Changes in the Incidence of Candidiasis in Neonatal Intensive Care Units

WHAT'S KNOWN ON THIS SUBJECT: The incidence of invasive candidiasis in hospitalized infants is related to postnatal exposures, but large-scale studies relating the incidence of invasive candidiasis to changes in exposures over time are not available.

WHAT THIS STUDY ADDS: This study describes the association between the incidence of invasive candidiasis and changes in use of antifungal prophylaxis, empirical antifungal therapy, and broad-spectrum antibacterial antibiotics over time.

abstract

OBJECTIVE: Neonatal invasive candidiasis is associated with significant morbidity and mortality. We describe the association between invasive candidiasis and changes in use of antifungal prophylaxis, empirical antifungal therapy, and broad-spectrum antibacterial antibiotics over time.

METHODS: We examined data from 709 325 infants at 322 NICUs managed by the Pediatrix Medical Group from 1997 to 2010. We determined the cumulative incidence of invasive candidiasis and use of antifungal prophylaxis, broad-spectrum antibacterial antibiotics, and empirical antifungal therapy by year.

RESULTS: We identified 2063 (0.3%) infants with 2101 episodes of invasive candidiasis. Over the study period, the annual incidence of invasive candidiasis decreased from 3.6 episodes per 1000 patients to 1.4 episodes per 1000 patients among all infants, from 24.2 to 11.6 episodes per 1000 patients among infants with a birth weight of 750–999 g, and from 82.7 to 23.8 episodes per 1000 patients among infants with a birth weight <750 g. Fluconazole prophylaxis use increased among all infants with a birth weight <1000 g (or <1500 g), with the largest effect on birth weights <750 g, increasing from 3.8 per 1000 patients in 1997 to 110.6 per 1000 patients in 2010. The use of broad-spectrum antibacterial antibiotics decreased among all infants from 275.7 per 1000 patients in 1997 to 48.5 per 1000 patients in 2010. The use of empirical antifungal therapy increased over time from 4.0 per 1000 patients in 1997 to 11.5 per 1000 patients in 2010.

CONCLUSIONS: The incidence of invasive candidiasis in the NICU decreased over the 14-year study period. Increased use of fluconazole prophylaxis and empirical antifungal therapy, along with decreased use of broad-spectrum antibacterial antibiotics, may have contributed to this observation. *Pediatrics* 2014;133:236–242

AUTHORS: Sofia Aliaga, MD, MPH,^a Reese H. Clark, MD,^b Matthew Laughon, MD, MPH,^a Thomas J. Walsh, MD,^{c,d,e} William W. Hope, MD, PhD,^f Daniel K. Benjamin, PhD,^g David Kaufman, MD,^h Antonio Arrieta, MD,ⁱ Daniel K. Benjamin Jr, MD, PhD,^{j,k} and P. Brian Smith, MD, MPH, MHS^{j,k}

^aDivision of Neonatal-Perinatal Medicine, University of North Carolina, Chapel Hill, North Carolina; ^bPediatrix-Obstetrics, Greenville, South Carolina; ^cTransplantation-Oncology Infectious Disease Program and Departments of ^dPediatrics and ^eMicrobiology, Weill Cornell Medical Center, New York, New York; ^fDepartment of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, United Kingdom; ^gDepartment of Economics, Clemson University, Clemson, South Carolina; ^hDepartment of Pediatrics, University of Virginia Health Systems, Charlottesville, Virginia; ⁱDepartment of Pediatrics, Children's Hospital of Orange County, Orange, California; ^jDepartment of Pediatrics, Duke University, Durham, North Carolina; and ^kDuke Clinical Research Institute, Durham, North Carolina

KEY WORDS

invasive candidiasis, fluconazole prophylaxis, premature infants

ABBREVIATIONS

CI—confidence interval

ELBW—extremely low birth weight

OR—odds ratio

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Address correspondence to P. Brian Smith, MD, MPH, MHS, Department of Pediatrics, Duke Clinical Research Institute, Duke University, PO Box 17969, Durham, NC 27715. E-mail: brian.smith@duke.edu

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Invasive candidiasis is an important cause of sepsis in the NICU. *Candida* infections in infants are associated with significant mortality and morbidity, including neurodevelopmental impairment, among survivors.^{1–3} The incidence of invasive candidiasis ranges from 2.6% to 13.2% in very low birth weight infants (<1500 g) and from 6.6% to 26.0% in extremely low birth weight (ELBW) infants (<1000 g).^{1–11}

Previously identified risk factors for invasive candidiasis in the NICU include low birth weight, prematurity, presence of central catheters, days of mechanical ventilation, abdominal surgery, and exposure to broad-spectrum antibacterial antibiotics (eg, third-generation cephalosporins).^{1,11,12} The incidence of invasive candidiasis varies significantly by center.^{1,3,13} Variation in the incidence of invasive candidiasis and its association with poor outcomes should prompt evaluation of how changes or differences in clinical practices might influence the risk of acquiring this disease.

Invasive candidiasis in hospitalized infants appears to be decreasing. We hypothesized that increased use of antifungal prophylaxis and empirical antifungal therapy as well as avoidance of broad-spectrum antibacterial antibiotics may explain the decreasing incidence. Herein, we use a large multicenter cohort to describe the incidence of candidiasis in the NICU and parallel changes in the use of antifungal prophylaxis, broad-spectrum antibacterial antibiotics, and empirical antifungal therapy over a 14-year period.

METHODS

We examined a cohort of all infants discharged from 322 NICUs managed by the Pediatrix Medical Group from 1997 to 2010. Data were collected prospectively from daily progress notes generated by clinicians. We determined the cumulative incidence of invasive candidiasis and the use of antifungal prophylaxis, broad-spectrum antibacterial

antibiotics, and empirical antifungal therapy by year.

Definitions

Evaluations for infection were performed by using standard-of-care practices at each NICU. We defined invasive candidiasis as the presence of a positive culture (blood, urine, cerebrospinal fluid, or a combination of these). Urine cultures were included only if obtained via in-and-out catheterized or suprapubic aspiration. Multiple positive cultures for *Candida* within 21 days were considered a single episode of infection.

We defined antifungal prophylaxis as a combination of the following: (1) antifungal started in the first 5 postnatal days, (2) course of treatment lasting >7 days, and (3) no positive *Candida* culture before or on the day the antifungal prophylaxis was started. We defined empirical antifungal therapy as a combination of the following: (1) presence of a culture obtained while the patient was receiving antifungal therapy, (2) no positive *Candida* cultures within the previous 14 days, and (3) excluding therapy defined as antifungal prophylaxis. We defined the administration of a broad-spectrum antibacterial antibiotic as exposure to a third-generation cephalosporin or carbapenem at any time during the NICU hospitalization.

Statistical Analysis

We organized our data in 3 separate ways: at the national level for each year, at the site level for each year, and at the culture level for each patient. At the national and site levels, for each year we calculated the incidence (episodes per 1000 patients) of invasive candidiasis. We also calculated the use (per 1000 patients) of antifungal prophylaxis, broad-spectrum antibacterial antibiotics, and empirical antifungal therapy. Both nationally and by site, the annual incidence of candidiasis, use of antifungal prophylaxis,

use of broad-spectrum antibacterial antibiotics, and use of empirical antifungal therapy were calculated for all infants in our sample, as well as for those in each of 4 birth weight groups: ≥ 1500 g, 1000–1499 g, 750–999 g, and <750 g.

To examine the association between broad-spectrum antibacterial antibiotic use and the incidence of invasive candidiasis at the site level, we accounted for 2 key aspects of the data. In many cases, especially among heavier infants, the incidence of invasive candidiasis at a site was 0. In addition, the number of observations varied substantially across sites over time. We used Tobit models to account for the censoring of the data at 0 and weighted the observations by the number of patients at each site in each year to account for differences in sample size across sites.¹⁴

We used multivariable logistic regression to examine the relationship between exposure to broad-spectrum antibacterial antibiotics in the 7 days before a culture and the development of invasive candidiasis, controlling for gestational age. The unit of observation for this analysis was the culture. Because cultures were obtained on widely varying days of life across infants, we used conditional logistic regression in which infants were stratified according to the postnatal day the culture was obtained.¹² All analyses were performed by using Stata 12.0 (StataCorp, College Station, TX). The Duke University Institutional Review Board and the Western Institutional Review Board approved this study.

RESULTS

We included 709 325 infants in the final analysis. A total of 2063 (0.3%) infants had 2101 episodes of invasive candidiasis. The median gestational age of infants with invasive candidiasis was 26 weeks (interquartile range: 24–29 weeks) compared with 35 weeks (33–38 weeks) for those without invasive candidiasis ($P < .001$) (Table 1). The

median birth weight for infants with invasive candidiasis was 791 g (640–1193 g) compared with 2486 g (1825–3200 g) for those without invasive candidiasis ($P < .001$). Mortality was higher for infants with invasive candidiasis (19.9% vs 2.1%; $P < .001$). Over the 14-year period, the annual incidence of invasive candidiasis decreased from 3.6 per 1000 infants to 1.4 per 1000 infants, with the greatest decrease among infants with a birth weight <750 g (82.7 to 23.8 per 1000 infants) and infants with a birth weight of 750–999 g (24.2 to 11.6 per 1000 infants) (Fig 1). The incidence of invasive candidiasis decreased beginning in 2001 and continued to decrease through the remainder of the study period.

We identified 2831 (0.4%) infants who received antifungal prophylaxis. Fluconazole was the antifungal drug most frequently used for prophylaxis ($n = 2625$, 92.7%). We observed increasing use of fluconazole antifungal prophylaxis beginning in 2002 (Fig 2). Over the study period, the use of fluconazole for antifungal prophylaxis increased among all infants from 0.1 per 1000 patients to 7.4 per 1000 patients. The greatest increase was observed among infants with a birth weight <750 g, from 3.8 to 110.6 per 1000 patients.

We identified 7494 (1.1%) infants who received ≥ 1 courses of empirical antifungal therapy, including 1417 infants who received ≥ 2 courses. The median duration of empirical courses was 8 days (4, 14 IQR). Empirical treatment included 3959 courses of amphotericin products and 4209 courses of fluconazole. Among infants who received empirical antifungal therapy, 599 (8.0%) developed invasive candidiasis while receiving therapy. Over the study period, we observed an increase in empirical antifungal therapy among all infants, from 4.0 per 1000 patients in 1997 to 11.5 per 1000 patients in 2010. We observed the greatest increase among

TABLE 1 Demographic Characteristics

	Invasive <i>Candida</i> Infection	No Invasive <i>Candida</i> Infection
<i>N</i>	2063	707 262
Gestational age, %		
<26 weeks	48.0	2.9
26–28 weeks	26.0	5.2
29–33 weeks	15.1	22.2
34–36 weeks	5.3	29.8
≥ 37 weeks	5.6	40.0
Birth weight, %		
<750 g	43.5	2.8
750–999 g	24.2	3.5
1000–1499 g	15.4	9.2
≥ 1500 g	16.9	84.5
Race/ethnicity, %		
White	40.3	53.9
African American	29.5	17.1
Hispanic	27.1	24.2
Other	3.1	4.9
Gender, %		
Male	57.1	56.1
Apgar score (5 min), %		
0–3	8.1	1.7
4–6	25.4	6.6
7–10	66.5	91.8
Inborn, %	75.0	85.1
Died, %	19.9	2.1
Antenatal steroid use, %	66.1	34.1
Cesarean delivery, %	50.7	54.9

FIGURE 1
Candidiasis by year and birth weight.

infants with birth weight <750 g, from 67.7 to 206.0 per 1000 patients.

Over the study period, the use of broad-spectrum antibiotics decreased among all infants from 275.7 to 48.5 per 1000 patients (Fig 3). Exposure to broad-spectrum antibacterial antibiotics was associated with an increased risk of invasive candidiasis (adjusted odds ratio

[OR]: 1.88; 95% confidence interval [CI]: 1.72–2.07; c statistic = 0.87). This finding was broadly mirrored at the level of different sites. Among the 3 smaller birth weight groups (1000–1499 g, 750–999 g, and <750 g), each 10% decrease in the incidence of broad-spectrum antibacterial antibiotic use was associated with a 2.9% to 7.3% decrease in

FIGURE 2
Fluconazole prophylaxis by year and birth weight.

the incidence of invasive candidiasis (Table 2). There was no significant association between broad-spectrum antibacterial antibiotic use and invasive candidiasis among infants with a birth weight of ≥ 1500 g ($P = .18$).

DISCUSSION

In this large cohort of hospitalized infants we observed a decrease in the incidence of invasive candidiasis over the study period. We observed the largest decrease among infants with birth weights of <750 g and 750 – 999 g. During this same time period, we also observed an increased use of antifungal

prophylaxis and empirical antifungal therapy, as well as decreased use of broad-spectrum antibacterial antibiotics. These changes in clinical practice may have contributed to the decreased incidence of invasive neonatal candidiasis.

The decreasing incidence of invasive candidiasis found in this study is similar to previously published data from 130 523 infants admitted to 128 NICUs participating in the National Nosocomial Infections Surveillance System.¹³ Data from the system revealed a small decrease in the incidence of *Candida* bloodstream infection in infants with a birth weight <1000 g, from 6.6% in

1995–1999 to 5.1% in 2000–2004.¹³ Our data reveal further decreases in invasive candidiasis among infants <1000 g after 2004. Changes in neonatal clinical practice are at least partially responsible for the decreasing trend of invasive candidiasis. These changes in practice, including increased use of antifungal prophylaxis and decreased use of broad-spectrum antibacterial antibiotics, are supported by findings from randomized clinical trials and observational studies. A meta-analysis of 656 infants from 5 randomized trials found that fluconazole antifungal prophylaxis in high-risk infants reduces the incidence of invasive candidiasis in very low birth weight infants by 52% (number needed to treat = 11; 95% CI: 7–33).^{8,9,15} Results from the first randomized controlled trials of fluconazole prophylaxis published in 2001 and the first Cochrane review published in 2004 likely influenced practice in NICUs in our data set.^{5,9,16} Our findings suggest that providers are administering antifungal prophylaxis according to the most common recommendations that prophylaxis should target infants with birth weights <1000 g, although the majority of infants with a birth weight <1000 g are not exposed to antifungal prophylaxis.^{17,18}

Previous studies support an association between invasive *Candida* infections and exposure to broad-spectrum antibacterial antibiotics.^{2,11,12,19} Broad-spectrum antibacterial antibiotic exposure in a cohort of 3702 ELBW infants was associated with invasive candidiasis (OR: 2.16; 95% CI: 1.42–3.27).¹¹ Similarly, we observed an association between broad-spectrum antibacterial antibiotics and increased risk of invasive candidiasis at the culture level (OR: 1.88; 95% CI: 1.72–2.07). In our cohort, use of broad-spectrum antibacterial antibiotics decreased over time, mirroring the decrease in invasive candidiasis. Indeed, the Tobit regression

FIGURE 3
Broad-spectrum antibacterial antibiotic use by year and birth weight.

TABLE 2 Effect of a 10% Decrease in Antibiotic Use on Incidence of Candidiasis (Tobit Regressions)

Birth Weight, g	Decrease in Candidiasis, per 1000 Infants	Decrease in Candidiasis, %	P
<750	3.0	7.3	<.001
750–999	1.3	5.7	<.001
1000–1499	0.2	2.9	<.001
≥1500	<0.1	0.4	.18

results imply that, on average, sites that reduced broad-spectrum antibiotic use the most had the largest decrease in candidiasis.

Many ELBW infants are exposed to empirical courses of antifungal agents for suspected fungal sepsis. The increased use of empirical antifungal therapy observed during the study period likely reflects an increased awareness of the need for early therapeutic intervention for improved outcome from *Candida* sepsis and of the association between invasive candidiasis and mortality and neurodevelopmental impairment in this high-risk population. The diagnosis of invasive candidiasis is made difficult by the nonspecific clinical presentation of the disease and low sensitivity of current microbiologic diagnostic techniques.¹⁷ Widespread use of empirical antifungal therapy could potentially contribute to a reduction in the incidence of invasive candidiasis by decreasing or eliminating fungal colonization. The effect of empirical antifungal therapy on outcomes will likely be more significant if treatment courses target infants at higher risk of fungal sepsis.^{5,12,20}

We acknowledge that other unmeasured practice changes could contribute to the decrease in invasive candidiasis. A growing number of NICU quality improvement initiatives targeting central catheter management and designed to decrease central line–associated bloodstream infections may have contributed to our findings. From 1999 to 2009, data from the National Nosocomial Infections Surveillance System and the National Healthcare Safety

Network revealed that the overall incidence of central line–associated bloodstream infections due to *Candida* spp. decreased from 0.92 to 0.2 per 1000 central line days.²¹ Hand-washing has been identified as an important practice to decrease hospital-acquired infections.^{22,23} The introduction of central catheter management bundles and hand-washing compliance was not measured but may have contributed to the reduction in invasive candidiasis. However, the incidence of bacteremia remained stable at 30 per 1000 infants in the years 1997–2001 versus 32 per 1000 infants from 2006 to 2010. Antifungal treatment of neonatal candidiasis has also changed over the past decade, with higher dosing recommendations for fluconazole therapy and the introduction of newer antifungal agents, such as the class of echinocandins.^{24–28} Decreased exposure to other risk factors might also explain the decreased incidence of candidiasis. For example, overall histamine-2 blocker use decreased from 66 per 1000 infants in the years before the decrease in candidiasis (1997–2001) to 52 per 1000 infants later in the study period (2006–2010). Similarly, exposure to mechanical ventilation decreased from 280 to 229 per 1000 infants.

The decline in the incidence of invasive candidiasis has a profound effect on required sample size for well-powered trials to evaluate the efficacy of antifungal agents for both prophylaxis and treatment. For example, fluconazole prophylaxis results in a relative risk reduction in the incidence of invasive candidiasis of between 50% and 80%.^{15,29}

The sample size required to observe this difference in the context of a clinical trial is now dramatically higher, given the decrease in the incidence of neonatal candidiasis. The decrease in the incidence of invasive candidiasis will also have a large impact on enrollment in antifungal efficacy trials. Most moderately sized NICUs admit ~500 infants per year. We estimate that, given difficulties obtaining parental consent, exposure of infected infants to previous empirical antifungal agents, and exclusion criteria, only one-third of infected infants could be enrolled in a randomized efficacy trial. Given a cumulative incidence of 1.4 infections per 1000 infants, a 250-infant study would require 10 years and 100 NICUs to complete enrollment.

Strengths of this study include the large number of infants in the analysis, particularly a significant proportion of hospitalized ELBW infants from across the United States. Given that the majority of episodes of neonatal invasive candidiasis occur in ELBW infants and in the NICU setting, our findings are likely representative of the actual burden of disease in this population. This study provides evidence for an overall downward trend of invasive candidiasis in the NICU population across the country. Of course, not all individual units may have experienced the same degree of change. Given the retrospective nature of these data, we are not able to examine causal relationships between changes in all clinical practices and the reduced incidence of invasive candidiasis. It is also possible that later use of fluconazole (after the first 5 days) was targeted prophylaxis in infants being treated with prolonged antibiotics or that necrotizing enterocolitis was included in the empirical antifungal category. We also acknowledge the possibility that other changes in clinical care, such as changes in ventilator management, central line

care, and feeding practices, may have influenced the risk of acquiring invasive candidiasis. For example, although invasive candidiasis began to decrease in 2001, the increase in antifungal prophylaxis did not begin until 2002.

CONCLUSIONS

Our findings show a substantial decrease in the incidence of invasive candidiasis in the NICU setting. This

decrease was likely the result of progressive changes in neonatal clinical practice. The decreased incidence of invasive candidiasis will likely not only reduce overall health care costs but also improve neonatal outcomes. Each NICU should closely monitor its incidence of invasive candidiasis because low rates are achievable. Similar to preventing central line–associated bloodstream infections and group B

Streptococcus, we want to eliminate these infections. Additional clinical trials addressing the efficacy of antifungal prophylaxis and empirical antifungal therapy may not be feasible given the current incidence of the disease. A comparison of practices between NICUs with high and low rates of candidiasis may be helpful in providing further evidence for best practices in the prevention of this disease.

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