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EXCESS MORTALITY, HOSPITAL STAY, AND COST DUE TO CANDIDEMIA: A CASE–CONTROL STUDY USING DATA FROM POPULATION-BASED CANDIDEMIA SURVEILLANCE

Juliette Morgan, MD; Martin I. Meltzer, PhD; Brian D. Plikaytis, MSc; Andre N. Sofair, MD; Sharon Huie-White, MPH; Steven Wilcox; Lee H. Harrison, MD; Eric C. Seaberg, PhD; Rana A. Hajjeh, MD; Steven M. Teutsch, MD

ABSTRACT
OBJECTIVE: To determine the mortality, hospital stay, and total hospital charges and cost of hospitalization attributable to candidemia by comparing patients with candidemia with control-patients who have otherwise similar illnesses. Prior studies lack broad patient and hospital representation or cost-related information that accurately reflects current medical practices.

DESIGN: Our case–control study included case-patients with candidemia and their cost-related data, ascertained from laboratory-based candidemia surveillance conducted among all residents of Connecticut and Baltimore and Baltimore County, Maryland, during 1998 to 2000. Control-patients were matched on age, hospital type, admission year, discharge diagnoses, and duration of hospitalization prior to candidemia onset.

RESULTS: We identified 214 and 529 sets of matched case-patients and control-patients from the two locations, respectively. Mortality attributable to candidemia ranged between 19% and 24%. On multivariable analysis, candidemia was associated with mortality (OR, 5.3 for Connecticut and 8.5 for Baltimore and Baltimore County; $P < .05$), whereas receiving adequate treatment was protective (OR, 0.5 and 0.4 for the two locations, respectively; $P < .05$). Candidemia itself did not increase the total hospital charges and cost of hospitalization; when treatment status was accounted for, having received adequate treatment for candidemia significantly increased the total hospital charges and cost of hospitalization ($6,000 to $29,000 and $3,000 to $22,000, respectively) and the length of stay (3 to 13 days).

CONCLUSION: Our findings underscore the burden of candidemia, particularly regarding the risk of death, length of hospitalization, and cost associated with treatment (Infect Control Hosp Epidemiol 2005;26:540-547).

Studies in the United States during the past two decades have documented the changes in pathogens causing nosocomial bloodstream infections (BSIs) and particularly the increase in Candida species.1-5 Candida species are now considered to be the fourth most common hospital-associated bloodstream pathogens, representing approximately 8% to 10% of all BSIs.6,8 In addition to the increasing incidence, the overall mortality due to fungal infections, among all infectious diseases, increased from 10th in 1980 to 7th in 1996.9 These changes are likely a reflection of the changes in medical care practices and number of susceptible hosts, given that Candida BSIs occur among patients who have serious underlying illnesses.

The resultant increases in the cost of medical care, length of hospitalization, and mortality caused by Candida BSIs are therefore difficult to determine because candidemia patients have concomitant conditions. Although various studies have found higher crude mortality rates associated with Candida BSIs compared with other pathogens causing BSI,3,10 few studies have addressed the excess mortality, length of hospitalization, and cost attributable to candidemia.11,14 These studies either were limited to patients hospitalized in one institution or relied on published data and expert opinion regarding treatment options and duration to calculate excess cost and length of hospitalization.

We conducted a case–control study that included patients with candidemia identified from active, population-based surveillance for candidemia. Our goal was to determine the excess mortality, length of hospitalization, and cost due to one episode of candidemia by comparing patients with candidemia with hospitalized patients without candidemia who were otherwise similar. These data can be used by clinicians and public health officials to assess the relative value of interventions aimed at reducing candidemia.

METHODS
Definitions
Cases of candidemia were identified through active, population-based surveillance performed through the Emerging Infection Program in Connecticut, Baltimore

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County, and the city of Baltimore, Maryland, from October 1, 1998, to September 30, 2000. A case of candidemia was defined as a blood culture positive for *Candida* species identified from a resident of either Connecticut or Baltimore and Baltimore County. Although some patients may have had more than one positive blood culture, we considered only the first (incident) positive blood culture. A control-patient was defined as a hospitalized patient without candidemia who was a resident of Connecticut, Baltimore, or Baltimore County.

**Principal Data Source**

The data for the cases, which were initially identified during the population-based surveillance, and for the controls were collected separately in Connecticut and Baltimore and Baltimore County from the hospital discharge databases in each state (ChimeData and Health Services Cost Review Commission [HSCRC] databases). The ChimeData and HSCRC databases incorporate statewide clinical, financial, and patient demographic data. Data are submitted voluntarily by each participating acute care facility. These databases contain demographic information, discharge diagnoses and procedures (coded by the International Classification of Diseases, 9th revision [ICD-9], codes and diagnostic-related groups [DRGs]), the charges for resources used during the hospitalization, and the payer (Medicare or Medicaid, private insurance, or patient). The information extracted from the ChimeData and HSCRC databases included the admitting hospital, fiscal year in which the patient was admitted to the hospital, age at admission, principal and first through sixth secondary ICD-9 discharge diagnostic codes, principal and first through sixth secondary ICD-9 surgical procedure codes and DRGs, total length of hospital stay, disposition at discharge, source of payment (payer), and total charges and source of charges (pharmacy, laboratory, and care level [ie, critical care] where available).

**Matching**

Only cases identified during the first year of the surveillance study (October 1, 1998, to September 30, 1999) from Connecticut were included in the Connecticut database. Cases identified from both years (October 1, 1998, to September 30, 2000) of surveillance were included for Baltimore and Baltimore County; however, during the second year of surveillance there, data were not collected for candidemia cases in which the *Candida* species was not *C. albicans*.

Criteria for matching control-patients were similar at each site using the following variables: age (aggregated into groups: 0 to 4 years, 5 to 9 years, 10 to 19 years, and continuing in 10-year increments up to 79 years, with the last age group older than 80 years); year of hospital admission (October 1, 1998, through September 30, 2000); admitting hospital (hospital group 1, large urban [400 or more beds and located in urban areas of Connecticut and Baltimore and Baltimore County]; hospital group 2, medium urban [250 to 399 beds and located in urban areas of the two locations]; and hospital group 3, small urban [fewer than 250 beds] and all community hospitals combined); principal and first through sixth secondary ICD-9 discharge diagnoses; surgical procedure diagnoses (or surgical DRGs); and length of hospital stay. The hospital stay for the control-patient had to be at least as long as the corresponding case-patient’s length of stay prior to the diagnosis of candidemia. Four control-patients were identified for each case-patient. Patients were excluded as control-patients if they had a discharge diagnosis ICD-9 code that indicated candidemia (code range, 112.0 to 112.9).

**Relaxing the Matching Criteria**

When a sufficient number of control-patients could not be identified for a case-patient using the established criteria, the criteria were sequentially relaxed as follows: the number of matching digits of the ICD-9 discharge diagnosis codes was reduced from five to three; the surgical or procedure codes were reduced from seven to five or to DRG codes; age groups (by only one age group); year of hospitalization (by 1 or 2 years from the year that the case-patient was hospitalized); and admitting hospital (hospital within the same group). The length of hospital stay criterion was never relaxed.

**Closeness of Matching**

The closeness of match between case-patients and control-patients was categorized into highest, middle, and lowest confidence levels. The highest confidence level included control-patients who were matched in terms of having been hospitalized in the same hospital and within 1 year, the same or next age group, and having five of the first seven ICD-9 discharge diagnoses (principal and six secondary) with at least three digits and five of seven surgical procedures or DRGs matching the corresponding case-patient. The lowest confidence level included control-patients who had three of the first seven ICD-9 discharge diagnoses (principal and six secondary) with three digits of each ICD-9 code or surgical procedure code or DRGs matched to their corresponding case-patients, and varying levels of “exactness” of the other criteria. Control-patients included in the middle level of confidence were those who were not categorized in either the highest or the lowest levels of confidence.

**Treatment Status**

The type and length of antifungal treatment administered to case-patients was ascertained from a detailed review of medical records during the surveillance study. Although recommended treatment for candidemia is amphotericin B, fluconazole, or caspofungin for 2 weeks after the last positive blood culture, we defined “adequate” treatment as any systemic antifungal medication (amphotericin B, any azole, echinocandin, flucytosine, or other) administered for a minimum of 7 days after the first blood culture positive for any *Candida* species. Patients who did not survive a minimum of 3 days after a positive blood culture were not considered for the analysis. For the analysis,
control-patients were considered to not have received adequate treatment.

**Analysis**

A preliminary analysis performed on the data from Connecticut and from Baltimore and Baltimore County separately revealed that there was insufficient homogeneity between the databases to combine them. Analyses were therefore performed, and results presented, separately.

We used Fisher’s exact test for univariate analysis for continuous variables where indicated. We calculated the mortality attributable to candidemia by subtracting the mortality of the control-patients from that of the case-patients. We used the GENMOD procedure in SAS software (version 8; SAS Institute, Inc., Cary, NC) to perform conditional logistic regression for the mortality analysis. We expressed the results as the odds ratio with 95% confidence interval, and statistical significance was defined as a P value of .05 or less. The dependent variable was dichotomous, death during hospitalization (yes or no).

We used multivariable linear regression models to analyze the length of hospital stay and total hospital charges (dependent variables). In the two linear regression models, the intercept terms represented either the total hospital charges or the length of hospital stay associated with a baseline patient. For both models, the baseline patient was 30 to 39 years old, did not have candidemia (or receive treatment for candidemia), was hospitalized in a medium-sized urban hospital, was alive at the time of discharge, had a hospital bill covered by federal health insurance, and did not stay in an intensive care unit.

The impact of each independent variable was then added to or subtracted from (depending on the sign of the coefficient) the length of hospital stay or total hospital charges of the baseline patient. Each model considered the impact of the following variables on the dependent variable: status as a case-patient or a control-patient, age group (defined as ages 0 to 4 years, 5 to 19 years, 20 to 59 years, and 60 to 80 years), hospital size and type (three groups as previously defined), type of health insurance (as previously described), and receipt of critical care (yes or no variable, available only for Connecticut). Dummy variables were created based on midpoints of the age groups. In addition, for the models examining the length of hospital stay and total hospital charges, we included a variable describing the outcome of hospitalization (patient died in the hospital, yes or no).

In multivariable models for length of hospital stay and total hospital charges that did not include the variable that takes into account the treatment status (data not presented), no significant differences between case-patients and control-patients regarding total hospital charges and cost of hospitalization were found for Connecticut. These counterintuitive findings prompted the introduction of the variable “adequate candidemia treatment” into the models for length of hospitalization and total hospital charges and cost of hospitalization (for both Connecticut and Baltimore and Baltimore County).

All statistical analyses were performed with SAS software, and the linear regressions used the REG procedure. We defined statistical significance at a P value of .05 or less. The data describing both the total hospital charges and the length of hospital stay were skewed and not normal. To correct for this, before estimating the two linear regressions, we transformed the data into natural logarithms. The resultant coefficients and confidence intervals were then converted back to natural units (eg, hospital-days or charges in U.S. dollars). The analysis was checked for collinearity and residual patterns plots and no abnormalities were found.

**Cost-to-Charge Ratios**

Hospital charges usually do not represent the true economic cost of delivering hospital-based medical care to a patient. For example, the Centers for Medicare & Medicaid Services annually publishes average operating cost-to-charge ratios that it uses to reimburse urban and rural hospitals that have provided services to patients covered by those programs. For fiscal year 1999, Connecticut had cost-to-charge ratios of 0.546 and 0.532 for urban and rural hospitals, respectively. In the same year, Maryland had ratios of 0.764 and 0.818, and for fiscal year 2000 the ratios were 0.764 and 0.821. Using these ratios, we constructed weighted cost-to-charge ratios of 0.545 and 0.764 for charge data for Connecticut and Baltimore and Baltimore County, respectively. (All data for Connecticut were collected from 1999, with 4.7% of all cases being from rural and community hospitals. Thus, the weighted average cost-to-charge ratio was calculated as \(0.047 \times 0.532 + 0.953 \times 0.546 = 0.545\). For Baltimore and Baltimore County, all data were from urban hospitals, and the cost-to-charge ratio was the same for both years studied—0.764. We used these weighted average ratios to convert from charges to costs the statistically significant results of the total hospital charges regression.

Although the medical care portion of the Consumer Price Index increased by 4.1% from 1999 to 2000, we did not make any inflation-related adjustments to the data for total hospital charges. We deemed that the adjustment would be relatively minor and would actually apply to less than half of the total database.

**RESULTS**

Ascertainment of the case-patients and control-patients is summarized in Table 1. There were 231 and 540 cases of candidemia from Connecticut and Baltimore and Baltimore County, respectively, ascertained during the surveillance study and subsequently identified in the ChimeData and HSCRC databases. Of these cases, 214 (93%) from Connecticut and 529 (98%) from Baltimore and Baltimore County had at least 1 control matched and were included in the analysis. The majority of case-patients had four matched control-patients. More than 60% of all control-patients from both surveillance sites were matched to their corresponding case-patients at the highest level of confidence (Table 1). The median ages of the case-patients and the control-
patients were similar at each surveillance site (Table 1); however, case-patients from Connecticut were significantly older than case-patients from Baltimore and Baltimore County, and the same was true for the respective control-patients ($P < .01$). The distribution of cases by age groups was bimodal; the largest number of cases occurred among the older age groups (approximately 50% of these patients were 60 years and older), but 7% of the cases occurred among children younger than 4 years. Most of these cases were among neonates.

The overall crude mortality rates for case-patients were similar between the two sites, ranging between 39% and 42% (Table 2). The overall mortality rate attributable to candidemia was calculated to be 19% and 24% for the two locations, respectively. On univariate analysis, case-patients from both surveillance sites were significantly more likely to die than were their respective control-patients. Candidemia treatment status, as defined above, was available for 178 (83%) and 257 (49%) of case-patients from Connecticut and from Baltimore and Baltimore County, respectively. Only 61% of case-patients from Connecticut and 70% from Baltimore and Baltimore County whose treat-
TABLE 3
MULTIVARIABLE ANALYSIS OF MORTALITY AMONG CASE-PATIENTS AND CONTROL-PATIENTS

<table>
<thead>
<tr>
<th></th>
<th>Connecticut</th>
<th>Baltimore and Baltimore County</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (CI 95%)</td>
<td>P</td>
</tr>
<tr>
<td>Case-patients</td>
<td>5.3 (3.1–9.2)</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Age group 0–19 y*</td>
<td>0.2 (0.1–0.6)</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Age group 20–59 y</td>
<td>0.4 (0.2–0.9)</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Age group ≥ 60 y</td>
<td>0.9 (0.6–1.2)</td>
<td>.7</td>
</tr>
<tr>
<td>Hospital group 1†</td>
<td>0.8 (0.6–1.2)</td>
<td>.3</td>
</tr>
<tr>
<td>Hospital group 3‡</td>
<td>0.8 (0.5–1.3)</td>
<td>.4</td>
</tr>
<tr>
<td>Private insurance or self-payment§</td>
<td>0.8 (0.5–1.2)</td>
<td>.3</td>
</tr>
<tr>
<td>Received adequate candidemia treatment¶</td>
<td>0.5 (0.2–0.9)</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Received critical care</td>
<td>6.0 (4.0–9.2)</td>
<td>&lt; .05</td>
</tr>
</tbody>
</table>

OR = odds ratio; CI 95 = 95% confidence interval; NA = not available.

*Because of low numbers in Baltimore and Baltimore County, age group 0 to 4 years was combined with age groups 5 to 9 years and 10 to 19 years for both sites. The reference age group for analysis was the 30 to 39 years age group.
†Large urban hospitals with 400 beds or more and located in urban areas of Connecticut and Baltimore and Baltimore County. The reference hospital group was hospital group 2, medium urban with approximately 250 to 399 beds and located in urban areas.
‡Small urban hospitals with fewer than 250 beds and all community hospitals combined.
§Non-federal or non–state-funded insurance programs or payment “out of pocket.” The reference insurance group was Medicare or Medicaid.
¶Any systemic antifungal medication (amphotericin B, any azole, flucytosine, or other) administered for a minimum of 7 days after the first blood culture positive for any Candida species. Patients who did not survive a minimum of 7 days after a positive blood culture were not considered for the analysis. Treatment status was available for 83% and 49% of case-patients from Connecticut and Baltimore and Baltimore County, respectively. Analysis may have been impacted by missing data.

TABLE 4
IMPACT ON LENGTH OF HOSPITAL STAY DUE TO CANDIDEMIA, AGE, FACILITY, OUTCOME OF HOSPITALIZATION, INSURANCE TYPE, AND CRITICAL CARE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Connecticut</th>
<th>Bacterial and Baltimore County</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hospital-Days</td>
<td>CI 95 (d)</td>
</tr>
<tr>
<td>Baseline patient†</td>
<td>7.3</td>
<td>9.5; 5.6</td>
</tr>
<tr>
<td>Candidemia</td>
<td>-2.0</td>
<td>-0.6; -3.1</td>
</tr>
<tr>
<td>Candidemia with adequate treatment‡</td>
<td>+3.4</td>
<td>+5.4; +1.7</td>
</tr>
<tr>
<td>Age group 0–4 y</td>
<td>+22.9</td>
<td>+33.3; +15.1</td>
</tr>
<tr>
<td>Age group 5–19 y</td>
<td>+8.0</td>
<td>+21.3; +0.7</td>
</tr>
<tr>
<td>Age group 20–59 y</td>
<td>+3.2</td>
<td>+6.2; +0.8</td>
</tr>
<tr>
<td>Age group ≥ 60 y</td>
<td>+3.9</td>
<td>+6.9; +1.6</td>
</tr>
<tr>
<td>Hospital group 1†</td>
<td>+2.6</td>
<td>+4.0; +1.3</td>
</tr>
<tr>
<td>Hospital group 3‡</td>
<td>-0.4</td>
<td>+1.0; -1.6</td>
</tr>
<tr>
<td>Patient died</td>
<td>+0.1</td>
<td>+1.2; -0.8</td>
</tr>
<tr>
<td>Private insurance or self-payment§</td>
<td>-0.7</td>
<td>+0.3; -1.7</td>
</tr>
<tr>
<td>Received critical care¶</td>
<td>+8.8</td>
<td>+10.9; +6.9</td>
</tr>
</tbody>
</table>

CI 95 = 95% confidence interval; NA = not available.

†A patient who did not have a hospital-acquired case of candidemia (or treatment for candidemia), was 30 to 39 years old, was hospitalized in a medium-sized urban hospital (> 250 but < 400 beds), survived the hospitalization, was insured by Medicare or Medicaid, and did not stay in an intensive care unit.
‡Any systemic antifungal medication (amphotericin B, any azole, flucytosine, or other) administered for a minimum of 7 days after the first blood culture positive for any Candida species. Patients who did not survive a minimum of 7 days after a positive blood culture were not considered for the analysis.
§Large urban hospitals with 400 beds or more and located in urban areas of Connecticut and Baltimore and Baltimore County.
¶Non-federal or non–state-funded insurance programs or payment “out of pocket.”
able mortality rates among the case-patients whose treatment status was known. The attributable mortality rate was lower among case-patients who received adequate treatment for candidemia (11% in Connecticut and 16% in Baltimore and Baltimore County) than among case-patients who did not receive adequate treatment (31% in Connecticut and 41% in Baltimore and Baltimore County).

On multivariable analysis (Table 3) we found that being a case-patient was associated with mortality and receiving adequate treatment was protective. In addition, older age groups in Baltimore and Baltimore County and stay in an intensive care unit in Connecticut were significantly associated with mortality.

The differences in length of hospital stay and total hospital charges and cost of hospitalization relative to a baseline case-patient were determined for each variable of interest and are presented in Tables 4, 5, and 6. Candidemia did not increase the length of hospital stay or the total hospital charges and cost of hospitalization independently. On the contrary, in Connecticut, the variable candidemia had a significantly shorter hospital stay and lower total hospital charges and cost of hospitalization than the baseline patient (by 2.0 days and by $4,749 and $2,558, respectively).

For both surveillance sites, the youngest age group had a significantly longer hospital stay (approximately 23 days) and higher total hospital charges and cost of hospitalization (approximately $17,000 to $35,000 and $13,000 to $19,000, respectively) than the baseline patients. Also, patients who were admitted to large urban hospitals had significantly higher total hospital charges and cost of hospitalization and, for those in Connecticut, a longer hospital stay than the respective baseline patients. Patients who died had significantly higher total hospital charges and cost of hospitalization, as did those who stayed in critical care (data available for Connecticut only), than the baseline patient. Patients in Connecticut who had stayed in critical care had a longer hospital stay than the baseline patient. For both surveillance sites, compared with the relevant baseline patient, having received adequate treatment for candidemia significantly increased both length of hospital stay (approximately 3 to 13 days) and total hospital charges and cost of hospitalization (approximately $6,000 to $29,000 and $3,000 to $22,000, respectively).

**DISCUSSION**

We have presented the results of the first case-control study to assess the impact of an episode of candidemia in terms of mortality, length of hospitalization, and hospital costs using data that have wide patient, treatment, and hospital representation. We found that excesses in hospital stay and hospital costs were related to the treatment of candidemia. Also, case-patients were more likely to die when inadequate candidemia treatment was administered. Our findings underscore the importance of timely treatment of candidemia for individual patients and for public health overall, as measured by the outcomes of length of hospital stay, hospital costs, and mortality.

For reasons that we were not able to assess in our
TABLE 6
IMPACT ON HOSPITAL COSTS* DUE TO CANDIDEMIA, AGE, FACILITY, OUTCOME OF HOSPITALIZATION, INSURANCE TYPE, AND CRITICAL CARE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Connecticut†</th>
<th></th>
<th></th>
<th>Baltimore City and County‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hospital Charges ($)</td>
<td>CI&lt;sub&gt;95&lt;/sub&gt; ($)</td>
<td></td>
<td>Hospital Charges ($)</td>
</tr>
<tr>
<td>Baseline patient§</td>
<td>9,619</td>
<td>12,425; 7,446</td>
<td></td>
<td>13,861</td>
</tr>
<tr>
<td>Candidemia</td>
<td>-2,588</td>
<td>-905; -3,947</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Candidemia with adequate treatment§</td>
<td>+3,337</td>
<td>+5,790; +1,275</td>
<td></td>
<td>+22,228</td>
</tr>
<tr>
<td>Age group 5–19 y</td>
<td>+10,915</td>
<td>+29,987; +1,027</td>
<td></td>
<td>-6,332</td>
</tr>
<tr>
<td>Age group 20–59 y</td>
<td>+3,522</td>
<td>+7,349; +559</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Age group &gt; 60 y</td>
<td>+3,446</td>
<td>+6,965; +674</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Hospital group 1†</td>
<td>+2,595</td>
<td>+4,349; +1,061</td>
<td></td>
<td>+6,511</td>
</tr>
<tr>
<td>Hospital group 3‡</td>
<td>NS</td>
<td>-3,247</td>
<td></td>
<td>-1,763; -4,549</td>
</tr>
<tr>
<td>Patient died</td>
<td>+2,566</td>
<td>+4,328; +1,027</td>
<td></td>
<td>+8,107</td>
</tr>
<tr>
<td>Private insurance or self-payment§</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Received critical care*‡</td>
<td>+23,566</td>
<td>+28,048; 19,617</td>
<td></td>
<td>NA</td>
</tr>
</tbody>
</table>

CI<sub>95</sub> = 95% confidence interval; NS = not statistically significant at P < .05; NA = not available.
*Costs have been calculated and are presented for statistically significant variables (P < .05) by converting the hospital charges given in Table 5 using the following weighted-average cost-to-charge ratios: Connecticut, 0.54; and Baltimore and Baltimore County, 0.764.
†For each variable of interest, additional charges were added to or subtracted from the baseline patient. Only statistically significant charges (P < .05) are presented.
‡A patient who did not have a hospital-acquired case of candidemia (or treatment for candidemia), was 30 to 39 years old, was hospitalized in a medium-sized urban hospital (> 250 but < 400 beds), survived the hospitalization, was insured by Medicare or Medicaid, and did not stay in an intensive care unit.
¶Any systemic antifungal medication (amphotericin B, any azole, flucytosine, or other) administered for a minimum of 7 days after the first blood culture positive for any Candida species. Patients who did not survive a minimum of 7 days after a positive blood culture were not considered for the analysis.
§Non-federal or non–state-funded insurance programs or payment “out of pocket.”
**Stay in an intensive care unit.

study or in the surveillance study, large numbers of case-patients from both surveillance sites did not receive any or the appropriate antifungal treatment. Thus, these patients did not have any or the expected charges related to candidemia treatment. Having not received adequate treatment was associated with greater mortality. The findings regarding length of hospital stay and total hospital charges and cost of hospitalization for candidemia presented in Tables 4, 5, and 6 represent patients who did not receive adequate treatment. These results suggest that inadequately treated patients use fewer resources than do treated patients; we hypothesize that this is due to the higher mortality associated with these patients. Another study to determine the rationale for withholding treatment for patients with candidemia is needed.

When the candidemia treatment status is taken into account, case-patients who received adequate treatment were found to have approximately 3 to 13 more hospital-days and $3,000 to $22,000 more in costs than the baseline patient. Treatment also impacted mortality, as demonstrated at both sites by the higher attributable mortality among case-patients who did not receive adequate treatment compared with those who did (31% vs 11% for Connecticut and 41% vs 16% for Baltimore and Baltimore County). Adequate treatment was also found to be independently associated with a lower likelihood of death on multivariable analysis. The large proportions of inadequately treated case-patients, based on information obtained from the surveillance study, was unexpected. The results of our analysis, using these data, emphasize the need for clinicians to routinely treat patients who have blood cultures positive for Candida species.

The data from Connecticut and from Baltimore and Baltimore County presented significant heterogeneity. For example, the median total hospital charges (data not presented) for all case-patients from Baltimore and Baltimore County was $44,696 (range, $1,980 to $625,591), whereas in Connecticut it was $77,534 (range, $4,695 to $911,280); these differences were less dramatic after multiplying these charges by the cost-to-charge ratios. The reasons for these differences are not known, but they may represent different patient-care management and local hospital financial strategies.

The source of our data is unique in that it offered wide representation, which therefore increases the robustness of our results. Case-patients were ascertained from active laboratory- and population-based surveillance that included two sites in the United States (population, > 4.5 million). Thus, in contrast to prior studies, 11,12,14,23 case-patients in our study had a broad spectrum of underlying conditions and other predisposing factors, treatment and management of candidemia, and wide representation across hospitals. In addition, in our study there were no assumptions regarding candidemia incidence or treatment regimens and their associated charges.13,24,25

However, we calculated the “excess” length of
hospital stay or charges due to candidemia in the multivariable analysis by determining a baseline patient. The baseline patient’s hospital stay ranged from approximately 7 to 14 days and cost approximately $10,000 to $14,000. Hospital stay is longer and the costs are greater when compared with an “average” hospitalization.26,27 However, this long hospital stay and high cost of hospitalization reflects the severity of underlying illness of the control-patients, from which the baseline patients were drawn.

There are limitations to our study. First, given the nature of this infection and the retrospective study design, inferences of causality must be made with caution. Second, ideally, control-patients would be matched based on previously known underlying conditions and severity of illness. However, the retrospective study design and the lack of a standard marker for severity of illness for all hospitalized patients, such as the Acute Physiology and Chronic Health Evaluation II score (which is available only for patients in the intensive care unit), limited our ability to do this. However, all control-patients in our study had comparable exposure periods (length of hospitalization prior to onset of candidemia in the corresponding case-patient) and most of the control-patients were closely matched by diagnosis at the time of hospital discharge, year of diagnosis, hospital type, and age group.

Candidemia represents a healthcare-related infection with a significant burden. If our results are extrapolated to the population of the United States, where the overall incidence of candidemia can be estimated to be 8 per 100,000 individuals,28,29 and assuming approximately 65% received at least 7 days of treatment, the excess hospital costs in 1 year due to candidemia treated for a minimum of 7 days are estimated to be $44 million to $320 million. If we consider the overall attributable mortality (range, 19% to 24%) for all candidemia in the United States, between 4,256 and 5,376 patients will die in 1 year due to their candidemia. These hospital costs and mortality could be ameliorated if more effective prevention and treatment measures could be identified and widely implemented.

REFERENCES