Decreasing Rates of Invasive Candidiasis in Pediatric Hospitals Across the United States

Brian T. Fisher,1,2 Rachael K. Ross,1 A. Russell Localio,2,4 Priya A. Prasad,1,2 and Theoklis E. Zaoutis1,2,3
1Division of Infectious Diseases and 2Center for Pediatric Clinical Effectiveness, Children’s Hospital of Philadelphia, Pennsylvania; 3Center for Clinical Epidemiology and Biostatistics and 4Department of Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia

Rates of invasive candidiasis (IC) in children between 2003 and 2011 were evaluated in a retrospective cross-sectional analysis. The rate of IC decreased 72% (P < .001) overall and 91% in neonates (P < .001). Improving infection control efforts is thought to be a contributing factor for this decrease.

Keywords. candidiasis; pediatrics; mortality.

In the final quarter of the last century, invasive candidiasis (IC) was identified as a major contributor to infection-related morbidity and mortality in hospitalized patients [1, 2]. The presumed source for this increased IC burden was a growing population of susceptible hosts such as recipients of transplants or intensive chemotherapeutic regimens, the elderly, and neonates [3–5]. More recent data, however, reveal a decline in IC among neonatal and pediatric populations [6–8]. Although these data are encouraging, they are not generalizable to all US pediatric institutions. We aimed to describe the epidemiology of pediatric IC across many children’s hospitals in the United States from 2003 to 2011.

METHODS

Study Design and Data Source

We performed a retrospective cross-sectional study of pediatric inpatients using data from the Pediatric Health Information System, a comparative administrative database that contains information from 43 tertiary US children’s hospitals, which represent 17 of the 20 major metropolitan areas.

Study Population

The study included patients who were aged <19 years and discharged between 1 January 2003 and 31 December 2011. Neonatal admissions were identified using All Patient Refined Diagnosis-Related Group (APR-DRG) codes and categorized by birth weight: <1500 g, 1500–2499 g, or ≥2500 g (Supplementary Table 1) [9]. Admissions without a neonatal APR-DRG code were considered nonneonatal pediatric admissions.

Outcomes

IC was identified by the International Classification of Diseases, Ninth Revision (ICD-9) diagnosis code of 112.5 (disseminated systemic candidiasis). Among admissions with IC, in-hospital all-cause mortality was identified using discharge disposition.

Fluconazole Prophylaxis

Fluconazole prophylaxis was examined for neonatal patients weighing <1500 g as guidelines have suggested prophylaxis for this patient group [10]. Patients who were admitted on the first or second day of life were included in the analysis. We defined fluconazole prophylaxis as receipt of ≥2 days of fluconazole in the first 7 days of the admission.

Statistical Analysis

Rates of IC are presented as number of cases per 10,000 inpatient days. To assess the trend of IC, Poisson regression models were fit with time as an independent variable, and expected rates and incidence rate ratios (IRRs) were obtained.

To assess how changes in rates of IC varied by hospital, we implemented mixed-effects Poisson regression models with a random intercept for hospital and a random slope for time. We used log-likelihood ratio tests to assess the significance of the random effects for time (slope) across hospitals.

To investigate changes in fluconazole prophylaxis, we fit a logistic regression with receipt of prophylaxis as the outcome. To assess the trend in mortality, a logistic regression model was fit with death as the outcome and time as an independent variable.

In marginal analyses, standard errors and confidence intervals were adjusted for clustering by hospital. Analyses were completed using Stata software version 12.1 (StataCorp, College Station, Texas).
RESULTS

Epidemiology of IC
During the 9-year study period, there were 4,164,341 admissions, which included 4,456 IC admissions. The crude rate of IC decreased from 2.46 cases per 10,000 inpatient days in 2003 to 0.77 in 2011. Based on the fit model, there was a 72% decrease (IRR = 0.28; 95% confidence interval [CI], 0.22–0.37) over the study period.

In the nonneonatal pediatric population, there were 3,854 IC admissions. Over the study period, the crude nonneonatal IC rate decreased from 2.5 to 0.92 per 10,000 days (Figure 1A). Based on the fit model, there was a decline of 67% (IRR = 0.33; 95% CI, 0.25–0.44). In the mixed-effects model, hospital-specific predictions showed an increase in IC rate at a single hospital (10% increase, IRR = 1.10) whereas rates at all other hospitals decreased, ranging from 4% to 93%. The variation by hospital was significant (P < .001).

Figure 1. Crude and expected rates of invasive candidiasis as cases per 10,000 inpatient days, 2003–2011. A, Nonneonatal pediatric patients. B, Neonatal patients. Neonatal patients were identified by All Patient Refined Diagnosis-Related Group (APR-DRG) code. Patients without a neonatal APR-DRG code were considered nonneonatal pediatric patients.
In the neonatal population, there were 602 IC admissions. Over the study period, the crude IC rate decreased from 2.5 to 0.27 per 10,000 days (Figure 1B). Based on the fit model, there was a decline of 91% (IRR = 0.09; 95% CI, 0.06–1.15). The decrease was statistically significant across all 3 neonatal birth-weight groups: 93% decrease among neonates ≥2500 g (IRR = 0.07; 95% CI, 0.04–0.14), 88% decrease among neonates 1500–2499 g (IRR = 0.12; 95% CI, 0.04–0.32), and 90% decrease among neonates <1500 g (IRR = 0.10; 95% CI, 0.06–0.19). In the mixed-effects model including all neonatal admissions, all hospitals had a decrease in the IC rate, although the decrease varied significantly from 48% to 98% (P = 0.001).

**Fluconazole Prophylaxis**

In the neonatal population, among 30,956 patients who weighed <1500 g and were admitted to a Pediatric Health Information System institution on the day of or day after birth, 229 (0.74%) had IC. The crude rate of IC declined from 3.51 per 10,000 days in 2003 to 0.26 in 2011, and the proportion of patients receiving prophylaxis increased from 2.5% to 7.0% (Supplementary Figure 1). The increase in prophylaxis approached statistical significance (P = 0.07).

**In-Hospital All-Cause Mortality in Patients With IC**

Discharge disposition was available for 4426 IC admissions, of which 631 (14%) resulted in death. Mortality varied by year. In 2003 and 2011, 17.3% and 11.6%, respectively, of IC admissions ended in death (Supplementary Figure 2). Mortality was lowest in 2010 (10.7%). There was a 31% decrease in the odds of mortality over the study period (odds ratio = 0.69; 95% CI, 0.48–0.98).

**DISCUSSION**

In this retrospective observational study, we observed a significant reduction in the rate of IC at US children's hospitals. Similar declines have been reported in prior observational studies. One observed a decline in central venous catheter (CVC)–associated neonatal candidemia in neonatal intensive care units [7], and another observed a decline in pediatric candidemia in Atlanta and Baltimore [8]. These prior studies described an IC decline specifically among neonatal patients or within certain geographic regions. Our cohort uniquely describes a decline in both neonatal and nonneonatal patients at a national level.

Multiple hypotheses might explain the observed decline. The Centers for Disease Control and Prevention reported a 58% decrease in CVC-associated bloodstream infections in US intensive care units [11]. This reduction was attributed to hospital infection control initiatives. It is likely that these same efforts have contributed to some of the decrease of IC we observed; however, we were unable to investigate this hypothesis due to our use of administrative data. Administration of fluconazole prophylaxis in high-risk groups may also have contributed to a decline in IC [10]. We attempted to explore the impact of prophylaxis by examining the initiation of fluconazole in the first week of life in neonates weighing <1500 g. Fluconazole prophylaxis rates increased as IC declined. Whereas this increase may explain some of the IC decline, it is not likely the primary driver, as significant declines were also observed in larger neonates and in the nonneonatal population, where fluconazole prophylaxis is not routinely recommended.

Although there was a substantial decline of IC overall, there was significant variation across institutions. The etiology for this variation is not clear. Further research to identify interventions at institutions with the greatest decline is warranted to establish best practices.

The all-cause in-hospital mortality for admissions with IC was similar to previous published data [5]. Although the rate in our study fluctuated, there was an encouraging 31% decrease. The decline may be related to increased awareness of IC, earlier initiation of antifungal therapy, and/or improved therapeutic options. Adult data support a mortality benefit for echinocandins as compared to other antifungal agents [12]. Nonetheless, mortality remains >10%, highlighting an ongoing need to improve IC outcomes.

Our study has limitations. First, there are no published multicenter data to validate the ICD-9 code 112.5. This code is likely to be highly specific but may have limited sensitivity, and thus we may have underestimated the true incidence. However, this should not affect the observed trend. Furthermore, our results are consistent with previous publications that utilized microbiology data to define candidemia. Second, we defined fluconazole prophylaxis based on exposure in the first week of life, which may underestimate the number of patients receiving prophylaxis. Thus, we may underappreciate the impact of prophylaxis. Additionally, the prophylaxis analysis included neonates weighing <1500 g whereas the current recommendations are for those <1000 g [10]. Because we used a combination of APR-DRG codes, we were unable to limit this analysis to patients weighing <1000 g. Finally, we identified neonates using APR-DRG codes, which may result in misclassification. The majority of patients identified as neonates (63%) were admitted on day of birth, and the maximum age at the time of admission was 14 days, which supports that this approach captured a neonatal population.

Our results indicate a significant decrease in IC at US children's hospitals. The etiology of this decline is likely multifactorial. Future efforts should focus on identifying successful interventions so standard practices can be applied across institutions. The decrease of in-hospital mortality of IC patients is encouraging; however, mortality rates remain >10% and thus improved management is necessary.
Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Note

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