

# Attributable Mortality of *Candida* Bloodstream Infections in the Modern Era: A Propensity Score Analysis

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**Background.** This study quantifies the mortality attributable to *Candida* bloodstream infections (BSI) in the modern era of echinocandins.

**Methods.** We conducted a retrospective cohort study of adult patients admitted to Barnes Jewish Hospital, a 1368-bed tertiary care academic hospital, in Saint Louis, Missouri, from 1 February 2012 to 30 April 2019. We identified 626 adult patients with *Candida* BSI that were frequency-matched with 6269 control patients that had similar *Candida* BSI risk-factors. The 90-day all-cause mortality attributable to *Candida* BSI was calculated using three methods—propensity score matching, matching by inverse weighting of propensity score, and stratified analysis by quintile.

**Results.** The 90-day crude mortality was 42.4% (269 patients) for *Candida* BSI cases and 17.1% (1083 patients) for frequency-matched controls. Following propensity score-matching, the attributable risk difference for 90-day mortality was 28.4% with hazard ratio (HR) of 2.12 (95% confidence interval [CI], 1.98–2.25,  $P < .001$ ). In the stratified analysis, the risk for mortality at 90 days was highest in patients in the lowest risk quintile to develop *Candida* BSI (hazard ratio [HR] 3.13 (95% CI, 2.33–4.19)). Patients in this lowest risk quintile accounted for 81 (61%) of the 130 untreated patients with *Candida* BSI. Sixty-nine percent of untreated patients (57/83) died versus 35% of (49/127) of treated patients ( $P < .001$ ).

**Conclusions.** Patients with *Candida* BSI continue to experience high mortality. Mortality attributable to *Candida* BSI was more pronounced in patients at lowest risk to develop *Candida* BSI. A higher proportion of these low-risk patients went untreated, experienced higher mortality, and should be the target of aggressive interventions to ensure timely, effective treatment.

**Keywords.** *Candida*; mortality; fluconazole; amphotericin; echinocandin.

*Candida* species are the second most common group of pathogens causing healthcare-associated bloodstream infections (BSI) and the most common etiology of fungal BSI in the United States [1]. The crude mortality of *Candida* BSI has been cited as high as 70%, but crude mortality is a poor measurement of the impact of *Candida* BSI on mortality. Patients at highest risk to develop *Candida* BSI frequently have comorbid medical conditions that are also associated with high mortality rates and poor long-term survival [2–4].

Several studies have quantified mortality attributable to *Candida* BSI with estimates ranging from 15% to 49% [5–8]. These prior studies, conducted before the development of echinocandins, provided useful insights but were limited by sample size (88–108 cases) [5–7] or by a larger encounter-level data set that, by design, would underestimate attributable mortality [8]. The wide range of estimates suggests this debate over the mortality attributable to *Candida* BSI remains

unsettled. Our study aims to provide additional data and perspective to the mortality attributable to *Candida* BSI using a rich, clinical dataset and propensity score methodology to minimize the confounding that is inherent to observational studies.

## METHODS

### Study Population

This study was conducted at Barnes-Jewish Hospital (BJH), a 1368-bed tertiary care academic hospital located in St. Louis, Missouri, and approved by the Washington University School of Medicine Research Protection Office with a waiver of informed consent. All patients 18 years of age or older with *Candida* spp. isolated from a blood culture from 1 February 2012 through 30 April 2019 were eligible for inclusion in the study as *Candida* BSI case patients. The first positive blood culture with *Candida* spp. was deemed the index blood culture. The time of collection of the index blood culture was considered the index time for all time-related variables and outcomes for *Candida* BSI cases.

Candidates for the control comparison group were selected from the population of inpatient and observation patients from 1 February 2012 through 30 April 2019 who did not develop *Candida* BSI. The control subjects were identified as having at least one factor associated with increased risk of *Candida* BSI

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identified by ICD-9/10 diagnosis or procedure codes (Table 1, codes in Supplementary Table 1). The conditions imparting similar risk to develop *Candida* BSI were arranged to form 10 categorical groups. These well-established risk factors included diagnosis of hematologic malignancy, myelodysplastic syndrome (MDS), and/or BMT recipient; metastatic cancer; presence of a central venous catheters (CVC) and/or hemodialysis (HD) catheters; SOT recipient; pancreatitis, abdominal fistulas, or abdominal surgery; cardiac surgery; chronic liver disease; drug abuse; acute renal failure; and bacteremia [2, 4]. Other classic risk factors such as intensive care unit (ICU) admission and antibiotic exposure were not considered in favor of conditions that impart risk to develop *Candida* BSI in the population (eg, presence of CVC in ICU patients) and underlying diagnoses resulting in antibiotic exposure (eg, bacteremia, immunosuppression), and our selected conditions are present in > 95% of cases, adequately capturing the at risk group.

*Candida* BSI case patients and control candidates were assigned to the first category in the hierarchical order for which they had a compatible diagnosis. A frequency match was then performed using a ratio of 1:10 (cases:controls) to create the pool of control candidates for subsequent analyses. For each

control patient, a random admission meeting the hierarchical category assignment was selected as the index hospitalization. Within that index hospitalization, a reference date was randomly chosen to replicate the distribution of first positive culture dates of the *Candida* BSI cases using a negative binomial distribution. (Supplementary Figure 1) If the date fell outside a control patient's hospitalization, the negative binomial distribution was resampled until a date within the hospitalization occurred. Finally, cases and control patients who died within 24 hours of admission of index hospitalization were excluded due to missing important predictor variables.

#### Covariates

Demographic characteristics, comorbidities, surgical history, microbiological data, vital signs, laboratory values, and antimicrobial administration data were obtained from the BJH Clinical Data Repository and explored for potential covariates. The complete list of covariates is listed in Supplementary Table 2.

Comorbidities were identified during the index hospitalization or in the preceding year. ICD-9/10-CM diagnosis codes were used to identify standard comorbidities [9], malignancies, receipt of SOT, receipt of BMT, concomitant infectious diseases, and National Health Safety Network (NHSN) surgical codes (codes provided in Supplementary Table 1).

Laboratory values and vital signs measured during the 24 hours preceding the index time (collection time of the index blood culture or derived control index time) considered for potential covariates included: parameters from complete blood counts (CBC), complete metabolic panels (CMP) and the extremes of the following vital signs: highest temperature, highest respiratory rate, highest heart rate, and lowest mean-arterial blood pressure. Cases with untreated *Candida* BSI were identified by medical record review.

#### Outcomes

Ninety-day all-cause mortality was the primary outcome. Mortality beyond 90 days is unlikely to be related to the index *Candida* BSI, whereas shorter durations (eg, 30 days) miss related mortality events. Thirty-day all-cause mortality was a secondary outcome to allow for comparison to previously published literature. The date of death was obtained from the medical record. Those who did not have a death date and did not have a follow-up in our electronic medical record after 90 days were supplemented with data from the Social Security Death Index [10].

#### Statistical Analysis

For bivariate analyses, categorical variables were evaluated with  $\chi^2$  tests; continuous variables were evaluated with Student *t* or Mann-Whitney *U* tests, as appropriate.

To determine the attributable mortality of *Candida* BSI, a propensity score for the risk to develop *Candida* BSI was

**Table 1. Demographics and Medical Comorbidities of *Candida* BSI Case Patients and Frequency-Matched Control Patients**

Characteristic	<i>Candida</i> Cases N = 626 n (%)	Matched Controls N = 6269 n (%)
Age, median (IQR) years	58 (46–66)	61 (52–70)
Sex		
Female	268 (42.8)	2952 (47.1)
Race		
White	437 (69.8)	4603 (73.4)
Black	146 (23.3)	1343 (21.4)
Other	43 (6.9)	323 (5.2)
Hierarchical categories <sup>a</sup> of medical conditions (hierarchical rank)		
Leukemia, myelodysplastic syndrome, bone marrow transplant (1)	143 (22.8)	1416 (22.6)
Central venous catheter, dialysis catheter (2)	338 (54.0)	3379 (53.9)
Solid organ transplant (3)	3 (0.5)	30 (0.5)
Lymphoma, metastatic cancer (4)	40 (6.4)	408 (6.5)
Fistula, pancreatitis, abdominal surgery (5)	35 (5.6)	368 (5.8)
Bacteremia (6)	24 (3.8)	233 (3.7)
Cardiac surgery (7)	8 (1.3)	80 (1.3)
Chronic liver disease (8)	18 (2.9)	189 (3.0)
Drug abuse (9)	6 (1.0)	60 (1.0)
Acute renal failure (10)	11 (1.7)	107 (1.7)

The 1:10 frequency-match distribution of the hierarchical categories is not exact due to patients excluded due death occurring within 24 hours of admission.

Abbreviations: BSI, bloodstream infection; IQR, interquartile range.

<sup>a</sup>*Candida* BSI cases and frequency-matched controls were placed into the first risk factor category for which they had a qualifying diagnosis. They remained in that category without regards to subsequent risk factors. Finally, for the control candidates, if they did not match with a *Candida* BSI case patient, they could not be bumped to a risk factor category lower in the hierarchy.

developed using multivariable logistic regression with *Candida* BSI as the dependent variable and all potential predictors for developing *Candida* BSI or mortality included in the model as independent variables, regardless of significance [11]. Continuous variables were explored with splines. The logit of the propensity score was used to match cases and controls in a 1:1 ratio, using a greedy algorithm without replacement and caliper of 0.2 times the standard deviation (SD) of the logit of the propensity score [12]. Balance of covariates was assessed using standardized differences (SDs) before and after matching (Supplementary Table 2), with SDs of 0.1 or greater indicating imbalance [13].

McNemar's test was used to compare mortality in the propensity score-matched pairs. Hazard ratios (HR) for mortality were calculated for *Candida* BSI cases, and their propensity score-matched controls using a Cox-proportional-hazards model stratified by the matched pairs, with *Candida* BSI as the only independent variable. The mortality attributable to *Candida* BSI was calculated by subtraction of the mortality rate of the propensity score-matched controls from the mortality rate of the cases. Cox proportional hazards models were performed with a robust variance estimator to account for the matching [14], with calculation of 95% confidence intervals (CI).

A second analysis was performed using a Cox proportional-hazards model with inverse weighting by the propensity score and *Candida* BSI as the sole variable [14]. The population was trimmed by removing the top and bottom 2% of the propensity score distribution to account for instability of weights at the ends of the distribution.

A third analysis was performed by stratification by the propensity score. The quintiles of the propensity score for the *Candida* BSI cases were used and applied to the controls, resulting in variable numbers of control patients per stratum. Analysis of mortality in the five strata was performed using Cox proportional-hazards models with *Candida* BSI as the sole independent variable. A Cox proportional-hazards model was created for each quintile and hazard ratios were reported for each quintile separately. A sensitivity analysis was conducted using adjusted models that included covariates with the largest standardized differences in each model (Supplementary Table 2).

All analyses were performed using SAS, version 9.4 Software (SAS Institute. Cary, North Carolina, USA). All statistical tests were 2-tailed, and  $P < .05$  was considered statistically significant.

## RESULTS

In total, 634 patients with *Candida* BSI were identified with 6340 frequency-matched controls. Eight cases (1%) and 71 controls (1%) died within 24 hours of admission to the index hospitalization and were excluded from analysis. Age, sex, and race were similar between both groups (Table 1).

Table 1 shows the distribution of *Candida* BSI case patients with frequency-matched control patients amongst the hierarchical categories. The first 2 hierarchical categories accounted for the majority of patients for both cases and controls (Leukemia/MDS/BMT 22.8% and 22.6%, CVC/HD 54% and 53.9%, respectively). The distribution of other medical conditions identified as risk factors for *Candida* BSI are shown in Supplementary Table 3.

In total, 83 additional risk factors were identified and used in the propensity score analysis. The standardized differences of covariates and distribution of propensity scores before and after weighting are shown in Supplementary Table 2 and Supplementary Figure 2. The propensity score model had good balance of covariates; there was a single covariate out of 93 with an SD  $> .1$  (SOT recipient, SD = .1275), suggesting a well-balanced model.

## Mortality

The 90-day crude all-cause mortality for patients with *Candida* BSI was 269/626 (42.4%) compared to 1083/6269 (17.1%) for the frequency-matched controls ( $P < .001$ ) with a crude mortality rate difference of 25.3%. The median time to death was 41 days for cases with *Candida* BSI vs 64 days for controls ( $P < .001$ ). The 30-day crude mortality for patients with *Candida* BSI was 156/626 (24.6%) compared to 729/6269 (11.5%) for the control group ( $P < .001$ ) with a crude mortality rate difference of 13.1% (Table 2). Crude mortality of *Candida* BSI case patients by *Candida* species and antifungal class is shown in Supplementary Tables 4 and 5.

In the propensity score-matched pairs analysis, the matching was successful in 528 of 626 *Candida* BSI cases (84.4%). The hazard ratio (HR) for 90-day all-cause mortality associated with *Candida* BSI was 2.1 (95% CI, 2.0–2.3) with an attributable risk difference of 28.4% compared to the propensity score-matched controls. The 30-day all-cause mortality HR associated with *Candida* BSI was 1.7 (95% CI, 1.6–1.8) with an attributable risk difference of 20.6% compared to the propensity score-matched controls (Table 3).

In the analysis using inverse weighting by the propensity score, the HR for 90-day all-cause mortality associated with *Candida* BSI was 2.1 (95% CI, 2.0–2.3,  $P < .001$ ) compared to the control population.

**Table 2. Crude Mortality of *Candida* BSI Case Patients and Frequency-Matched Control Patients**

Mortality	<i>Candida</i> BSI Cases N = 626 N (%)	Controls N = 6269 N (%)	Crude Mortality Difference (%)
30 days	156 (24.6)	729 (11.5)	13.1
90 days	269 (42.4)	1083 (17.1)	25.3

Abbreviation: BSI, bloodstream infection.

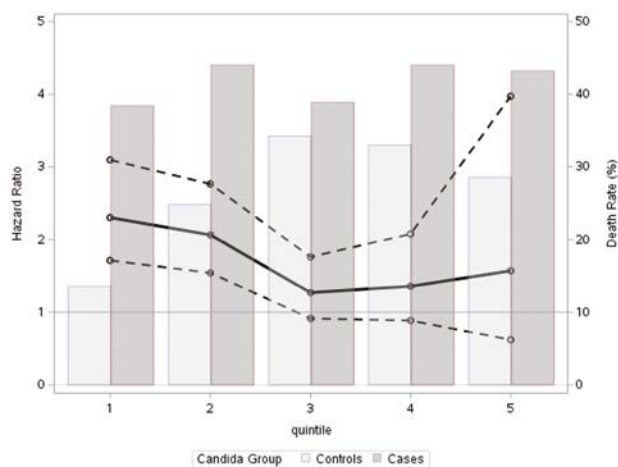
**Table 3. Mortality Attributable to *Candida* BSI From Propensity Score-Matched Analysis**

Propensity-Matched Pairs		
Mortality	Hazard Ratio (95% CI)	Attributable Risk Difference, %
30 Days	1.68 (1.56–1.80)	20.64
90 Days	2.12 (1.98–2.25)	28.44

Abbreviations: BSI, bloodstream infection; CI, confidence interval.

In the stratified analysis, 90-day all-cause mortality for *Candida* BSI cases was stable across quintiles of risk for developing *Candida* BSI (range 38.3% to 44%) (Figure 1). Conversely, the 90-day mortality of the control patients increased from 13.6% for the first quintile group to 34.2%, 33%, and 28.6% in quintiles 3 through 5, respectively. The pattern of high crude mortality across all quintiles of risk to develop *Candida* BSI in *Candida* case subjects and more variable crude mortality in the control population was also present in the 30-day all-cause mortality analysis (Table 4). The increase in mortality risk at 90 days was highest in patients in the two lowest-risk quintiles (HR 3.13 [95% CI 2.33–4.19] and HR 1.97 [95% CI, 1.46–2.67]). The hazard ratios for the third through fifth quintiles were 1.15 (95% CI, .83–1.61), 1.42 (95% CI, .93–2.18), and 1.63 (95% CI, .70–3.79), respectively (Figure 1). Similarly, 30-day mortality was significantly higher in patients with *Candida* BSI from the 2 lowest-risk quintiles (Table 4). The distribution of hierarchical medical conditions in each quintile is available in Supplementary Table 6.

The same pattern (highest HRs in the lowest propensity score quintiles) was also present in the sensitivity analysis when the covariates with the highest standardized differences were included as covariates in the adjusted model



**Figure 1.** Hazard ratio for 90-day all-cause mortality superimposed on death rate (%) per propensity score quintile of *Candida* BSI risk. Abbreviation: BSI, bloodstream infection.

(Supplementary Table 7). *Candida* BSI was associated with 2.3-fold higher 90-day mortality (95% CI 1.71–3.10) and 1.7-fold higher 30-day mortality (95% CI 1.28–2.34) in the first risk quintile. Similarly, in the second quintile, the 90-day mortality was 2.07 (95% CI 1.52–2.80) and 1.81 (95% CI 1.33–2.45) for 30-day mortality. *Candida* BSI was not associated with significantly increased risk of 30-day or 90-day all-cause mortality in the upper 3 quintiles in the sensitivity analysis (Table 4, Supplementary Table 7).

Of the 626 *Candida* BSI cases, there were 32 patients were not treated; 22/32 (68.7%) were in the lowest 2 quintiles of risk to develop *Candida* BSI (Supplementary Table 8). We analyzed this further using an expanded dataset available from a prior study [15]. There were 130 patients with untreated *Candida* BSI in the expanded data set out of 1820 cases total. Untreated *Candida* BSI cases were predominately (81/130, 62%) in the lowest risk quintile for development of *Candida* BSI (Supplementary Table 8). In the first quintile, 56/81 (69.1%) untreated patients died compared to 364/540 (40.3%) of treated patients ( $P < .001$ ); the remaining quintiles are presented in Supplementary Table 9. The odds ratio (OR) for mortality of untreated *Candida* BSI in the first quintile was 3.3 (95% CI 2.0–5.4).

## DISCUSSION

Compared with propensity score-matched controls, patients with *Candida* BSI had 2.1-fold higher 90-day all-cause mortality; the mortality attributable to *Candida* BSI was 28.4%. This finding was consistent over 3 separate analyses, and similar for 30-day mortality.

Our study, starting with data collected in 2012, was conducted entirely during the era of echinocandin empiric therapy, distinguishing it from most of the other studies conducted [7, 8, 16]. The crude mortality in our study (42.4%) was lower than the mortality found in the landmark University of Iowa studies in 1988 (57%) [7] and 2003 (61%) [6]. These studies were conducted when amphotericin deoxycholate and fluconazole, respectively, were the recommended empiric antifungals. The estimated attributable mortality from the 1988 and 2003 studies were higher (38% and 49%) compared to our study (28.4%) [6, 7]. The decrement observed in attributable mortality is likely multifactorial with potential contributions from the widespread use of echinocandins, more rapid diagnoses and improved supportive care.

Zaoutis et al conducted a propensity score analysis of the 2000 Nationwide Inpatient Sample (NIS), a nationwide sampling of administrative hospital data. They reported a crude mortality of 30.6% and attributable mortality of 14.5% [8]. Both are lower than our study and others [3, 7, 8, 17, 18]. The NIS data set, predictably, underestimates attributable mortality because it does not allow identification of individual patients and recurrent hospitalizations of a single patient are treated as



**Table 4. Comparison of Mortality Rates and Hazard Ratios of 30-day and 90-day Mortality by Propensity Score Quintile With *Candida* BSI as Only Covariate**

Baseline Risk of Developing Candidemia	<i>Candida</i> BSI Cases		Control Cases		Mortality Difference (%)	Hazard Ratio (95% CI)
	Total No. of patients	Mortality	Total No. of Patients	Mortality		
<b>30-day</b>						
First quintile (lowest risk)	125	19.2%	5088	8.7%	11.0%	2.35 (1.75–3.15)
Second quintile	125	32.0%	718	17.7%	14.0%	1.78 (1.32–2.41)
Third quintile	126	22.2%	339	23.0%	0.8%	1.09 (.78–1.52)
Fourth quintile	125	23.2%	103	16.5%	6.7%	1.25 (.81–1.91)
Fifth quintile (highest risk)	125	21.6%	21	19.1%	2.3%	1.25 (.54–2.92)
<b>90-day</b>						
First quintile (lowest risk)	125	38.4%	5088	13.6%	24.8%	3.13 (2.33–4.19)
Second quintile	125	44.0%	718	24.8%	19.2%	1.97 (1.46–2.67)
Third quintile	126	38.3%	339	34.2%	4.1%	1.15 (.83–1.61)
Fourth quintile	125	44.0%	103	33.0%	11.0%	1.42 (.93–2.18)
Fifth quintile (highest risk)	125	43.2%	21	28.6%	14.6%	1.63 (.70–3.79)

Abbreviations: BSI, bloodstream infection; CI, confidence interval.

new “patients” [19]. Subsequently, a patient with *Candida* BSI transferred to a higher level of care or discharged on hospice is counted as having survived. This systematically biases the NIS data set to underreporting mortality.

Similarly, the clinical trials used to obtain Food and Drug Administration (FDA) approval for the echinocandins had relatively low mortality [18, 20–22]. The trials likely underestimated the mortality as they excluded patients at risk for poor outcomes and those who died prior to having an opportunity to be screened for study randomization. Examples include exclusion of neutropenic patients [22], endocarditis/meningitis [18], life expectancy <5 days at randomization [20], and refractory *Candida* infection [21]. Excluding patients based on these criteria would underestimate both crude and attributable mortality of *Candida* BSI. Furthermore, the strict inclusion and exclusion criteria of clinical trials are often not reflective of real-world clinical practice, limiting generalizability.

Our study is unique in that we focused on 90-day all-cause mortality, not previously used in studies quantifying mortality attributable to *Candida* BSI [5–8, 17, 23–26]. The median time to death in *Candida* BSI cases in our study was 41 days. Protracted hospitalizations observed in *Candida* BSI patients demonstrate a 30-day endpoint would underestimate mortality. Using in-hospital mortality as a primary endpoint can also underestimate mortality, as demonstrated by the NIS database [19]. Furthermore, using in-hospital mortality limits comparisons between studies as hospitalization and discharge practices vary across medical institutions and healthcare systems. We advocate for use of 90-day all-cause mortality as a primary endpoint use in future studies because it more accurately captures short- and long-term mortality.

Interestingly, the stratified analysis demonstrating the mortality attributable to *Candida* BSI was highest in those at lowest risk of developing *Candida* BSI. Of the 130 untreated *Candida* BSI cases identified in our cohort, 75% (97/130) were in the

lowest 2 quintiles of risk with a significantly higher proportion of death. Mischaracterization of *Candida* BSI as contaminants and unawareness by the treating clinician of the *Candida* BSI accounted for 91% of untreated cases. We hypothesize that treating clinicians incorrectly adjudicated the risk of *Candida* BSI in these patients due to fewer traditional risk factors, resulting in more instances of untreated *Candida* BSI. Predictably, our data showed that there was a significant increase in mortality in patients with untreated *Candida* BSI, particularly in those at lowest risk. Appropriate and timely treatment of all *Candida* BSI, even in those deemed low risk, is imperative to lowering mortality. We believe the lowest risk groups should be the focus of future study and subsequent interventions as they likely have the highest potential for mortality reduction. For instance, obtaining Infectious Disease consultation for all patients has been associated with fewer untreated patients and lower mortality [15, 27].

Our study had several limitations. Patients expiring within 24 hours of index blood culture were excluded to avoid deaths occurring in the emergency room or very early in a hospitalization before initiation of treatment. We favored this more conservative approach and subsequent estimation of attributable mortality. These patients accounted for only 1% of cases and controls. Unmeasured confounding is an issue with all observational studies. However, the propensity score was developed from an extensive list of predisposing risk factors for the development of *Candida* BSI and prognostic comorbidities for death [28, 29], with good balance of the covariates, ensuring comparable case-control matches for the matched-pairs analysis. To adjust for residual confounding, a sensitivity analysis was done by adding variables into the models, with similar results. Finally, the data used in this study was from a single tertiary referral center, limiting the generalizability of our findings.

Overall, *Candida* BSI was associated with 2.3-fold increased risk of 90-day all-cause mortality. High mortality observed has persisted over decades despite treatment advances, though

mortality attributable to *Candida* BSI has decreased compared to most historical studies. The increased mortality attributable to *Candida* BSI was more pronounced in patients at low baseline risk to develop *Candida* BSI, possibly due to lower proportion receiving treatment. It is imperative that clinicians maximize efforts to adhere to guideline recommendations [30, 31] and seek Infectious Disease consultation to assist in timely, efficacious treatment of *Candida* BSI [15].

### Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

### Notes

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