

Empirical Anti-*Candida* Therapy among Selected Patients in the Intensive Care Unit: A Cost-Effectiveness Analysis

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Background: Mortality from invasive candidiasis is high. Low culture sensitivity and treatment delay contribute to increased mortality, but nonselective early therapy may result in excess costs and drug resistance.

Objective: To determine the cost-effectiveness of anti-*Candida* strategies for high-risk patients in the intensive care unit (ICU).

Design: Cost-effectiveness decision model.

Data Sources: Published data to 10 May 2005, identified from MEDLINE and Cochrane Library searches, ICU databases, expert estimates, and actual hospital costs.

Target Population: Patients in the ICU with suspected infection who have not responded to antibacterial therapy.

Time Horizon: Lifetime.

Perspective: Societal.

Interventions: Fluconazole, caspofungin, amphotericin B, or lipid formulation of amphotericin B given as either empirical or culture-based therapy and no anti-*Candida* therapy.

Outcome Measures: Incremental life expectancy and incremental cost per discounted life-year (DLY) saved.

Results of Base-Case Analysis: Ten percent of the target population will have invasive candidiasis. Empirical caspofungin

therapy is the most effective strategy but is expensive (\$295 115 per DLY saved). Empirical fluconazole therapy is the most reasonable strategy (\$12 593 per DLY saved) and decreases mortality from 44.0% to 30.4% in patients with invasive candidiasis and from 22.4% to 21.0% in the overall target cohort.

Results of Sensitivity Analysis: Empirical fluconazole therapy is reasonable for likelihoods of invasive candidiasis greater than 2.5% or fluconazole resistance less than 24.0%. For higher resistance levels, empirical caspofungin therapy is preferred. For low prevalences of invasive candidiasis, culture-based fluconazole is reasonable. For prevalences exceeding 60%, empirical caspofungin therapy is reasonable. For caspofungin to be reasonable at a prevalence of 10%, its cost must be reduced by 58%.

Limitations: Less severe illness and limited use of broad-spectrum antimicrobial agents, typical of smaller hospitals, could result in a lower risk for invasive candidiasis.

Conclusions: In patients in the ICU with suspected infection who have not responded to antibiotic treatment, empirical fluconazole should reduce mortality at an acceptable cost. The use of empirical strategies in low-risk patients is not justified.

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Over the last 2 decades, *Candida* species have emerged as causes of substantial morbidity and mortality in hospitalized individuals (1–3). Isolation of *Candida* from blood or other sterile sites, excluding the urinary tract, defines invasive candidiasis (4). *Candida* species are currently the fourth most common cause of bloodstream infections (that is, candidemia) in U.S. hospitals and occur primarily in the intensive care unit (ICU), where candidemia is recognized in up to 1% of patients and where deep-seated *Candida* infections are recognized in an additional 1% to 2% of patients (1, 5–8). Despite the introduction of newer anti-*Candida* agents, invasive candidiasis continues to have an attributable mortality rate of 40% to 49%; excess ICU and hospital stays of 12.7 days and 15.5 days, respectively; and increased care costs (7, 9–19). Post-mortem studies suggest that death rates related to invasive candidiasis might, in fact, be higher than those described because of undiagnosed and therefore untreated infection (20–22). The diagnosis of invasive candidiasis remains challenging for both clinicians and microbiologists. Reasons for missed diagnoses include nonspecific risk factors and clinical manifestations (8, 23–26), low sensitivity of microbiological culture techniques, and unavailability of deep tissue cultures because of risks associated with the

invasive procedures used to obtain them (20, 27–38). Thus, a substantial proportion of invasive candidiasis in patients in the ICU is assumed to be undiagnosed and untreated. Yet even when invasive candidiasis is diagnosed, culture diagnosis delays treatment by 2 to 3 days, which contributes to mortality (27, 29, 30, 39, 40).

Interventions that do not rely on a specific diagnosis and are implemented early in the course of *Candida* infection (that is, empirical therapy) or before *Candida* infection occurs (that is, prophylaxis) might improve patient survival and may be warranted (5, 41, 42). Selective and nonselective administration of anti-*Candida* prophylaxis is

See also:

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Web-Only

Appendix
Appendix Table
Appendix Figures
Conversion of figures and tables into slides

Context

Invasive candidiasis has several treatments. How to balance their costs and effectiveness is not known.

Contribution

According to this cost-effectiveness analysis, empirical caspofungin therapy is the most effective strategy for patients in the intensive care unit (ICU) with suspected infection that has not responded to antibacterial therapy. However, because of its high cost, caspofungin is less cost-effective than empirical fluconazole (incremental cost of \$295 115 vs. \$12 593 per discounted life-year saved). Therapies with empirical amphotericin B and the lipid form of amphotericin (L-amphotericin) were the least effective strategies, largely because of drug toxicities.

Implications

The authors recommend empirical fluconazole therapy for patients in the ICU with suspected infection because it reduces mortality at an acceptable cost.

—The Editors

practiced in some ICUs (43, 44). Several trials have tested this (45–49), but results were limited by low statistical power and choice of outcomes. Thus, the role of anti-*Candida* prophylaxis for patients in the ICU remains controversial (5, 42, 50–53). Initiating anti-*Candida* therapy for patients in the ICU who have suspected infection but have not responded to antibacterial therapy (empirical therapy) is practiced in some hospitals. This practice, however, remains a subject of considerable debate. These patients are perceived to be at higher risk for invasive candidiasis and therefore are likely to benefit from empirical therapy. Nonetheless, empirical anti-*Candida* therapies have not been evaluated in a randomized trial and would share shortcomings that are similar to those described for prophylactic strategies. Current treatment guidelines by the Infectious Diseases Society of America (IDSA) do not specify whether empirical anti-*Candida* therapy should be provided to immunocompetent patients (51). If such therapy is given, IDSA recommends that its use should be limited to patients with *Candida* colonization in multiple sites, patients with several other risk factors, and patients with no uncorrected causes of fever (51). Without data from clinical trials, determining an optimal anti-*Candida* strategy for patients in the ICU is challenging. Identifying such a strategy can help guide clinicians in choosing adequate therapy and may improve patient outcomes. In our study, we developed a decision analytic model to evaluate the cost-effectiveness of empirical anti-*Candida* therapy given to high-risk patients in the ICU, defined as those with altered temperature (fever or hypothermia) or unexplained hypotension despite 3 days of antibacterial therapy in the ICU.

METHODS**Target Population**

Patients hospitalized in the ICU who, despite receiving antibacterial therapy in the ICU for 3 days, have fever, hypothermia, or unexplained hypotension constituted the target cohort for our decision model. Although not specific for invasive candidiasis, fever, hypothermia, and unexplained hypotension are common manifestations of invasive candidiasis (54). We excluded patients who responded to antibacterial treatment (that is, those who became normothermic and normotensive within 3 days of antibacterial therapy) from the target cohort because they would probably have a bacterial rather than a fungal infection.

Decision Model

By using a standard computer program (Decision Maker 7.07, Pratt Medical Group, Boston, Massachusetts), we constructed a decision tree to model the effect of 9 different clinical strategies on our study cohort: 4 empirical anti-*Candida* strategies, 4 culture-based anti-*Candida* strategies, and 1 no anti-*Candida* treatment strategy (Appendix Figure 1, available at www.annals.org). Empirical strategies consisted of therapy with amphotericin B, lipid formulations of amphotericin B (L-amphotericin), caspofungin, or fluconazole started before culture results are available; continued even if fungal culture results are negative; and given to all patients in the ICU with fever, hypothermia, or unexplained hypotension that persisted despite 3 days of antibacterial therapy. Culture-based strategies consisted of therapy with amphotericin B, L-amphotericin, caspofungin, or fluconazole only when cultures are reported to grow *Candida*. For dose and duration of therapy, we applied IDSA treatment guidelines that advise a 14-day course of an anti-*Candida* agent after the last positive culture result for invasive candidiasis (51).

Data and Assumptions

Data sources used to derive the probability estimates in the decision tree included published data to 10 May 2005, ICU databases from 3 U.S. tertiary care academic medical centers (Tufts-New England Medical Center and Beth Israel Deaconess Medical Center, Boston, Massachusetts, and Long Island Jewish Medical Center, New Hyde Park, New York), manufacturers of automated blood culture systems (BACTEC system, Becton Dickinson, New Jersey, and BacT/Alert system, Organon Teknika, North Carolina), and expert opinion. We obtained actual direct costs of care in U.S. dollars from the pharmacy and billing departments at Tufts-New England Medical Center. Table 1 presents the base-case probability estimates and the ranges tested in sensitivity analyses. When data were unavailable, we used the most conservative estimate, thereby biasing the results against empirical therapy.

Table 1. Baseline Values for the Decision Model and Ranges Used in Sensitivity Analyses*

Variable	Value at Baseline	Sensitivity Range	References
Culture sensitivity (ratio of IC diagnosis in patients with IC)	0.7	0.5–0.9	20, 27–30, 32–38
Rate of culture contamination by <i>Candida</i> (false-positive result)	0.05	0.01–0.20	
Average age of ICU survivors, y	60.7	20–80	Available ICU databases
Discount factor	0.03	0.00–0.10	55, 56
Duration of anti- <i>Candida</i> therapy, <i>d</i>	14	7–21	51
Efficacy of anti- <i>Candida</i> therapy (decrease in mortality from IC)			
Amphotericin B	0.6	0.6–1.0	57–61
L-amphotericin	0.6	0.6–1.0	57, 62–67
Fluconazole	0.6	0.6–1.0	58–61, 68
Caspofungin	0.6	0.6–1.0	69
Probability of fluconazole resistance (decrease in efficacy)	0.05	0.01–0.50	70–86
Probability of caspofungin resistance (decrease in efficacy)	0	0.01–0.50	81, 82
Increased treatment efficacy if administered early†	0.3	0.0–0.5	40, 87, 88
Severe toxicity related to anti- <i>Candida</i> therapy			
Amphotericin B (kidney toxicity and anaphylaxis)	0.12	0.05–0.20	89–93
L-amphotericin (kidney toxicity and anaphylaxis)	0.08	0.03–0.20	91, 92, 94
Fluconazole (anaphylaxis)	0.0001	0.0001–0.0100	58–61, 68, 95
Caspofungin (anaphylaxis)	0.0001	0.0001–0.0100	69, 96–100
Probability of mortality			
From untreated IC (i.e., IC-attributable mortality)	0.4	0.20–0.80	9–12
In the ICU (vs. later in the ward)	0.8	0.5–1.0	Available ICU databases
From reasons unrelated to IC (i.e., other than IC)	0.2	0.10–0.40	Available ICU databases
In the ICU (vs. later in the ward)	0.5	0.2–1.0	Available ICU databases
From severe drug-related nephrotoxicity	0.3	0.05–0.50	89, 90, 93, 101
In the ICU (vs. later in the ward)	1.0	0.4–1.0	Available ICU databases
Annual excess probability of mortality in ICU survivors‡			
First year after ICU discharge	0.049	–	102–106
Second year after ICU discharge	0.036	–	102–106
Third year after ICU discharge	0.019	–	102–106
Fourth year after ICU discharge	0.018	–	102–106
Fifth year after ICU discharge	0.006	–	102–106
>5 years after ICU discharge	0	–	102–106
Length of hospital stay, <i>d</i>			
ICU survivors with no IC or drug toxicity	14	7–21	Available ICU databases
Survivors of IC	14	7–21	Available ICU databases
Survivors of drug-related severe toxicity	20	10–30	Available ICU databases
Early death from IC	9	3–15	Available ICU databases
Late death from IC	44	20–60	Available ICU databases
Death from drug-related nephrotoxicity	17	5–30	Available ICU databases
Early death unrelated to IC or drug toxicity	3	1–10	Available ICU databases
Late death unrelated to IC or drug toxicity	17	5–30	Available ICU databases
Cost, \$			
<i>Candida</i> culture§	0	–	
ICU day	2000	1000–3000	Hospital billing department
ICU day if died of drug-related nephrotoxicity	3200	2100–4300	Hospital billing department
Non-ICU (floor) day	1200	600–2400	Hospital billing department
Amphotericin B: cost per day of treatment	15	5–30	Average wholesale price
Fluconazole: cost per day of treatment¶	108	20–150	Average wholesale price
L-amphotericin: cost per day of treatment (3 mg/kg of body weight per day)	483	150–600	Average wholesale price
Caspofungin: cost per day of treatment¶¶	381	100–500	Average wholesale price

* IC = invasive candidiasis; ICU = intensive care unit; L-amphotericin = lipid formulation of amphotericin.

† Increase in the efficacy of early therapy compared with waiting until culture results were positive (0.6×1.3).

‡ Excess probability of mortality among ICU survivors compared with age-matched general population.

§ *Candida* cultures are assumed to be obtained from all patients regardless of treatment strategy. Thus, the cost of culture would not affect the analysis and was therefore estimated to be \$0.

¶ For an intravenous dose of 800 mg given on the first day of therapy followed by 400 mg intravenously daily for 6 days, followed by 400 mg orally daily for 7 days.

¶¶ For an intravenous dose of 70 mg given on the first day of therapy followed by 50 mg daily for 13 days.

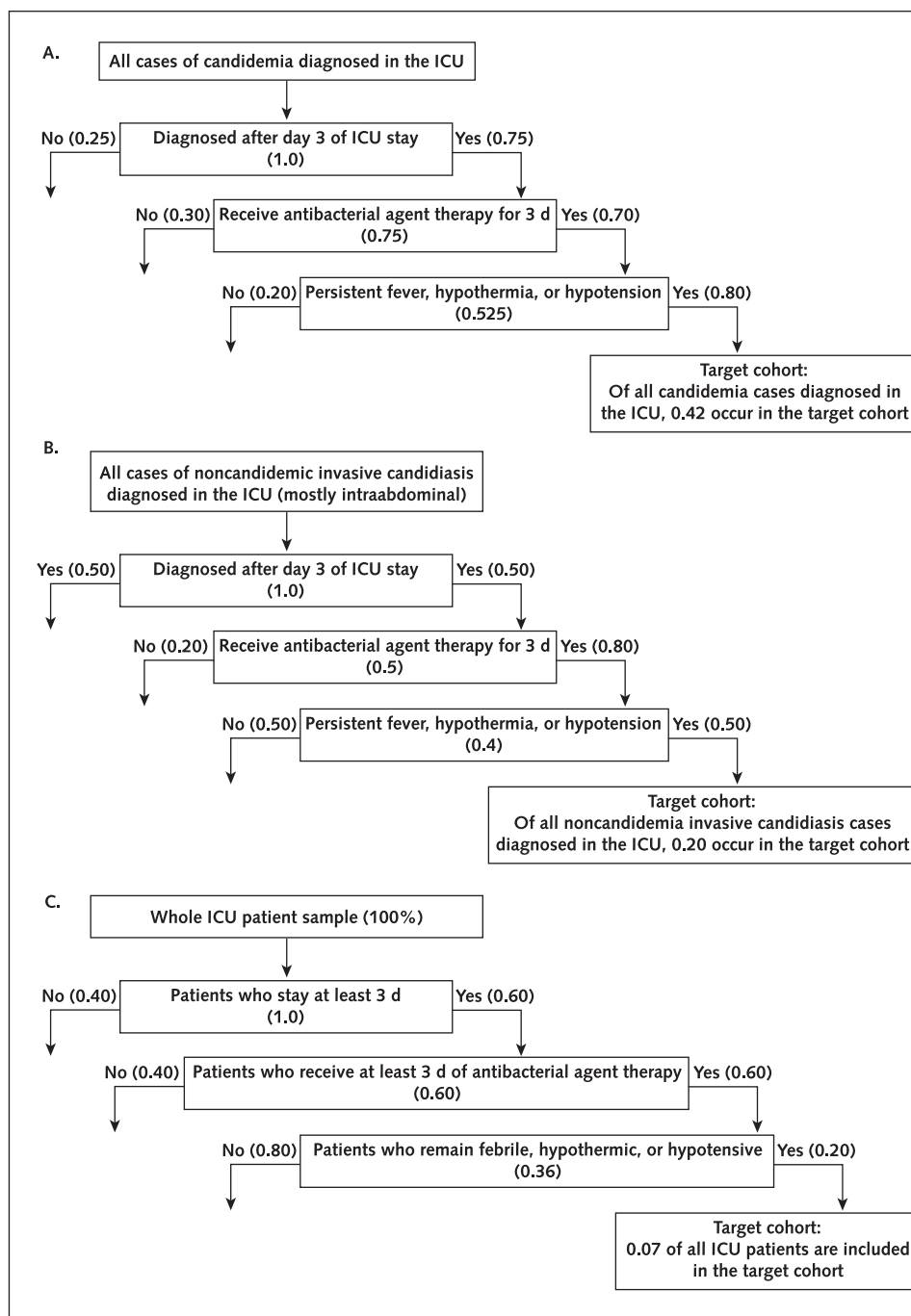
Prevalence of Invasive *Candida* Infections in the Study Cohort

We calculated the prevalence of diagnosed invasive candidiasis in the target cohort in a multistep procedure as the combination of prevalences of candidemic and noncandidemic invasive candidiasis in the target cohort (Figure 1; Appendix, available at www.annals.org).

Culture Availability, Sensitivity, and Specificity

The culture diagnosis of *Candida* infections requires that specimens of infected blood or tissue be obtained and that *Candida* grow in culture. We assumed that specimens of the involved site were obtained in all patients with invasive candidiasis. According to surveyed manufacturers of automated blood culture systems and the published litera-

Figure 1. Estimating the fraction of candidemic and noncandidemic invasive candidiasis and the fraction of intensive care unit (ICU) population that is included in the target group.



A. Estimating the fraction of candidemic invasive candidiasis (IC) included in the target group ($\text{FRACTION}_{\text{candidemicIC}}^{\text{target}}$). On the basis of available ICU databases, the proportion of cases of ICU candidemia that are diagnosed on day 4 or later in the ICU is 0.75. Of these, 0.7 occur in patients who received at least 3 days of antibacterial therapy, and 0.8 of these patients with candidemia present with fever, hypothermia, or unexplained hypotension. These patients are unlikely to resolve their symptoms with antibacterial therapy. B. Estimating the fraction of noncandidemic IC included in the target group ($\text{FRACTION}_{\text{noncandidemicIC}}^{\text{target}}$). On the basis of available ICU databases, 0.5 of all diagnosed cases of noncandidemic IC in patients in the ICU (mostly intraabdominal) are diagnosed on day 4 or later in the ICU. Of these, 0.8 occur in patients who received at least 3 days of antibacterial therapy. Of those who receive at least 3 days of antibacterial therapy, 0.5 remain febrile, hypothermic, or hypotensive. This relatively low fraction reflects the fact that many intraabdominal isolates of *Candida* are not clinically relevant; thus, 0.5 of patients with *Candida* isolated from their intraabdominal cavity resolve symptoms when receiving antibacterial therapy. C. Estimating the fraction of the ICU population included in the target group ($\text{FRACTION}_{\text{allICUpts}}^{\text{target}}$). On the basis of available ICU databases, 0.6 of patients stay in the ICU for more than 2 days. Of patients who stay more than 2 days, 0.6 will receive 3 or more days of antibacterial therapy. Of those who receive 3 or more days of antibacterial therapy, 0.2 remain febrile, hypothermic, or hypotensive despite therapy. In summary, 0.07 of all patients in the ICU are included in the study's target cohort.

ture, the sensitivity of automated blood culture systems for detecting *Candida* growth ranges from 55% to 70% (20, 27–30, 32–38). We used the higher estimate of 70% in our model to favor culture-based strategies. Although *Candida* growth in blood cultures should generally be considered true infection, contamination of blood cultures with *Candida* may occur. We assumed a 5% false-positive rate.

Outcomes

We analyzed 2 outcomes for each treatment strategy: life expectancy and expected cost of care. We measured life expectancy as the mean number of discounted life-years (DLYs) saved (see Costs of Care) through the use of each clinical strategy. We determined this by using hospital survival rate and life expectancy after hospital discharge. Factors influencing hospital survival included mortality due to invasive candidiasis; anti-*Candida* drug toxicity; and other causes, primarily underlying comorbid conditions. We estimated survival after hospital discharge by using life tables that were modified to include the effect of excess comorbid conditions among ICU survivors. We calculated the cost-effectiveness ratio as incremental dollars spent per additional DLY saved. We did not adjust for quality of life because we assumed that survivors of invasive candidiasis or nephrotoxicity related to anti-*Candida* medications are unlikely to have long-term consequences related to these conditions.

Life Expectancy of ICU Survivors and Mortality from Invasive Candidiasis, Drug Toxicity, and Other Causes

The Appendix (available at www.annals.org) describes the procedures used to estimate life expectancy of ICU survivors and mortality from invasive candidiasis, from toxicity related to anti-*Candida* agents, and from conditions unrelated to invasive candidiasis or drug toxicity. For our model, we assumed an invasive candidiasis-attributable mortality rate of 40%, of which 40% occurred early (in the ICU) and 60% occurred late (either in the ICU or in the ward).

Effectiveness of Anti-*Candida* Therapy

Clinical trials suggest that high-dose fluconazole, amphotericin, L-amphotericin, and caspofungin are equally effective in treating invasive candidiasis, barring resistance (57–69, 96, 107). We performed a systematic literature review and included all randomized, controlled trials that reported the effectiveness of first-line use of anti-*Candida* agents that are included in our model on mortality from invasive candidiasis (Appendix, available at www.annals.org). We searched MEDLINE, the Cochrane Library, reference lists of articles, and selected conference proceedings. Date of latest search is 10 May 2005. Two reviewers independently decided which trials to include. We excluded studies in which anti-*Candida* therapy was given to patients who had unproven invasive candidiasis, who had other fungal infections, and who were younger than 13

years of age. By using a random-effects model, we performed a meta-analysis of studies that used fluconazole as a treatment group. On the basis of our review, we assumed that all agents could prevent 60% of the 40% of deaths that are attributable to invasive candidiasis (that is, decrease mortality due to invasive candidiasis from 40% to 16%).

The efficacy of fluconazole may be decreased by drug resistance of the organism. Current data suggest that resistance to the tested dose of fluconazole among ICU *Candida* blood isolates remains low, approximately 3% (70–86). To adjust for a potential decrease in fluconazole susceptibility, we reduced its efficacy to 95% of that of amphotericin B, L-amphotericin, and caspofungin, and we subjected this estimate to sensitivity analysis. Resistance among *Candida* species to caspofungin and lipid or standard amphotericin is currently very low (70, 71, 76, 77, 79, 81, 82), so we assumed no resistance to therapy with these agents in the base-case analysis but examined the effect of emergence of resistance to these agents in sensitivity analyses.

Costs of Care

Costs of care included the actual direct costs of ICU stay, ward stay after discharge from the ICU, anti-*Candida* medications, in-hospital dialysis, and physician reimbursement. We calculated the mean cost per patient for each treatment strategy.

Marginal Cost-Effectiveness

We used the marginal cost-effectiveness ratio to compare the performance of treatment strategies. We considered strategies with a marginal cost-effectiveness ratio of less than \$50 000 per DLY saved to be acceptable.

Sensitivity Analyses

To assess the robustness of our results, we subjected each probability estimate in our model to a univariate sensitivity analysis. We evaluated the effect of varying the value of each probability estimate within a plausible range on the outcomes of interest, incremental life expectancy, and incremental cost-effectiveness. Where applicable, we calculated the threshold values, reflecting a change in a reasonable strategy or cost exceeding \$50 000 per DLY saved. We examined probability estimates that had a high effect on the analytic results or that we felt were likely to markedly change over time in 2-way and 3-way sensitivity analyses.

Role of the Funding Sources

Pfizer Inc. and the National Library of Medicine funded the study. The funding sources had no role in the design, conduct, or reporting of the study or in the decision to submit the manuscript for publication.

Table 2. Cost-Effectiveness of 9 Anti-*Candida* Therapy Strategies for Selected Patients in the Intensive Care Unit*

Anti- <i>Candida</i> Treatment Strategy	Expected Cost per Patient, \$†	Patients Discharged Alive, %‡	Discounted Life Expectancy, y§	Marginal Cost, \$	Marginal Effectiveness, y¶	Marginal Cost-Effectiveness, \$/y**
No anti- <i>Candida</i> treatment	21 722	76.00	10.972			
Culture-based amphotericin B	21 901	77.32	11.121	180	0.149	Extended dominance by culture-based fluconazole
Culture-based fluconazole	21 926	77.60	11.154	205	0.182	1122
Culture-based caspofungin	22 373	77.68	11.164	447	0.010	Extended dominance by empirical fluconazole
Culture-based L-amphotericin	22 574	77.44	11.135	648	-0.019	Simple dominance by culture-based caspofungin
Empirical fluconazole	23 272	78.96	11.261	1346	0.107	12 593
Empirical amphotericin B	23 554	75.52	10.868	282	-0.393	Simple dominance by empirical fluconazole
Empirical caspofungin	27 080	79.12	11.274	3808	0.013	295 115
Empirical L-amphotericin B	29 125	76.72	11.003	2046	-0.271	Simple dominance by empirical caspofungin

* Treatment strategies are presented in order of cost per patient with the least expensive strategy at the top. L-amphotericin = lipid formulation of amphotericin.

† Expected cost per patient calculated as cost for the whole cohort divided by the total number of patients.

‡ Percentage of patients who are expected to be discharged from the hospital alive.

§ Strategy's effectiveness is the average number of discounted life-years experienced per patient. Calculated as years gained for the whole cohort (number of survivors multiplied by expected discounted life-years) divided by total number of patients.

|| Calculated as average cost per patient in this strategy minus average cost per patient in the previous most effective strategy (top to bottom).

¶ Calculated as the average number of discounted life-years gained per patient in this strategy minus the number of discounted life-years gained per patient in the previous most effective strategy (top to bottom).

** Marginal cost per patient divided by marginal effectiveness per patient. Each strategy is compared with the previous most effective strategy (top to bottom). A strategy is eliminated by simple dominance if it has a higher cost and lower effectiveness than another strategy. A strategy is eliminated by extended dominance if another strategy provides additional effectiveness at a lower marginal cost-effectiveness ratio. If any strategy is eliminated, all other cost-effectiveness ratios are recalculated with the dominated strategy removed from consideration (108).

RESULTS

Prevalence of Invasive Candidiasis in the Target Cohort

The prevalence of candidemic and noncandidemic invasive candidiasis in patients in the ICU is approximately 1% and 2%, respectively (6, 8). We found similar rates in the available databases. The analyzed target cohort includes 42% and 20% of all ICU cases of candidemic and noncandidemic invasive candidiasis, respectively (Figure 1, parts A and B), and 7% of all patients in the ICU (Figure 1, part C). Therefore, the calculated prevalence of diagnosed invasive candidiasis in the target cohort was 11.7%. We used a prevalence estimate of 10% in our base-case analysis to bias (slightly) against empirical therapy.

Base-Case Analysis

Empirical amphotericin B treatment and L-amphotericin therapies were the least effective strategies because of drug toxicities (Table 2). Although empirical amphotericin B reduced mortality from 64% to 32% in patients with invasive candidiasis, it increased mortality from 24% with no anti-*Candida* therapy to 24.5% in the whole cohort. Culture-based conventional or L-amphotericin therapy was more effective than no anti-*Candida* therapy but was less effective than culture-based or empirical fluconazole or caspofungin therapy. Among the 9 strategies that we examined, empirical fluconazole therapy was the preferred clinical strategy (that is, the most effective strategy at an acceptable cost). When compared with culture-based fluconazole therapy (the next most effective strategy), empirical fluconazole therapy decreased mortality from 44.0% to 30.0% in patients with invasive candidiasis and from 22.4% to 21.0% in the entire target cohort. To save 1 life, 71 patients (with fever, hypothermia, or unexplained hy-

potension despite 3 days of antibiotic therapy) in the ICU needed to be treated with empirical fluconazole. Empirical caspofungin therapy was the most effective strategy but was unacceptably expensive. Compared with empirical fluconazole, empirical caspofungin therapy decreased mortality from 30.0% to 29.0% in patients with invasive candidiasis and from 21.0% to 20.9% in the entire cohort. To save 1 life, 250 patients needed to be treated with empirical caspofungin compared with empirical fluconazole.

Our cost-effectiveness analysis suggested that empirical caspofungin is an unacceptable treatment strategy. It is considerably more expensive than empirical fluconazole, but its marginal effectiveness over empirical fluconazole is very small, resulting in a marginal cost-effectiveness ratio of \$295 100 per DLY saved, a ratio that exceeds our accepted threshold of \$50 000 per DLY saved. Our analysis suggested that empirical fluconazole has an acceptable marginal cost-effectiveness ratio of \$12 600 per DLY saved.

Sensitivity Analyses

We performed 2 sets of analyses to examine the effect of varying the value of base-case estimates on the marginal cost-effectiveness ratio of empirical fluconazole and caspofungin. Because empirical fluconazole was an attractive treatment strategy in our base-case analysis, we explored the limits of its attractiveness in sensitivity analyses. Empirical caspofungin was unacceptably expensive in our base-case analysis, so we examined factors in sensitivity analyses that could make it an acceptable strategy. Figure 2 presents analyses with cost-effectiveness ratios within the range of \$0 to \$150 000 per DLY saved. Other results are described in the text.

Prevalence of Invasive Candidiasis in the Target Cohort

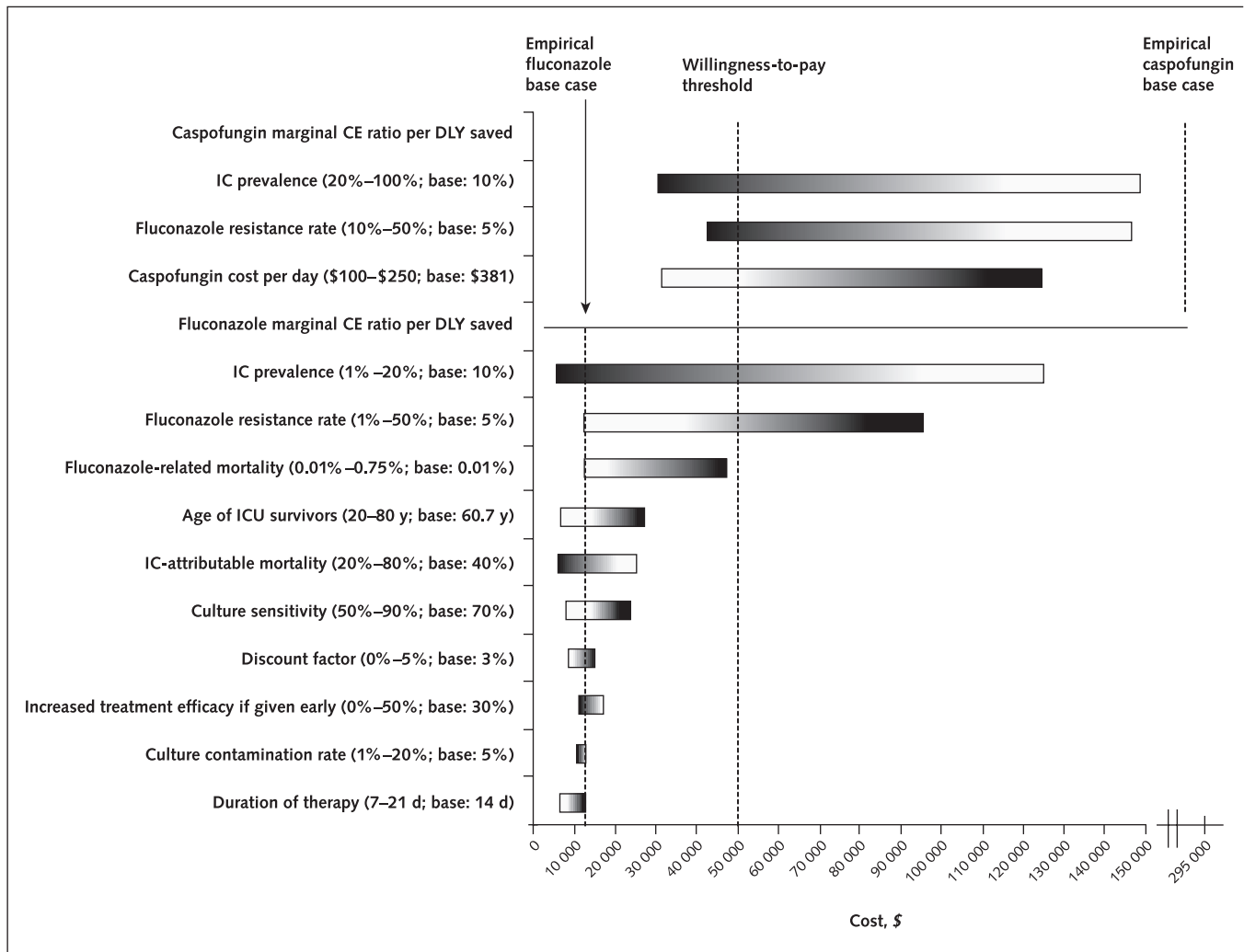
We tested the marginal cost-effectiveness of empirical fluconazole and empirical caspofungin across invasive candidiasis prevalence rates of 0% to 100%. If prevalence decreased to less than 2.5%, empirical fluconazole exceeded the willingness-to-pay threshold of \$50 000 per DLY saved. At this prevalence, culture-based fluconazole was preferred. The cost-effectiveness of both strategies improved for higher prevalences of invasive candidiasis. At a prevalence of 60%, empirical caspofungin is preferred, at a

willingness-to-pay threshold of less than \$50 000 per DLY saved.

Drug Resistance Rates

Given no resistance to caspofungin, a 28% threshold of fluconazole resistance is required for empirical caspofungin to have a marginal cost-effectiveness ratio less than \$50 000 per DLY saved. Any increase of 1 percentage point in caspofungin resistance results in a 1–percentage point increase of this threshold (that is, if the caspofungin

Figure 2. Tornado diagram for marginal cost-effectiveness (CE) ratio per discounted life-year (DLY) saved.



The darker portion of each bar represents the higher values for the corresponding sensitivity range tested. For example, for fluconazole-related mortality, 0.75% is to the right of the bar. For invasive candidiasis (IC) prevalence, 20% is to the left of the bar. The upper 3 analyses and the lower 10 analyses examined the effect of varying the value of base-case estimates on the marginal CE ratio of empirical caspofungin and fluconazole, respectively. The horizontal axis represents the discounted incremental CE ratio for each value on the vertical axis. The width of the bar associated with each variable illustrates the range for the CE ratio. The upper and lower limits followed by the base-case value for each variable tested are in parentheses. The bars are ordered from least width at the bottom to the greatest width at the top. The comparator for analyses of fluconazole CE ratio, excluding the analysis of fluconazole resistance rates, is culture-based fluconazole, the next most effective treatment strategy. For the analysis of fluconazole resistance rates, culture-based fluconazole is replaced with culture-based caspofungin as the next most effective strategy at a fluconazole resistance rate of 17%. The comparator for analyses of caspofungin CE ratio, excluding the analysis of fluconazole resistance rates, is empirical fluconazole, the next most effective treatment strategy. For the analysis of fluconazole resistance rates, empirical fluconazole is replaced with culture-based caspofungin at a fluconazole resistance rate of 34%. Because the effectiveness and cost of both empirical and culture-based caspofungin are not affected by fluconazole resistance, any further increase in fluconazole resistance rates has no effect on the marginal CE ratio of empirical caspofungin. ICU = intensive care unit.

resistance rate were 5%, the cost-effectiveness ratio of empirical caspofungin would be less than \$50 000 per DLY saved at a fluconazole resistance rate of 33%).

Cost of Caspofungin

At existing invasive candidiasis prevalence and fluconazole resistance rates, the average cost of caspofungin therapy per day must be less than \$159 (current cost is \$381) to have an acceptable cost-effectiveness ratio.

Life Expectancy of ICU Survivors

The cost-effectiveness ratio of empirical fluconazole remained reasonable even at survivor life expectancies as low as 3.3 years (equivalent to a “physiologic” age of 88 years, where the mean incremental cost-effectiveness ratio is \$50 000 per DLY saved). Empirical caspofungin remained unacceptably expensive even at the highest life expectancies tested (that of a 20-year-old patient).

Medication-Related Toxicity

For rates of severe nephrotoxicity less than 5.0%, culture-based standard and L-amphotericin therapies were acceptable strategies, but empirical fluconazole therapy remained preferred. For a fluconazole-related mortality rate of 0.75%, the marginal cost-effectiveness of empirical fluconazole remained acceptable, while empirical caspofungin remained unacceptable.

Other Analyses

We did not observe any major change in the marginal cost-effectiveness ratio of empirical fluconazole and empirical caspofungin with changing rates of culture sensitivity (50% to 80%), culture false positivity (0% to 20%), invasive candidiasis-attributable mortality (35% to 70%), annual discount rate (0% to 5%), and daily cost of ward (\$600 to \$1200) and ICU (\$1000 to \$3000) care or when we assumed that the efficacy of empirical therapy equaled that of therapy delayed until culture results returned. Results of multiway sensitivity analyses are available from the authors upon request.

DISCUSSION

Invasive candidiasis is emerging as an important nosocomial infection, particularly among patients in the ICU, and its mortality remains high. A treatment strategy that does not depend on positive culture results and can be initiated early is particularly attractive because it might overcome problems of culture sensitivity and irreversibility of advanced infection. However, such an early intervention strategy will expose many patients without invasive candidiasis to anti-*Candida* agents, risking morbidity related to drug toxicity, perhaps increasing costs of care, and contributing to an accelerated emergence of drug resistance. Empirical therapy is an early intervention strategy, but a clinical trial has not yet evaluated it. Before our analysis, the

theoretical disadvantages of such a strategy seemed to offset its potential advantages. Consequently, using conservative probability estimates, we developed a decision analysis model that compared the cost-effectiveness of empirical fluconazole or caspofungin therapy given to selected patients in the ICU with that of other treatment strategies.

We aimed to study a clinically relevant group of patients for whom data are available. The clinical criteria of fever, hypothermia, or unexplained hypotension, despite 3 days of antibacterial therapy administered in the ICU, define a group of patients in the ICU for whom empirical anti-*Candida* therapy is sometimes prescribed or debated (5, 51–53). Our analysis suggests that empirical fluconazole therapy given to this group of patients is a reasonable treatment strategy. The marginal cost-effectiveness ratio for empirical fluconazole is much less than the widely used threshold of \$50 000 per DLY saved. A therapy with a threshold less than this may be considered to be cost-effective and is within the range of other widely accepted or mandated medical interventions, such as treating hypertension, coronary artery bypass surgery, and hemodialysis or screening for colorectal or breast cancer (109–113). This strategy should remain a reasonable plan over a broad range of event probability estimates. Nevertheless, at prevalence rates of invasive candidiasis less than 2.5%, perhaps in a different clinically defined cohort, the cost of empirical fluconazole becomes unacceptably expensive.

We purposely biased the base-case analysis against empirical fluconazole by choosing unfavorable probability estimates. If we had chosen less conservative estimates for the model, empirical fluconazole would have been even more cost-effective. For example, our choice of 70% for culture sensitivity is in contrast with the 56% that was recently reported for the last model of a widely used blood culture system (28). The performance of culture-independent strategies would improve at lower culture sensitivities. We also assumed that cultures are always obtained, although this is not the case. Thus, the sensitivity of culture-based strategies is probably lower than we assumed. In addition, we based our calculation of invasive candidiasis prevalence on available rates of diagnosed invasive candidiasis. If we had also included undiagnosed invasive candidiasis, the estimated prevalence of invasive candidiasis would have been higher and, hence, would have favored empirical strategies.

A concern about the empirical use of fluconazole is the emergence of fluconazole-resistant or fluconazole-tolerant *Candida* isolates. This has been observed among invasive isolates from immunocompromised patients (83–85) and, inconsistently, among noninvasive isolates from immunocompetent patients (43, 114). However, despite the large increase in fluconazole use in ICUs during the last decade, the increase in fluconazole-resistant *Candida* blood isolates from immunocompetent patients has remained small (71–80, 82, 86, 114, 115). Nevertheless, providing anti-*Candida* prophylaxis to patients indiscriminately might eventually substantially increase rates of resistance (43, 44). By

using the criteria of suspected infection and including no response to antibiotic therapy in the target cohort, we limited exposure to empirical anti-*Candida* therapy in our model to 7% of patients in the ICU. Such a selective approach should decrease the risk for resistance emergence, as compared with current practice. As expected, our model shows that the cost-effectiveness ratio of empirical fluconazole increases at high fluconazole resistance rates. However, empirical fluconazole remains cost-effective up to a resistance rate of 43% (vs. culture-based fluconazole). Although surprisingly high, this implies that gains related to early initiation of therapy and to treatment of patients with undiagnosed invasive candidiasis (that is, those with false-negative culture results) offset losses related to treatment failures due to drug resistance. Another strategy might be to begin empirical anti-*Candida* therapy but to discontinue it if culture results are negative. Although we did not explicitly consider this strategy, it is, in essence, a culture-based strategy and is prone to shortcomings related to low culture sensitivity and the difficulties in obtaining tissue. Consequently, this strategy will be dominated by empirical anti-*Candida* therapy.

We found empirical caspofungin to be the most effective strategy in our base-case analysis. However, its marginal cost-effectiveness was much higher than the acceptable threshold because of its very small marginal effectiveness and very large marginal cost compared with empirical fluconazole. Factors that can improve the marginal cost-effectiveness ratio of empirical caspofungin include a decrease in its cost, an increase in its marginal effectiveness (should fluconazole effectiveness decrease from increased resistance), and a higher prevalence of invasive candidiasis in the treated population. At current cost, an increase in fluconazole resistance beyond 24% or an invasive candidiasis prevalence beyond 59% will render empirical caspofungin acceptable. At an invasive candidiasis prevalence of 10% and current levels of fluconazole resistance rates, the daily cost of caspofungin therapy would need to decrease from \$381 to \$159 to become an acceptable strategy. On the other hand, the expected reduction in fluconazole prices, related to expiration of its patent, and the possible increase in caspofungin resistance rates, related to increased use, could result in an even less favorable marginal cost-effectiveness ratio for empirical caspofungin.

The poor performance of empirical amphotericin B and L-amphotericin therapies is not surprising and is related to their frequent nephrotoxicity, which offsets their activity against invasive candidiasis. Given empirically, both agents put the entire target cohort at risk for nephrotoxicity, while only a small portion of the cohort, those with invasive candidiasis, would benefit. The high costs attributable to nephrotoxicity in our model are similar to costs reported in the medical literature (90, 116), and they explain the unfavorable cost-effectiveness ratio for both

standard and lipid amphotericin given empirically or as a culture-based strategy.

A major limitation of any decision model relates to the accuracy of probability estimates used in the model. Although most estimates we used (including activity against invasive candidiasis, toxicity levels, and mortality rates) were extensively evaluated, some estimates had less literature support. One such estimate is the prevalence of invasive candidiasis in the target cohort. This critical estimate directly affects the cost-effectiveness of empirical fluconazole. Using data from the National Epidemiology of Mycosis Survey (NEMIS) (8), together with several other published reports and information available from ICU databases, we expected a rate of invasive candidiasis of 2% to 3% in the entire ICU population. The cohort of patients with suspected infection and no response to antibiotic therapy is a high-risk subset of the entire ICU population that probably has higher rates of invasive candidiasis that are clearly less than the cost-effectiveness threshold calculated in sensitivity analysis (2.5%). Hence, the estimate of invasive candidiasis prevalence should not affect the robustness of our model's conclusions.

Probability estimates used in our model might not apply to some ICUs. Differences between ICUs in patient demographic characteristics, case mix, and the practice of medicine contribute to variable risk for invasive candidiasis and fluconazole resistance and to potential benefit from empirical anti-*Candida* therapy. Probability estimates used in our model best reflect the reality in ICUs of large referral hospitals. Less severe illness and limited use of broad-spectrum antimicrobial agents, typical of smaller hospitals, could result in a lower risk for invasive candidiasis and a lower level of fluconazole resistance in those hospitals. While a lower invasive candidiasis risk might reduce the potential benefit from empirical anti-*Candida* therapy, lower fluconazole resistance rates could increase such benefit. We performed several sensitivity analyses to examine the use of the model in environments other than that reflected by our choice of base-case estimates. Results of these analyses suggest that empirical fluconazole therapy should be an attractive strategy even in patient populations with an invasive candidiasis risk lower than 10%, a fluconazole resistance rate higher than 5%, and an average ICU survivor age as high as 80 years. Nevertheless, the use of empirical fluconazole in patients with suspected infection and no response to antibacterial therapy might not be warranted in selected ICU populations and must be assessed carefully before providing such therapy.

From a broader perspective, our decision model suggests that an early culture-insensitive treatment strategy, such as empirical therapy, for invasive candidiasis in patients in the ICU is an attractive approach that needs further investigation. Although our findings suggest that empirical therapy with fluconazole should be a reasonable treatment strategy, prophylaxis with this agent also might conceivably be reasonable because prophylaxis might pre-

vent an infection that is difficult to eradicate rather than treating it after its appearance. However, we have not examined the strategy of prophylaxis in our paper. Similar to empirical therapy, prophylaxis given to all patients in the ICU will result in unnecessary exposure of low-risk patients to an antifungal agent, might be expensive, and might trigger the emergence of drug resistance. Rather, we suggest defining and studying a group of patients at high risk for developing invasive candidiasis. In our model, we did not explicitly consider many of the well-defined risk factors for invasive candidiasis, including the presence of central lines, receipt of parenteral nutrition, and major operations (8). The inclusion of additional risk factors could have resulted in increased prevalence of invasive candidiasis in the selected ICU cohort. Research to develop a clinical prediction rule for invasive candidiasis and survival is ongoing and should help refine the selection of patients who would benefit from *prophylactic* treatment of invasive candidiasis.

In conclusion, the evidence of benefit from the use of antifungal agents in ICUs is scant. On one hand, antifungal therapies are prescribed unselectively in some ICUs. On the other hand, antifungal therapies are not prescribed even when evidence suggests that they might be beneficial. Our analysis explores both ends of the spectrum. It provides guidance on when empirical anti-*Candida* therapy should be beneficial and when it should be unacceptable. Because data from clinical trials are currently lacking, results of our analysis can help guide physicians in the appropriate choice of antifungal treatment and may improve patient outcomes at an acceptable cost.

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