or suspected causal relationship to the study drug, were recorded in the case report form by the principal investigators. These investigators also assessed causality. Serious adverse events were reported to the sponsor within 24 hours. Such events were those that resulted in death, hospitalization or prolongation of hospitalization, persistent or clinically significant disability or incapacity, or a congenital anomaly or birth defect and those that were life-threatening.

The data safety monitoring board, made up of individuals not involved in the trial or affiliated with the sponsor, did a planned interim analysis. In accordance with the statistical analysis plan, an interim analysis was conducted at 50% trial completion. The analysis was done in participants who met the entry criteria, had at least 1 postbaseline clinical evaluation, and applied to the primary efficacy variable. To preserve the overall 5% significance level, we used the Lan–DeMets stopping procedure with an O'Brien–Fleming stopping rule. The study was to be terminated and the null hypothesis rejected at the 0.0052 level at the interim analysis. After the interim analysis, the board recommended closing the study to further enrollment because of lack of a difference in the primary end point between the 2 treatment groups. Two hundred seventy participants had enrolled when the decision was made to stop the trial.

Statistical Analysis

The study was designed to have a statistical power of 80% to detect an absolute 15% reduction in the composite end point between the 2 groups, assuming a rate of occult invasive candidiasis of 30% in the placebo group ($\alpha = 0.05$, 2-sided). The target sample size was 134 evaluable participants in each group.

The primary analysis included participants who received at least 1 dose of study medication, were not excluded after entry for not meeting entry criteria, and had at least 1 postbaseline clinical evaluation. We chose this to

Table 1. Patient Characteristics at Baseline*

Characteristic	Fluconazole Recipients (n = 122)	Placebo Recipients (n = 127)
Mean age (SD), y	53 (19)	51 (19)
Women, n (%)	29 (24)	28 (22)
Median previous ICU stay (range), d	9.5 (4–171)	9 (4–57)
Median previous hospital stay (range), d	11 (5–173)	11 (4–58)
Median baseline APACHE II score (range)	22 (9–28)	20 (11–42)
Corticosteroids, n (%)	19 (16)	15 (12)
Total parenteral nutrition, n (%)	70 (57)	65 (51)
Renal insufficiency, n (%)†	70 (57)	65 (51)
Colonized with yeast in ≥1 site, n (%)	28 (23)	24 (19)
Diabetes mellitus, n (%)	23 (19)	26 (20)
Cancer, n (%)	12 (10)	8 (6)
Surgery within 7 d before study entry, n (%)	65 (53)	65 (51)

APACHE = Acute Physiology and Chronic Health Evaluation; ICU = intensive care unit.
* Excludes 11 fluconazole and 10 placebo recipients who were randomly assigned and received study drug but did not meet entry criteria or did not have a postbaseline evaluation.
† Defined as a creatinine level >150.03 μmol/L (>1.7 mg/dL).

reflect the objective of the trial, which was to study the empirical use of fluconazole in febrile ICU patients with risk factors for invasive candidiasis.

We compared the composite outcome of success by using Mantel–Haenszel chi-square tests (2-sided). When outcomes from the blinded oversight committee were missing, we assumed an outcome of failure and did sensitivity analyses that treated these missing outcomes as successes or excluded them. We used SAS software, version 8.2 (SAS Institute, Cary, North Carolina).

Role of the Funding Source

Our study was initiated and designed by investigators. Pfizer (New York, New York) sponsored and monitored the trial, assisted in protocol development and creation of the case report form, provided the study drug, and maintained the database. The sponsor assisted in analysis but not in interpretation of the data. The sponsor was not involved in the decision to publish the results.

RESULTS

Study Sample

Of the 270 participants enrolled at 26 centers, 133 were assigned to fluconazole and 137 to placebo. No crossovers occurred during the trial. **Table 1** shows the baseline characteristics of the participants. The median duration of ICU stay before study entry was 9.5 days for fluconazole recipients and 9 days for placebo recipients. The median APACHE II score at the time of enrollment was 22 for those who received fluconazole and 20 for those who received placebo. **Table 2** lists the diagnostic evaluations and therapeutic maneuvers that were done to investigate the cause of the index fever but were not required by protocol.

Table 2. **Diagnostic Tests and Therapeutic Maneuvers Used to Investigate the Cause of Index Fever***

Diagnostic Test or Maneuver	Fluconazole Recipients (*n* = 122), *n* (%)	Placebo Recipients (*n* = 127), *n* (%)
CT or radiography of sinuses	17 (14)	14 (11)
CT of chest or abdomen	41 (34)	36 (28)
Stool for *Clostridium difficile*	21 (17)	28 (22)
Change intravenous catheters	79 (65)	84 (66)
Change antibiotics	30 (25)	38 (30)
Evaluation for pulmonary emboli	3 (3)	7 (6)
Funduscopy	17 (14)	29 (23)

CT = computed tomography.
* Excludes 11 fluconazole and 10 placebo recipients who were randomly assigned and received study drug but did not meet entry criteria or did not have a post-baseline evaluation.

Disposition of Participants

The **Figure** shows the disposition of the study participants. Patients received fluconazole for a median of 12 days (range, 1 to 23 days) and placebo for 12 days (range, 1 to 22 days). As the study was monitored, 11 fluconazole and 10 placebo recipients were identified who either did not meet entry criteria or did not have at least 1 postbaseline clinical evaluation. These 21 patients were excluded from baseline summaries and primary analyses.
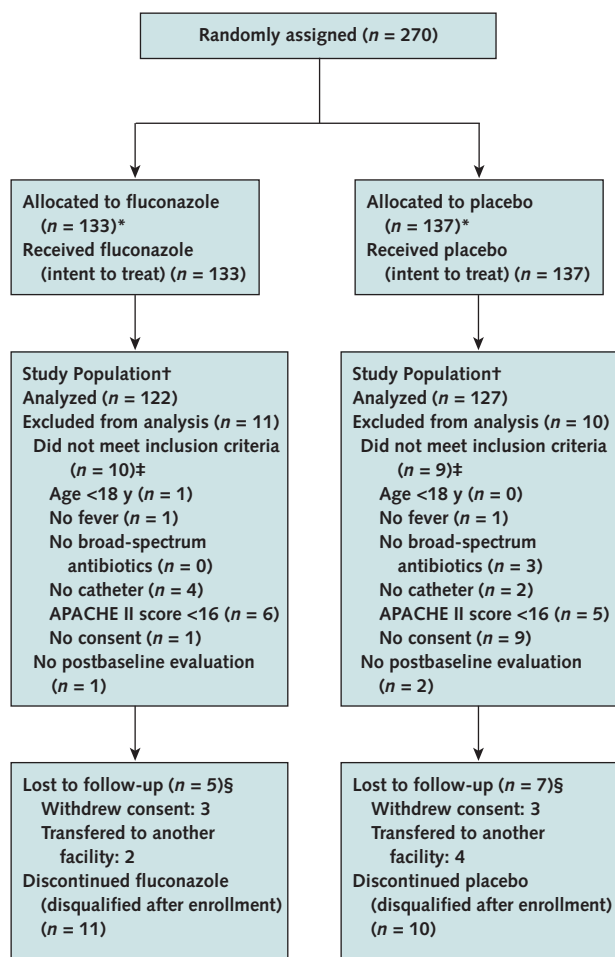
Measurements and Outcomes

Success, as defined by the composite end point, occurred in 44 (36%) participants receiving fluconazole and 48 (38%) of those receiving placebo (relative risk [RR], 0.95 [95% CI, 0.69 to 1.32]; *P* = 0.78). Outcome data were not available from the blinded oversight committee for 11 participants who received fluconazole and 6 who received placebo, and these cases were coded as failures. Because there was no known systematic reason for why these outcomes were missing, coding these cases as failures represents a conservative approach. The results were similar for the sensitivity analyses in which patients with missing outcomes were coded as successes, patients with missing outcomes were excluded, or an investigator determined the outcome rather than the blinded oversight committee (**Table 3**).

Outcomes for 7 of the 21 excluded patients (who did not meet entry criteria or had ≤1 baseline evaluation) were available and assessed by both the blinded oversight committee and the investigators and are in agreement. Five of the excluded fluconazole recipients were coded as failures; 1 was coded as a success. One of the placebo recipients was coded as a failure. **Table 4** shows the reasons for failure. The most common reason for failure—lack of fever resolution—was the same in patients who received fluconazole and placebo and occurred in approximately half of the patients. Documented invasive fungal infections occurred in 6 (5%) participants who received fluconazole and 11 (9%) who received placebo (RR, 0.57 [CI, 0.22 to 1.49];

P = 0.24). No cases of candidemia occurred in patients who received fluconazole, and only 2 cases occurred in patients who received placebo. When patients who were positive for *Candida* on urine or catheter tip culture were excluded in an unplanned exploratory analysis, 1 (0.8%) case of invasive candidiasis was found in fluconazole recipients and 6 (4.7%) cases were found in placebo recipients (RR, 0.17 [CI, 0.02 to 1.42]; *P* = 0.12). Too few infections occurred to make meaningful comparisons about the *Candida* species causing documented infection in patients who received placebo versus fluconazole, and for some of the nonblood isolates, species identification was not done. Only 3 *Candida glabrata* infections occurred, however, and all occurred in the placebo recipients.

Because of the a priori hypothesis that fluconazole would be more beneficial than placebo in persons colo-

Figure. **Study flow diagram.**

APACHE = Acute Physiology and Chronic Health Evaluation.
* Safety sample.
† Analysis sample.
‡ Outcomes were recorded for all of these patients and were included in the primary analysis.
§ Patients could have >1 reason for not meeting inclusion criteria.

Table 3. Outcomes during the Primary Observation Period*

Outcomes	Fluconazole Recipients (n = 122), n (%)	Placebo Recipients (n = 127), n (%)	Relative Risk (95% CI)	P Value
Primary analysis†‡				
Success	44 (36)	48 (38)	0.95 (0.69–1.32)	0.78
Failure	78 (64)	79 (62)	–	–
Sensitivity analysis†§				
Success	55 (45)	54 (43)	1.06 (0.80–1.40)	0.68
Failure	67 (55)	73 (57)	–	–
Sensitivity analysis†‖				
Success	44 (36)	48 (38)	1.00 (0.73–1.37)	0.99
Failure	67 (55)	73 (57)	–	–
Sensitivity analysis†¶				
Success	45 (37)	52 (41)	0.90 (0.66–1.23)	0.51
Failure	77 (63)	75 (59)	–	–

* Outcomes are determined by the oversight committee and exclude 11 fluconazole and 10 placebo recipients who were randomly assigned and received study drug but did not meet entry criteria or did not have a postbaseline evaluation.
† 11 fluconazole and 6 placebo recipients did not have outcomes determined by the oversight committee.
‡ Assumes failure in patients with missing outcomes.
§ Assumes success in patients with missing outcomes.
‖ Excludes patients with missing outcomes.
¶ Assumes investigator determined outcome in patients with missing outcomes.

nized with *Candida* species, we conducted a planned subgroup analysis 7 days before study entry of the 32 fluconazole recipients and the 36 placebo recipients who were colonized with *Candida* species at more than 1 site. Success rates, as defined by composite end point, for patients who received fluconazole and placebo were 10 (31%) and 10 (28%), respectively (RR, 1.13 [CI, 0.54 to 2.35]). Five of 32 (15%) patients colonized with *Candida* species at baseline who received fluconazole developed invasive fungal infection (by protocol definition) compared with 9 of 36 (25%) patients who received placebo (RR, 0.63 [CI, 0.23 to 1.67]; $P = 0.34$). Twenty-nine (24%) fluconazole recipients and 22 (17%) placebo recipients (RR, 1.36 [CI, 0.82 to 2.24]; $P = 0.23$) died within 30 days. Similarly, time to discharge from the ICU or the hospital did not differ between the groups.

Seven (5%) fluconazole recipients and 10 (7%) placebo recipients had study medication discontinued because of an adverse event (**Table 5**). **Table 6** shows an overall list of adverse events. **Table 7** presents clinically significant laboratory abnormalities. Study medication was discontinued for tests associated with abnormal liver function in 3 (2%) fluconazole recipients and 5 (4%) placebo recipients.

DISCUSSION

This randomized, multicenter, blinded, clinical trial compared fluconazole with placebo for empirical antifungal therapy in ICU patients with several risk factors for invasive candidiasis. Success, as defined by the composite end point, occurred in 44 (36%) fluconazole recipients and 48 (38%) placebo recipients (RR, 0.95 [CI, 0.69 to 1.32]; $P = 0.78$). To our knowledge, this is the largest multicenter study to date aimed at empirical antifungal therapy

in this high-risk population. A MEDLINE search for studies published in English to February 2008 revealed several relevant clinical trials. Most had small sample sizes, had broad definitions of invasive candida infections, or were conducted in single institutions or among select patient samples. Eggimann and coworkers (12) randomly assigned patients with evidence of gastrointestinal perforation to receive fluconazole, 400 mg daily, or placebo. The rate of candidal peritonitis was 7% among the 20 placebo recipients and 1% among the 23 fluconazole recipients. Although these results are compelling despite the small sample size, they are relevant to a selected patient sample and not generalizable to most ICU patients.

Ables and colleagues (13) randomly assigned 125 ICU patients to antifungal prophylaxis with fluconazole, 400 mg daily, or placebo. Rates of invasive candidal infection

Table 4. Reasons for Failure at the End of the Primary Observation Period*

Outcome	Fluconazole Recipients (n = 122), n (%)	Placebo Recipients (n = 127), n (%)
Total failures	67 (55)	73 (57)
No resolution of fever	62 (51)	68 (54)
Documented invasive fungal infection	6 (5)†	11 (9)‡
Need for alternative antifungal agent	12 (10)	20 (16)

* Outcomes were determined by the oversight committee and exclude 11 fluconazole and 10 placebo recipients who were randomly assigned and received study drug but did not meet entry criteria or did not have a postbaseline evaluation.
† Sites of *Candida* infection included urine (n = 3), peritoneum (n = 1), catheter tip (n = 1), and unknown (n = 1).
‡ Sites of *Candida* infection included urine (n = 5), peritoneum (n = 3), blood (n = 2), and thoracic drain (n = 1).

Table 5. Adverse Events

Description	Fluconazole Recipients (n = 133), n (%)	Placebo Recipients (n = 137), n (%)
Any adverse event	133 (100)	135 (99)
Adverse event related to study drug*	14 (11)	20 (15)
Treatment stopped because of adverse event	7 (5)	10 (7)
Treatment stopped because of abnormal test results associated with liver function	3 (2)	5 (4)
Treatment stopped because of adverse event related to study drug†	1 (1)	1 (1)

* As judged by the investigator.
† For all randomly assigned patients.

did not differ in the 2 groups (8 [13%] in the fluconazole group and 11 [19%] in the placebo group). Case definitions for invasive candidal infection included patients with positive sputum cultures, which may not be clinically relevant. Garbino and coworkers (14) randomly assigned 220 ICU patients on mechanical ventilation who were receiving selective gastrointestinal decontamination with nonabsorbable antibacterial agents to receive fluconazole, 100 mg daily, or placebo in a multicenter trial. Almost half of the patients were colonized with *Candida* at enrollment. The study was underpowered to detect a difference in the primary end point—severe candidal infection—which occurred in 3.8% of the fluconazole group versus 9.9% of the placebo group. One case of candidemia occurred in the fluconazole group and 9 occurred in the placebo group (*P* = 0.008). Pelz and colleagues (15) randomly assigned 260 ICU patients to fluconazole, 400 mg daily, or placebo. Rates of invasive candidiasis were 15.3% in the placebo group and 8.5% in the fluconazole group (*P* = 0.07). The study demonstrated a benefit of fluconazole over placebo in a time-to-event analysis at 2 to 3 weeks. The patients enrolled in the study were from a single institution and had high rates of liver failure and other comorbid conditions that might limit the generalizability of this prophylactic trial. Cruciani and coworkers (27) did a meta-analysis of 9 randomized clinical trials of antifungal prophylaxis in ICU patients and found that prophylaxis with a triazole antifungal was associated with reduced rates of candidemia (RR, 0.3 [CI, 0.10 to 0.82]) and reduced mortality rates attributable to candidal infection (RR, 0.25 [CI 0.08 to 0.80]). Patient characteristics, risk factors, and relevant outcomes varied substantially.

We cannot exclude a relative benefit of fluconazole of up to 32% difference in success (defined by the composite end point) between fluconazole and placebo recipients. The rates of invasive fungal infection were lower than expected and confidence limits were wide. Benefit below this threshold would be clinically significant.

Our study has several limitations. Although we incorporated several established risk factors for invasive candidiasis into our study design, the rate of invasive candidiasis in

the placebo group (9%) was lower than expected, suggesting that the risk factors we selected for inclusion criteria were not associated with a high enough risk for fungal infection. Data about colonization with yeast at baseline were not prospectively collected. Of interest, the rate of invasive candidiasis in patients colonized with *Candida* at baseline was 25% in the placebo group and 15% in the fluconazole group. Previous studies have yielded conflicting data about the importance of colonization with *Candida* species as a risk factor (3–5, 7, 9, 10). By including other risk factors, such as colonization with *Candida* species, recent surgery on the gastrointestinal tract, or acute renal failure, as additional enrollment criteria, we could have selected a study sample at higher risk for invasive fungal infection.

We excluded 11 (8%) fluconazole recipients and 10 (7%) placebo recipients from analysis because they did not meet entry criteria (**Figure**). Sensitivity analyses, however, revealed similar results when these patients were coded as successes or failures. Some patients in each group received the study drug for more than 14 days (permitted in accordance with protocol). Because the recommended duration of treatment for documented candidemia is 14 days, results may be biased toward the null because we allowed fever to

Table 6. Most Frequent Adverse Events*

Event	Fluconazole Recipients (n = 133), n (%)	Placebo Recipients (n = 137), n (%)
Body		
Enlarged abdomen	15 (11)	14 (10)
Sepsis	24 (18)	26 (19)
Device complication	14 (11)	11 (8)
Cardiovascular		
Hypotension	23 (17)	16 (12)
Cardiac arrest	14 (11)	8 (6)
Digestive		
Diarrhea	22 (17)	21 (15)
Liver function abnormality	11 (8)	15 (11)
Heme and lymphatic: anemia	11 (8)	14 (10)
Metabolic and nutritional: peripheral edema	17 (13)	18 (13)
Nervous: agitation	9 (7)	21 (15)
Respiratory		
Pneumonia	13 (10)	14 (10)
Respiratory disorder	37 (28)	31 (23)
The respiratory distress syndrome	16 (12)	17 (12)
Skin		
Rash	11 (8)	22 (16)
Skin disorder	14 (11)	13 (10)
Skin ulcer	17 (13)	17 (12)
Urogenital: urinary tract infection	11 (8)	20 (15)

* <10% for all randomly assigned patients.

Table 7. Clinically Significant Laboratory Abnormalities

Adverse Event	Fluconazole Recipients, n (%)		Placebo Recipients, n (%)	
	Total*	Clinically Significant Abnormality†	Total*	Clinically Significant Abnormality†
Elevated liver function test results (possibly due to study drug)	133	3 (2)	137	5 (4)
Elevated neutrophil count ($>1.5 \times$ ULN)	117	87 (74)	128	84 (66)
Elevated creatinine level ($>1.3 \times$ ULN)	129	39 (30)	134	25 (19)
Elevated platelet count ($>700 \times 10^9$ cells/L)	127	15 (12)	131	24 (18)
Elevated alanine aminotransferase level ($>3.0 \times$ ULN)	112	26 (23)	122	37 (30)

ULN = upper limit of normal.
* Total number of participants with ≤1 observation of the given laboratory parameter.
† Number of participants with a clinically significant abnormality while receiving study treatment or during lag time.

occur for new reasons when patients received therapy for a longer period.

Another limitation of the study was the composite end point. Many variables affect fever in ICU patients with complicated conditions, and fever may be a poor surrogate marker in this population. It is also possible that by requiring a relatively high APACHE II score, we selected patients who were sick enough from various other causes that success according to the composite end point did not occur, despite treatment of occult candidal infection. However, using documented invasive candidal infection as a primary end point would not address the problem that only approximately half of all cases of candidemia are identified by current blood culture technology. Surrogate markers, such as β-glucan, should also be examined as potential inclusion criteria in future trials.

This trial provides data about the safety of fluconazole, 800 mg daily, and shows that the treatment was seldom discontinued because of an adverse event (judged by the investigator to be related to the study medication). From an epidemiologic standpoint, a potentially globally important repercussion from use of fluconazole in this setting, however, is the emergence of fluconazole-resistant *Candida* species. Because of the few documented infections, we could not assess the possibility of selecting for resistance. Future trials will need to evaluate this carefully, particularly if the benefits of empirical antifungal therapy are found to be marginal. A recent decision-analytic model for the cost-effectiveness of empirical antifungal therapy in high-risk ICU patients reported that empirical fluconazole is reasonable from an economic standpoint if the likelihood of invasive candidiasis exceeds 2.5% (24). A high-risk ICU patient was defined as having fever or hypothermia or unexplained hypotension, despite receiving antibiotics in the ICU for 3 days. Large clinical trials are necessary to determine whether the assumptions used in this model are clinically accurate. More work is clearly needed to refine, weigh, and prioritize the most important set of risk factors for invasive candidiasis in the ICU population.

Empirical antifungal therapy with fluconazole cannot be recommended for routine use in ICU patients who have only those risk factors included in our study sample; rather, it should be reserved for treating documented infection. Our study was not designed to detect a statistically significant difference among patients with additional recognized risk factors, such as colonization with *Candida* species, use of corticosteroids, recent surgical procedure, acute renal failure, or total parenteral nutrition. Future studies should consider incorporating additional risk factors. Careful refinement of risk factors, duration of exposure, and selection of a patient sample that is not past the point of potential recovery should then be incorporated into the design of larger, randomized, multicenter trials that include such end points as ICU or hospital discharge or death. Monitoring for emerging drug-resistant *Candida* species is important as well.

Requests for Single Reprints: Mindy G. Schuster, MD, University of Pennsylvania, Infectious Diseases, 3 Silverstein, Suite E, 3400 Spruce Street, Philadelphia, PA 19104; e-mail, schustem@mail.med.upenn.edu.

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Current Author Addresses: Dr. Schuster: University of Pennsylvania, Infectious Diseases, 3 Silverstein, Suite E, 3400 Spruce Street, Philadelphia, PA 19104.

Dr. Edwards: UCLA Medical Center, 1000 West Carson Street, Torrance, CA 90509.

Dr. Sobel: Wayne State University, 3990 John R, Detroit, MI 48201.

Dr. Darouiche: Michael E. DeBakey Veterans Affairs Medical Center, 2002 Holcombe Boulevard, Houston, TX 77030.

Dr. Karchmer: Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, MA 02215.

Dr. Hadley: Tufts-New England Medical Center, 750 Washington Street, Box 41, Boston, MA 02111.

Dr. Slotman: 1765 Springdale Road, Cherry Hill, NJ 08003.

Drs. Panzer and Biswas: Pfizer, 235 East 42nd Street, New York, NY 10017.

Dr. Rex: AstraZeneca Pharmaceuticals, Alderley House, Alderley Park, Macclesfield SK10 4TF, United Kingdom.

APPENDIX: PRINCIPAL INVESTIGATORS AND PARTICIPATING SITES

Steven J. Berman, Queens Medical Center, Honolulu, Hawaii; Robert E. Condon, Medical College of Wisconsin, Milwaukee, Wisconsin; Rabih O. Darouiche, Veterans Administration Medical Center, Houston, Texas; Steven H. Dougherty, Texas Tech University, El Paso, Texas; John E. Edwards, University of California, Los Angeles, Los Angeles, California; Gus J. Slotman, University Medical Center, Cooper Hospital, Camden, New Jersey; Bryan P. Simmons, Methodist University Hospital, Memphis, Tennessee; Gerard J. Fulda, Christiana Care Health Services, Newark, Delaware; Susan Hadley, Beth Israel Deaconess Medical Center, Boston, Massachusetts; Daniel L. Herr, Medlantic Research Institute, Washington, DC; Adolf W. Karchmer, Beth Israel Deaconess Medical Center, Boston, Massachusetts; Arnold Luterman, University of South Alabama, Mobile, Alabama; Sheldon B. Maltz, Illinois Masonic Medical Center, Chicago, Illinois; Joseph P. Minei, University of Texas Southwestern Medical Center, Dallas, Texas; Thomas F. Patterson, University of Texas Health Sciences Center at San Antonio, San Antonio, Texas; John H. Rex, University of Texas Health Science Center at Houston, Houston, Texas; Mindy G. Schuster, University of Pennsylvania, Philadelphia, Pennsylvania; Jack D. Sobel, Wayne State University, Detroit, Michigan; Patrick A. Flume, Medical University of South Carolina, Charleston, South Carolina; Peter N. Benotti, Englewood Hospital, Englewood, New Jersey; Pablo Tebas, Washington University, St. Louis, Missouri; Judith E. Wolf, Graduate Hospital, Philadelphia, Pennsylvania; Andrew A. Quartin, Veterans Affairs Medical Center, Miami, Florida; Marcos J. Zervos, William Beaumont Hospital, Royal Oak, Michigan; Grace S. Rozycki, Emory University School of Medicine, Atlanta, Georgia; Daniel H. Kett, Veterans Affairs Medical Center, Miami, Florida; and Patricia A. O'Neill, Kings County Hospital, Brooklyn, New York.