MAJOR ARTICLE

The Epidemiology and Attributable Outcomes of Candidemia in Adults and Children Hospitalized in the United States: A Propensity Analysis

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(See the editorial commentary by Fridkin on pages 1240–1)

Background. *Candida* species are the fourth most common cause of bloodstream infection and are the leading cause of invasive fungal infection among hospitalized patients in the United States. However, the frequency and outcomes attributable to the infection are uncertain. This retrospective study set out to estimate the incidence of candidemia in hospitalized adults and children in the United States and to determine attributable mortality, length of hospital stay, and hospital charges related to candidemia.

Methods. We used the Nationwide Inpatient Sample 2000 for adult patients and the Kids' Inpatient Database 2000 for pediatric patients. We matched candidemia-exposed and candidemia-unexposed patients by the propensity scores for the probability of candidemia exposure, which were derived from patient characteristics. Attributable outcomes were calculated as the differences in estimates of outcomes between propensity score–matched patients with and without candidemia.

Results. In the United States in 2000, candidemia was diagnosed in an estimated 1118 hospital admissions of pediatric patients and 8949 hospital admissions of adult patients, yielding a frequency of 43 cases per 100,000 pediatric admissions (95% confidence interval [CI], 35–52 cases per 100,000 pediatric admissions) and 30 cases per 100,000 adult admissions (95% CI, 26–34 cases per 100,000 adult admissions). In pediatric patients, candidemia was associated with a 10.0% increase in mortality (95% CI, 6.2%–13.8%), a mean 21.1-day increase in length of stay (95% CI, 14.4–27.8 days), and a mean increase in total per-patient hospital charges of $92,266 (95% CI, $65,058–$119,474). In adult patients, candidemia was associated with a 14.5% increase in mortality (95% CI, 12.1%–16.9%), a mean 10.1-day increase in length of stay (95% CI, 8.9–11.3 days), and a mean increase in hospital charges of $39,331 (95% CI, $33,604–$45,602).

Conclusion. The impact of candidemia on excess mortality, increased length of stay, and the burden of cost of hospitalization underscores the need for improved means of prevention and treatment of candidemia in adults and children.

Candida species are the leading cause of invasive fungal infections in hospitalized patients and are the fourth most common isolates recovered from cases of nosocomial bloodstream infection in the United States [1, 2]. Candidemia is frequently associated with the signs and symptoms of sepsis syndrome [3, 4]. A recent study of the epidemiology of sepsis revealed that the annual number of cases of sepsis caused by fungal organisms increased by 207% between 1979 and 2000 [5]. The increase in invasive candidal infections is likely due to an increased prevalence of susceptible hosts, who receive intensive care therapies, immunosuppressive therapies associated with transplantation, and broad-spectrum antibiotics [6–8]. As a result, candidal infection is an emerging problem in hospital medical practice.

Previous epidemiologic outcome studies of candi-

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demia in the United States have produced very disparate estimates regarding associated mortality and have focused exclusively on adults. Furthermore, the studies have typically been limited to single institutions or have adjusted inadequately for the potential confounding effect of concurrent illnesses (which differ markedly between hospitalized children and hospitalized adults) that predispose patients both to candidemia and to poor outcomes [9–12].

We therefore conducted a retrospective cohort study of the epidemiology of candidemia and used propensity score analyses to determine the outcomes attributable to candidemia separately for both children and adults using 2 nationally representative databases of hospital discharges, prepared by the Agency for Healthcare Research and Quality (AHRQ).

METHODS

Study design. This retrospective cohort study used propensity-matched analyses to control for underlying comorbidities and prognostic imbalances in the determination of attributable mortality, length of stay, and hospital charges associated with candidemia.

Data sources. This study was performed using 2 AHRQ data sets: the 2000 Kids' Inpatient Database (KID 2000) and the Nationwide Inpatient Survey 2000 (NIS 2000). Both data sets contain hospital discharge information from US states that partnered with the AHRQ on the federally sponsored Healthcare Cost and Utilization Project [13] (detailed information is available from http://www.hcup-us.ahrq.gov). The data sets reflect discharge information from short-term, nonfederal, nonrehabilitation general and specialty hospitals. The KID 2000 contains hospital discharge information from 27 states and comprises a 10% sample of uncomplicated, in-hospital births and an 80% sample of all other pediatric admissions to the hospital for subjects ⩽20 years of age. The NIS 2000 contains information on discharges from the hospital from 28 partner states and constitutes a 20% sample of all hospital admissions.

Data regarding pediatric hospitalizations were drawn from the KID 2000. Because the epidemiology of candida among premature infants is markedly confounded by duration of survival (i.e., time at risk), we restricted our study to children outside the neonatal period by excluding all children admitted within the first 30 days of life. We used the US Census definition of adulthood as a cutoff point in the pediatric analysis and included any patient who was <18 years of age at admission to the hospital, yielding a data set of 1.3 million records from the 2.5 million records contained in the KID 2000.

Data regarding adult hospitalizations were drawn from the NIS 2000. As the KID 2000 more thoroughly represents US pediatric discharges, we excluded all patients <18 years of age from the NIS analysis, reducing the data set from 7.5 million to 6.1 million records.

Exposure classification. Exposure to candidemia during a hospitalization was identified by the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* code for disseminated/systemic candidiasis (112.5), which may have been reported as any of 15 diagnoses captured on the discharge record. Patients with diagnoses codes for mucosal candidiasis at a variety of body sites were not considered to have candidemia. We considered disseminated/systemic candidiasis to include or result from candidemia, because disseminated disease is believed to result from hematogenous spread of the organism.

Clinical and demographic data. We used Stata Statistical Software, version 8.2 (Stata), for all analyses. We examined candidemia-associated hospitalizations by age group, sex, race/ethnicity, location of hospital (US Census regions of Northeast, Midwest, South, or West), National Association of Children's Hospitals and Related Institutions hospital type (rural, urban nonteaching, or urban teaching), hospital size (small, medium, or large), comorbid diagnoses (up to 15 diagnoses), and clinical procedures (up to 15 procedures).

The presence of concurrent chronic illnesses was assessed using an *ICD-9-CM*–based diagnostic classification system for pediatric complex chronic conditions, partitioned into 9 categories: neuromuscular, cardiovascular, respiratory, renal, gastrointestinal, hematological or immunological, metabolic, malignancy, and genetic or other congenital defect conditions [14]. We augmented this system with separate pediatric- and adult-specific conditions, including persisting perinatal conditions, leukemia or lymphoma, diabetes mellitus, and cirrhosis of the liver.

In-hospital procedures were classified using the Clinical Classification Software (AHRQ), a tool developed by AHRQ for grouping diagnoses and procedures into a manageable number of clinically meaningful categories [15]. These included vascular catheterization, mechanical ventilation, enteral or parenteral nutrition, peritoneal dialysis, hemodialysis, chemotherapy, gastrointestinal procedures, solid-organ transplantion, and bone marrow transplantation. All variables were considered separately and were not integrated into any kind of summary comorbidity scoring system.

Propensity score model. The probability that any patient would develop candidemia during hospitalization (i.e., the propensity score) was estimated using a multivariable logistic regression model that incorporated available demographic, comorbid, and procedural variables, irrespective of their presumed clinical relevance. These models exhibited outstanding discrimination between patients who did and those who did not have candidemia: in the pediatric analysis, the c-statistic

was 0.96, and in the adult analysis, the c-statistic was 0.91. Next, for each candidemia-exposed patient, the 2 unexposed patients with the nearest propensity scores above and below the case patient score were selected. Candidemia-exposed index case patients who failed to match with 2 adjacent nonexposed control subjects (because the adjacent positions were occupied by exposed case patients) were dropped from the analysis.

To determine the effectiveness of the propensity score matching in controling for differences between exposed patients and selected, unexposed patients, univariate analyses were performed on each variable included in the propensity score model. Mann-Whitney rank sum tests were used to compare nonparametric distributions of age between patients with candidemia and matched patients without candidemia. The χ^2 test was used for unadjusted comparisons of categorical variables between patients with candidemia and matched patients without candidemia.

Propensity score matched analysis. The primary outcome in the propensity analysis was in-hospital mortality attributable to candidemia. Using the *svy* commands in Stata software (Stata), we performed bivariate analyses and linear combinations of estimation parameters to ascertain the independent effect of candidemia on mortality, length of stay, and total hospital charges. Attributable outcomes were determined by the difference in the means in exposed and matched unexposed patients. In other words, the attributable mortality due to candidemia was calculated as the mortality rate for patients with candidemia minus the mortality rate for propensity-matched patients without candidemia. Secondary outcomes of mean length of stay and hospital charges attributable to candidemia were determined in a similar fashion.

Hospital- and national-level analyses. To examine the variability of candidemia-associated mortality among the hospitals contained within the NIS sample frame, the proportion of hospital admissions for patient's who later died was calculated for all hospitals that had $\geqslant$5 candidemia-associated hospitalizations. Each of these hospitals was used as the unit of analysis to report median, range, and interquartile range of candidemia-associated mortality.

To generate national estimates of the number of hospitalizations, hospital length of stay, and hospital charges, we utilized the Hospital Cost and Utilization Project weighting methodology. We report the frequency of candidemia as the number of estimated cases per 100,000 hospital admissions.

Human subjects oversight. The conduct of this study was approved by the Committees for the Protection of Human Subjects at The Children's Hospital of Philadelphia (Philadelphia, PA).

RESULTS

During 2000, there were an estimated 1118 pediatric and 8949 adult cases of candidemia in the United States, yielding a frequency of 43 cases per 100,000 pediatric admissions (95% CI, 35–52 cases per 100,000 pediatric admissions) and 30 cases per 100,000 adult admissions (95% CI, 26–34 cases per 100,000 adult admissions). The median age for the pediatric population was 1 year old, whereas among adult patients, the median age was 65 years (table 1). The majority of pediatric patients with candidemia were male (53%), whereas 54% of adult patients with candidemia were female. The majority of adult patients with candidemia were white (54%), whereas only 42% of pediatric patients were white. For both patient populations, the majority of cases occurred in the South.

Chronic conditions and other comorbidities were reported in many cases of candidemia (table 1). More than one-quarter (26%) of all pediatric patients with candidemia had a perinatal condition persisting past 1 month of age. Malignancies were present in 23% of adult patients and in 17% of pediatric patients. Twenty-one percent of cases of pediatric candidemia occurred in children who had previously described risk factors, such as cancer and bone marrow or solid-organ transplantation. Inpatient procedures, such as vascular catheterization, mechanical ventilation, gastrointestinal procedures, and enteral or parenteral nutrition, were all common in patients with candidemia (table 1).

Outcomes in unmatched analysis. The crude mortality rate among all pediatric patients with candidemia was 15.8%, compared with a mortality rate of 0.5% in all pediatric patients without candidemia. The mean length of stay and hospital charges were 44.8 days and $183,645, respectively, among children with candidemia, compared with 4.2 days and $11,228 among all children without candidemia. The crude mortality rate among all adult patients with candidemia was 30.6%, compared with 2.3% among all adult patients without candidemia, for a crude difference of 28.3%. The mean length of stay and hospital charges were 18.6 days and $66,154, respectively, among adults with candidemia, compared with 4.9 days and $15,192 among all adults without candidemia.

Outcomes in propensity-matched analysis. Candidemia-exposed and -unexposed pediatric patients, matched by propensity score, were very similar overall in observed demographic and clinical characteristics (table 2). Exposed pediatric patients were more commonly seen in children's general hospitals (38%) and children's units in a general hospital (34%) than in nonchildren's hospitals (26%), whereas the matched control subjects were more evenly distributed among nonchildren's hospitals (35%), children's hospitals (32%), and children's units (30%).

After matching by propensity scores (table 3), candidemia

Table 1. Candidemia in pediatric and adult patients hospitalized in the United States, 2000.

Demographic or clinical characteristic	Pediatric patients (n = 1118)	Adult patients (n = 8949)
Age, median years (IQR)	1 (0–7)	65 (50–76)
Female sex	523 (47)	4847 (54)
Race		
White	464 (42)	4785 (54)
Black	211 (19)	1315 (15)
Hispanic	216 (19)	599 (7)
Asian or Pacific Islander	23 (2)	106 (1)
Native American	2 (<1)	5 (0)
Other	53 (5)	173 (2)
Unknown	149 (13)	1967 (22)
Hospital region		
Northeast	188 (17)	1745 (20)
Midwest	155 (14)	1897 (21)
South	505 (45)	3384 (38)
West	270 (24)	1923 (22)
NACHRI hospital type		
Children's general hospital	424 (38)	NA
Children's unit in a general hospital	385 (34)	NA
Not a children's hospital	294 (26)	NA
Hospital size		
Small	209 (19)	590 (7)
Medium	305 (27)	2028 (23)
Large	598 (53)	6330 (71)
Chronic condition		
Malignancy		
Solid tumor	102 (9)	1727 (19)
Leukemia or lymphoma	91 (8)	355 (4)
Cardiovascular	108 (10)	534 (6)
Neuromuscular	104 (9)	447 (5)
Gastrointestinal	63 (6)	242 (3)
Respiratory	140 (13)	25 (0)
Renal	37 (3)	461 (5)
Metabolic	34 (3)	218 (2)
Congenital or genetic defects	66 (6)	84 (1)
Hematological/immunological deficiencies	32 (3)	387 (4)
Perinatal	286 (26)	NA
Diabetes mellitus	6 (<1)	1683 (19)
Cirrhosis	NA	265 (3)
Inpatient procedure		
Vascular catheterization	645 (58)	4137 (46)
Mechanical ventilation	411 (37)	2769 (31)
Gastrointestinal procedure	344 (31)	3792 (42)
Enteral or parenteral nutrition	314 (28)	1698 (19)
Solid-organ transplantation	27 (2)	41 (0.5)
Bone marrow transplantation	25 (2)	25 (0.3)
Hemodialysis	35 (3)	1124 (13)
Peritoneal dialysis	29 (3)	34 (0.4)
Orthopedic procedure	47 (4)	453 (5)

NOTE. Data are no. (%) of patients, unless otherwise indicated. IQR, interquartile range; NA, not available; NACHRI, National Association of Children's Hospitals and Related Institutions.

in pediatric patients was associated with a mortality rate of 15.8%, compared with a mortality rate among the matched patients without candidemia of 5.9%, yielding an absolute 10.0% increase in mortality (95% CI, 6.2%–13.8%) attributable to candidemia. Pediatric candidemia also was associated with a mean 21.1-day increase in length of stay (95% CI, 14.4– 27.8 days) and a mean increase in total charges of $92,266 (95% CI, $65,058–$119,474). After propensity-score matching, adult exposure to candidemia resulted in a 14.5% increase in mortality (95% CI, 12.1%–16.9%), a mean increase of 10.1 days in length of stay (95% CI, 8.9–11.3 days), and a mean increase in hospital charges of $39,331 (95% CI, $33,604–$45,602).

Additional analyses. The propensity-score match did not distribute all covariates equally between admissions of candidemia-exposed patients and unexposed patients. To assess whether residual confounding was still present in the propensity-score matched analyses, we performed multivariable logistic regression for the mortality outcome, comparing models that contained only the candidemia-exposure variable with models that also adjusted for covariates that were nonuniformly distributed between the exposed and unexposed groups ($P <$ .1). There were no substantial differences in our estimates after adjustment for the nonuniformly distributed covariates. To better situate the results of this study in the context of previous reports, most of which were based on single-institution analyses of data from adult patients, we examined the variation in candidemia-associated mortality among the 129 hospitals in the NIS sample frame that had ⩾5 candidemia-associated adult admissions. The median crude mortality rate was 32% (interquartile range, 20%–42%). In the propensity-score matched analysis, 115 hospitals with ⩾5 candidemia-associated admissions had a median mortality rate of 13% (interquartile range, 0%–28%).

DISCUSSION

This nationally representative analysis of candidemia yields 2 major findings. First, the incidence of candidemia in patients hospitalized in the United States during 2000 was 43 cases per 100,000 hospital admissions of children and 30 cases per 100,000 hospital admissions of adults. Second, the mortality attributable to candidemia was 10.1% among children and 14.5% in adults. Because candidemia is considered a nosocomial infection, our use of the nationally representative KID 2000 and NIS 2000 data sets likely represents the majority of patients at risk for this infection. These estimates of candidemia incidence and attributable mortality are comparable to those of other infectious diseases for which large-scale preventative efforts have been made to reduce the incidence of infection, arguing for increased efforts in candidemia prevention [16].

Our estimates of the risk of mortality attributable to can-

Table 2. Propensity score–matched patients with and without candidemia hospitalized in the United States, 2000.

Demographic or clinical characteristic	Pediatric patients			Adult patients		
	With candidemia (n = 1118)	Without candidemia (n = 2062)	P	With candidemia (n = 8949)	Without candidemia (n = 17,267)	P
Age, median years (IQR)	1 (0–7)	1 (0–7)	.49	65 (50–76)	66 (50–77)	.06
Female sex	523 (47)	906 (44)	.41	4847 (54)	8826 (51)	.06
Race						
White	464 (42)	722 (35)		4785 (54)	9101 (53)	
Black	211 (19)	400 (19)		1315 (15)	2716 (16)	
Hispanic	216 (19)	406 (20)		599 (7)	1111 (6)	
Asian or Pacific Islander	23 (2)	45 (2)		106 (1)	242 (1)	
Native American	2 (<1)	6 (<1)		5 (0)	10 (0)	
Other	53 (5)	126 (6)		173 (2)	361 (2)	
Unknown	149 (13)	357 (17)	.41	1967 (22)	3726 (22)	.96
Hospital region						
Northeast	188 (17)	379 (18)		1745 (20)	3903 (23)	
Midwest	155 (14)	227 (11)		1897 (21)	3741 (22)	
South	505 (45)	892 (43)		3384 (38)	6013 (35)	
West	270 (24)	564 (27)	.65	1923 (22)	3610 (21)	.39
NACHRI hospital type						
Children's general hospital	424 (38)	660 (32)		NA	NA	
Children's unit in a general hospital	385 (34)	621 (30)		NA	NA	
Not a children's hospital	294 (26)	726 (35)	.06	NA	NA	NA
Hospital size						
Small	209 (19)	346 (17)		590 (7)	1472 (9)	
Medium	305 (27)	598 (29)		2028 (23)	4484 (27)	
Large	598 (53)	1091 (53)	.54	6330 (71)	11,296 (65)	.06
Chronic condition						
Malignancy						
Solid tumor	102 (9)	183 (9)	.87	1727 (19)	3825 (22)	.03
Leukemia or lymphoma	91 (8)	185 (9)	.65	355 (4)	663 (4)	.83
Cardiovascular	108 (10)	236 (11)	.27	534 (6)	1011 (6)	.87
Neuromuscular	104 (9)	302 (15)	.02	447 (5)	1025 (6)	.15
Gastrointestinal	63 (6)	121 (6)	.87	242 (3)	593 (3)	.14
Respiratory	140 (13)	265 (13)	.89	25 (0)	104 (1)	.08
Renal	37 (3)	75 (4)	.80	461 (5)	961 (6)	.56
Metabolic	34 (3)	67 (3)	.84	218 (2)	440 (3)	.82
Congenital or genetic defects	66 (6)	119 (6)	.96	84 (1)	199 (1)	.54
Hematological/immunological deficiencies	32 (3)	73 (4)	.39	387 (4)	932 (5)	.11
Perinatal conditions	286 (26)	486 (24)	.52	NA	NA	NA
Diabetes mellitus	6 (<1)	10 (<1)	.91	1683 (19)	3608 (21)	.10
Cirrhosis	NA	NA	NA	265 (3)	704 (4)	.04
Vascular catheterization	645 (58)	1319 (64)	.03	4137 (46)	8459 (49)	.11
Inpatient procedure						
Mechanical ventilation	411 (37)	782 (38)	.74	2769 (31)	4881 (28)	.05
Gastrointestinal procedure	344 (31)	682 (33)	.46	3792 (42)	7242 (42)	.76
Enteral or parenteral nutrition	314 (28)	510 (25)	.31	1698 (19)	2911 (17)	.12
Solid-organ transplantation	27 (2)	31 (2)	.22	41 (0.5)	75 (0.4)	.90
Bone marrow transplantation	25 (2)	15 (<1)	.12	25 (0.3)	47 (0.3)	.96
Hemodialysis	35 (3)	62 (3)	.89	1124 (13)	2099 (12)	.70
Peritoneal dialysis	29 (3)	22 (1)	.04	34 (0.4)	84 (0.5)	.61
Orthopedic procedure	47 (4)	86 (4)	.97	453 (5)	836 (5)	.74

NOTE. Data are no. (%) of patients, unless otherwise indicated. IQR, interquartile range; NA, not available; NACHRI, National Association of Children's Hospitals and Related Institutions.

Table 3. Outcomes attributable to candidemia in the United States, 2000.

Variable	Pediatric patients			Adult patients		
	With candidemia (n = 1118)	Without candidemia (n = 2062)	Attributable increase (95% CI)	With candidemia (n = 8949)	Without candidemia (n = 17,267)	Attributable increase (95% CI)
Mortality, %	15.8	5.9	10.0 (6.2–13.8)	30.6	16.1	14.5 (12.1–16.9)
Length of stay, mean no. of days per patient	44.8	23.7	21.1 (14.4–27.8)	18.6	8.5	10.1 (8.9–11.3)
Total charges, mean US$ per patient	183,645	91,379	92,266 (65,058–119,474)	66,154	26,823	39,331 (33,60–45,602)

NOTE. Patients with candidemia hospitalized in the United States in 2000 are compared with propensity score–matched control patients without candidemia.

didemia are more conservative than those of prior retrospective studies [910–11, 17] but accord with estimates generated with prospectively collected data from 2 randomized clinical trials of therapy for invasive candidiasis [18, 19]. Quantitative estimates of the adverse impacts caused by candidemia vary substantially across prior studies. In adult patients, the rate of mortality attributable to candidemia has ranged from 38% to 49% [10, 11], with a published case-fatality rate as high as 61% [11]. In contrast, 2 prospective clinical studies reported much lower attributable mortality rates of 5%–7% [18, 19]. The lower mortality rates observed in clinical trials may be due to patients with candidemia being deemed ineligible or otherwise not being enrolled in the trial. In the pediatric population, reports of candidemia-associated case-fatality rates in children range from 13% to 23% and are as high as 43%–54% in infants [9, 20–25]. Our estimate of the attributable length of stay for adults is also lower than previous estimates. Candidemia accounted for a mean of 21.6 additional hospital days in a study of hospitalized adult patients with candidemia and commensurate increases in total hospital costs [10–12]. To our knowledge, no such data for pediatric patients with candidemia has been reported.

Our conservative estimates of attributable outcomes are likely due to the adjustment of confounding effects on clinical outcomes by propensity-score matching for comorbidities and inpatient procedures. We also postulate that the nationally representative sample frame of this study mitigated a potential bias in the published literature, which may preferentially contain reports from single institutions where candidemia happens to have an above-average associated mortality rate. The use of nationally representative data sets may allow for greater generalizability of the findings than those of prior single-institution studies.

Use of these national administrative databases offers the unique advantage of allowing for the generation of nationwide estimates of adult and pediatric candidemia rates. Administrative data is limited, however, with regard to the possibility of miscoded or inaccurate information. Whereas the *ICD-9-CM* code used in this study is the only code that explicitly describes systemic disease and has been used in a previous study of candidemia that used administrative data [12], we are unaware of any analysis that has determined the sensitivity and specificity of this particular *ICD-9-CM* code in detecting cases, compared with, for example, a thorough review of all medical charts. In general, health services researchers believe that the procedure of using *ICD-9-CM* codes to identify cases in administrative databases, although high in specificity (i.e., few instances in which cases were not diagnosed with the condition), may be lower in sensitivity (i.e., the administrative diagnosis may fail to detect all true cases) [26, 272829]. There is a possibility of overestimation in rates caused by the inclusion of relapses or recurrences of infection requiring new hospitalizations, yet we believe this to be minimal on the basis of a previous study of candidemia at our center [30]. More likely, cases of candidemia may have been recorded with an *ICD-9-CM* code that we did not use to identify candidemia (e.g., 112.9, candidemia of unspecified site). Our employment of a case-identification procedure with imperfect specificity and lower sensitivity would have resulted in our underestimating the occurence of candidemia. It is also possible that other, less severe, forms of candidiasis (such as mucosal disease of the mouth, esophagus, skin, or vagina, which are specified by 6 other *ICD-9-CM* codes) were miscoded as disseminated candidiasis and thus included as cases. Inclusion of milder forms of candidiasis as cases of disseminated disease likely would have resulted in a more conservative estimate of the attributable mortality, as well.

In addition, the blood cultures for candidemia may only be 50%–60% sensitive, as suggested by autopsy studies. Nevertheless, in the absence of biopsy specimens, blood culture remains the standard for the diagnosis of candidemia. Furthermore, poor diagnostic sensitivity would result in misclassification of patients with candidemia but negative blood culture results as unexposed patients, likely causing underestimation of the impact of candidemia on outcomes.

We also note what we consider to be evidence of construct validity in the composition of the invasive candidiasis cases

identified in the data sets to support the specificity of our identification procedure. The majority of patients had comorbidities and had undergone procedures (such as vascular catheterization and mechanical ventilation) that are similar to the underlying conditions known to be common in patients with candidemia and systemic candidiasis.

Any analysis of a potential cause-and-effect relationship between candidemia and clinical outcomes would be strengthened by more information than this study and its data sets can provide regarding the temporal sequence of events and the severity of illness prior to the development of candidemia. As with all observational studies, propensity analyses cannot completely control for the effect of confounding, because it can only adjust for factors that were measured in the cohort, and residual confounding therefore remains a possibility. Finally, because we excluded patients who were <30 days old, our findings should not be generalized to the neonatal population.

In summary, the attributable mortality of candidemia is substantial in both children and adults. These results should provide a compelling rationale for new strategies to prevent and treat candidemia. Our results suggest that, in this population, 1 life would be saved for every 10 children or every 7 adults in whom candidemia could be prevented. Prophylactic and preventative strategies for candidemia have been studied in selected high-risk groups (such as recipients of bone marrow transplants) [31, 32], and strategies for other patient populations are currently being explored [33–35]. Clinical prediction rules that identify subsets of hospitalized patients who are at particularly high risk for candidemia are needed [36]. We hope that these findings will be useful in the design and implementation of future interventions for effective prevention and treatment of candidemia.

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