

## ORIGINAL ARTICLE

# Fluconazole prophylaxis for prevention of invasive fungal infections in targeted highest risk preterm infants limits drug exposure

J-H Weitkamp<sup>1</sup>, A Ozdas<sup>2</sup>, B LaFleur<sup>3</sup> and AL Potts<sup>4</sup>

<sup>1</sup>Division of Neonatology, Department of Pediatrics, Monroe Carell Jr Children's Hospital at Vanderbilt, Nashville, TN, USA; <sup>2</sup>Department of Biomedical Informatics, Vanderbilt University Medical Center, Nashville, TN, USA; <sup>3</sup>Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN, USA and <sup>4</sup>Department of Pharmacy, Monroe Carell Jr Children's Hospital at Vanderbilt, Nashville, TN, USA

**Objective:** Previous reports suggest a benefit of fluconazole prophylaxis in extremely low birth weight (ELBW) infants <1000 g. Our aim was to evaluate if limiting fluconazole prophylaxis to targeted highest risk infants effectively prevents invasive fungal infections, has no undesired side effects and limits unnecessary drug exposure.

**Study Design:** This nonrandomized retrospective pre-post intervention study compared two groups of infants: (1) Infants <26 weeks gestation and/or <750 g birth weight, requiring central vascular access and admitted to the Monroe Carell Jr Children's Hospital at Vanderbilt neonatal intensive care unit (NICU) prior to 5 days of age, who received fluconazole prophylaxis and (2) a matched control group from the year prior to prophylaxis. This target population was selected for fluconazole prophylaxis based on prior infection control data from our institution and a number needed to treat of <15 to prevent one episode of fungemia. Following implementation and integration through the institution's computerized physician order entry (CPOE) system, provider adherence to the protocol was assessed during the prophylaxis period.

**Result:** A total of 86 patients were included in the study, 44 in the no-prophylaxis group and 42 in the prophylaxis group. In the targeted prophylaxis group, no invasive fungal infections were observed as compared to nine infants with invasive infections in the no-prophylaxis group ( $P = 0.004$ ). No significant adverse effects were recorded. Targeting the highest risk infants reduced the number of infants <1000 g requiring prophylaxis from 80 to 42 (48% reduction) with no preventable infection missed. Provider compliance was 91% following implementation of this protocol through the CPOE system using a standardized order set.

**Conclusion:** Targeting the highest risk infants for fluconazole prophylaxis through CPOE can effectively prevent invasive fungal infections and limit drug exposure with no unwanted side effects. *Journal of Perinatology* advance online publication, 10 January 2008; doi:10.1038/sj.jp.7211914

**Keywords:** infants; fungemia; candidiasis; fluconazole; prophylaxis; computerized physician order entry system

## Introduction

Invasive fungal infections are associated with significant morbidity and mortality among preterm infants cared for in the neonatal intensive care unit (NICU). Fungal organisms account for 12% of first episode late-onset sepsis in very low birth weight (VLBW) infants <1500 g, half of which are caused by *Candida albicans*. Surpassed only by coagulase negative *Staphylococcus* and *Staphylococcus aureus*, *Candida* species are the third most common cause of late-onset sepsis in VLBW infants.<sup>1</sup> The incidence of candidemia and associated mortality is inversely related to birth weight. Approximately 30% of extremely low birth weight (ELBW) infants <1000 g receive systemic antifungal therapy during their NICU course. Of those with positive blood cultures for *Candida*, up to one-third of VLBW and half of ELBW will die from complications of candidemia.<sup>1</sup>

Besides gestational age and birth weight, neonates in the intensive care unit are at higher risk for developing infection because of their immature immune systems, gastrointestinal pathology, exposure to H2 blockers (famotidine, ranitidine), long term use of central vascular catheters, use of total parenteral nutrition (TPN), use of third-generation cephalosporins and need for mechanical ventilation.<sup>2–4</sup> Early colonization of the skin and mucous membranes with *Candida* species can progress to candidemia in up to 60% of ELBW infants.<sup>5–7</sup> In addition to

Correspondence: Dr J-H Weitkamp, Division of Neonatology, Department of Pediatrics, Monroe Carell Jr Children's Hospital at Vanderbilt, 1125 MRB IV/Light Hall, 2215 B Garland Avenue, Nashville, TN 37232-0656, USA.  
E-mail: hendrik.weitkamp@vanderbilt.edu  
Received 16 July 2007; revised 30 October 2007; accepted 28 November 2008

mortality, neonatal candidemia has been associated with increased NICU lengths of stay and hospital costs.<sup>8</sup>

Kaufman *et al.*<sup>7</sup> published the only prospective, randomized, double-blind clinical trial to date that demonstrates effectiveness and safety of fluconazole administration in preventing fungal colonization and invasive fungal infection in ELBW infants during the first 6 weeks of life. Later, the same group suggested a twice weekly dosing protocol with similar efficacy but decreased cost and less drug exposure.<sup>9</sup> In addition to reducing the incidence of invasive *Candida* infections, some reports suggested that prophylactic intravenous fluconazole may reduce mortality in high-risk infants.<sup>10,11</sup> In contrast, many other studies did not find a difference in overall mortality,<sup>7,9,12–14</sup> including a recent multicenter trial.<sup>15</sup> Concerns about development of azole resistance and unwanted drug side effects remain. One study reported an association between fluconazole use and a higher incidence of cholestasis.<sup>16</sup>

Based on the 2004/2005 microbiology data from our own institution, the incidence of invasive *Candida* infections was 10% in ELBW infants with an incidence of 6.8% for candidemia. All infected ELBW infants in that year were <26 weeks gestational age and/or <750 g birth weight. Previous reports suggest a benefit of fluconazole prophylaxis in ELBW infants <1000 g at high risk of fungal infections.<sup>7</sup> But instead of adopting a fluconazole prophylaxis protocol used by others,<sup>9</sup> we followed the recommendation by McGuire *et al.*<sup>17</sup> to select a target population that would benefit most from fluconazole prophylaxis. For infants <26 weeks gestational age and/or <750 g birth weight, we calculated a number needed to treat of 12 to prevent one episode of fungemia and 26 to prevent one death from fungemia. We integrated the prophylaxis protocol as part of an admission order set through our computerized provider order entry (CPOE) system. The purpose of this study was to evaluate the effectiveness and safety of limiting fluconazole exposure to the highest risk preterm infants admitted to our NICU.

## Methods

### *Study design*

This study was a nonrandomized retrospective pre-post intervention study. Two groups of infants were compared: (1) Infants <26 weeks gestation and/or <750 g birth weight, requiring central vascular access, and admitted prior to 5 days of age, who received fluconazole prophylaxis and (2) a matched historical control group from the year prior to prophylaxis. The primary outcome of interest was if implementing a fluconazole prophylaxis protocol targeting only highest risk infants will be (1) effective, (2) safe and (3) prevent unnecessary drug exposure. Provider compliance using the CPOE-integrated standardized order set was evaluated as a secondary outcome.

### *The prophylaxis protocol*

In Fall 2005, a fluconazole prophylaxis protocol was implemented in the NICU and integrated through the CPOE system as a standardized order set. All infants admitted to our NICU were eligible for fluconazole prophylaxis if they were <26 weeks gestation or <750 g, less than 5 days old and required central vascular access as an additional risk factor. The presence of liver failure was the only exclusion criterion. Fluconazole was administered intravenously at 3 mg kg<sup>-1</sup> twice weekly starting on the first day of admission for up to 6 weeks. Hepatic (aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), total and conjugated bilirubin), hematologic (white blood count and differential, platelet count) and renal function (blood urea nitrogen (BUN), creatinine) were screened weekly while receiving fluconazole. Prophylaxis was discontinued when central vascular access was no longer needed and removed or if an infant received empiric antifungal therapy for more than 48 h, if AST or ALT values were higher than 250 IU l<sup>-1</sup>, or if the infant was transferred to another institution, was discharged or died.

### *Comparison between the prophylaxis and no-prophylaxis periods*

All patients admitted to our NICU between 1 November 2005 and 31 October 2006 that met inclusion criteria for the prophylaxis protocol were identified. The no-prophylaxis cohort was a historical control that included patients meeting the same protocol criteria 1 year prior to prophylaxis. The prophylaxis cohort included all infants eligible for fluconazole prophylaxis 1 year after implementation of the protocol. The electronic medical record of each eligible infant in both cohorts was reviewed for demographics, need for antifungal treatment, use of antimicrobials, TPN days, laboratory monitoring, microbiological culture data and outcomes. Additionally, care provider compliance through a CPOE-integrated fluconazole protocol was evaluated. The study was approved by the Vanderbilt Institutional Review Board.

### *Computer systems*

CPOE was implemented in the NICU in March of 2003. The computer system was originally developed in 1994 by the faculty in the Department of Biomedical Informatics at Vanderbilt University and is now marketed as the Horizon Expert Orders system (McKesson, Atlanta, GA, USA). This system currently interfaces with the pharmacy computer system, Horizon Medications Manager and automated dispensing machines. The system provides decision support and dosing recommendations based on the patient's weight, gestational or postnatal age, location and indication. Additionally, the CPOE system offers a number of individualized order sets. To date, there are 56 NICU specific order sets available and at least 95% of medications ordered go through advanced decision support. As described in this article, the fluconazole prophylaxis protocol was added to the ELBW admission order set. Upon admission, the care provider selects the ELBW order set in the

CPOE system and is prompted to order diagnostic, monitoring and medication therapy based on unit-specific evidence-based protocols for ELBW infants.

*Statistical analysis*

We examined the difference between the no-prophylaxis and prophylaxis groups in birth weight and gestational age using the two-sample *t*-test statistics. The numbers of central lines, ventilator days, antibiotics and TPN days for each group were examined by using a likelihood ratio test statistic in a generalized linear model assuming a negative binomial distribution. The dichotomous variables, sex and survival were tested using the  $\chi^2$ -test statistic. We used a Fisher's exact test to compare the rates of invasive infections between the no-prophylaxis and prophylaxis groups. The safety variables were investigated by use of a repeated measures analysis of variance. This study was not powered to detect differences, or to establish equivalency between the no-prophylaxis and prophylaxis groups; therefore, not detecting differences does not statistically imply group equivalency. All analyses were performed using SAS version 9.1 (SAS Inc., Cary, NC, USA) and R (<http://www.Rproject.org>).

**Results**

Patient population characteristics for each group are listed in Table 1. There were no statistically significant differences between the study groups in the no-prophylaxis and prophylaxis periods. Broad-spectrum antimicrobials usage within the first 6 weeks of life is shown in Table 2.

*Comparison of invasive fungal infection rates and mortality between no-prophylaxis and prophylaxis periods*

A total of 44 infants were admitted within 5 days of age in the no-prophylaxis period who were <26 completed weeks gestational age and/or <750 g birth weight. We compared this group of infants with 42 similar highest risk infants that received fluconazole in the prophylaxis period. In the no-prophylaxis period, 9 of 44 (20%) infants developed invasive fungal infections

(candidemia, urinary tract infection and/or peritonitis) and all but one infection occurred within the first 6 weeks of life. Seven patients had positive cultures from more than one site accounting for the total number of 14 invasive fungal cultures (Table 3). All infections were caused by *Candida* species except for one. This patient with *Malassezia pachydermatitis* urinary tract infection was included in the analysis because the infant was symptomatic and received systemic antifungal therapy. A total of 5 (11.4%) of the 44 infants in the no-prophylaxis period developed candidemia, diagnosed between 1 and 6 weeks of age. One of these infants died from *Candida* sepsis within the first 36 h of life, suggesting congenital infection. *C. albicans* accounted for all but one *Candida* infection which was caused by *C. parapsilosis*. The overall mortality in this cohort of infants was 20% (9 of 44). One death was directly attributable to *Candida* infection (11%, 1 of 9). More than twice as many infants in the no-prophylaxis group received empiric antifungal therapy (11 of 44 (25%)) as compared to the prophylaxis group (5 of 42 (12%)).

All five patients with candidemia were evaluated for organ dissemination by echocardiography and ophthalmologic examination. Cardiac or retinal involvement was not documented. Two of these patients had spinal fluid evaluation and *Candida* meningitis was not detected. All eight patients with fungal urinary tract infection were evaluated by renal ultrasound. The only end organ involvement noted was possible fungal material in the renal collection system of two patients, which resolved within 2 weeks.

In the prophylaxis period, 42 infants were eligible for fluconazole prophylaxis based on the criteria of <26 completed weeks gestational age or <750 g birth weight and admission within 5 days of age plus need for central vascular access. All of these infants (100%) received prophylaxis according to our protocol. The mean length of prophylaxis was 3.7 weeks with a range of 1–9 weeks. No infant was diagnosed with invasive fungal infection within the first 6 weeks of life. Five (12%) infants received empiric antifungal therapy within the first 6 weeks of life for a maximum of 15 days. All cultures remained negative. A total of 11 infants died

**Table 1** Study population characteristics as means (s.d.) or percent (*n*)

	No-prophylaxis (n = 44)	Prophylaxis (n = 42)	P-value
Birth weight	698 (134.3)	669 (106.0)	0.24
Gestational age	25 (1.2)	25 (1.5)	0.88
Ventilator days	26 (24.5)	19 (21.1)	0.17
TPN days	32 (23.7)	33 (27.7)	0.72
Central line days	32 (26.9)	31 (34.3)	0.88
Male sex	50% (24)	43% (20)	0.52
Survival	73% (35)	67% (31)	0.65

Abbreviation: TPN, total parenteral nutrition.

**Table 2** Number of patients that received broad-spectrum antimicrobials in first 6 weeks of life

	No-prophylaxis (n = 44)	Prophylaxis (n = 42)	P-value
Third-generation cephalosporin	14	6	0.05
Cefepime	18	13	0.10
Vancomycin	32	30	0.89
Piperacillin–tazobactam	3	8	0.09
Meropenem	0	3	0.11

**Table 3** Breakdown of invasive fungal infections

Patient	Sites and species of positive fungal cultures			Fluconazole MICs <sup>a</sup>	Length of treatment (days) <sup>b</sup>
	Blood	Urine	Peritoneal fluid		
1	—	<i>C. albicans</i>	—	0.25 (S)	48
2	—	<i>C. albicans</i>	—	ND	13
3	<i>C. albicans</i>	<i>C. albicans</i>	<i>C. albicans</i>	0.25 (S)	54
4	—	<i>C. albicans</i>	—	≤ 0.12 (S)	30
5	<i>C. albicans</i>	—	—	ND	2 <sup>c</sup>
6	<i>C. albicans</i>	<i>C. albicans</i>	—	≤ 0.12 (S)	28
7	<i>C. parapsilosis</i>	<i>C. parapsilosis</i>	—	2.0 (S)	20
8	<i>C. albicans</i>	<i>C. albicans</i>	—	ND	35
9	—	<i>M. pachydermatitis</i>	—	ND	8

Abbreviations: MIC, minimum inhibitory concentrations; ND, not done; S, sensitive.

<sup>a</sup>MIC in  $\mu\text{g ml}^{-1}$ .

<sup>b</sup>Total treatment days including treatment with amphotericin and fluconazole.

<sup>c</sup>Patient died of *Candida* sepsis within 36 hours of life.

during the course of their hospitalization, resulting in a total mortality rate of 26% (11 of 42). None of these deaths was associated with fungemia.

#### Provider compliance

Provider compliance with the CPOE-integrated fluconazole prophylaxis protocol was 91%, because two patients were given fluconazole prophylaxis outside the CPOE order set. These two patients received a near-therapeutic dose of  $5 \text{ mg kg}^{-1}$  twice weekly, but appropriate prophylaxis dosing of  $3 \text{ mg kg}^{-1}$  was achieved 100% of the time when the standardized admission order set was used. Duration of therapy was continued beyond 6 weeks in two patients based on clinical judgment. For both patients, continuation of central venous access and use of broad-spectrum antibiotics were likely reasons for the extended duration of 8 and 9 weeks, respectively.

#### Limiting drug exposure by targeting highest risk infants

Previous reports on the benefit of fluconazole prophylaxis targeted infants <1000 g birth weight.<sup>7,9,10</sup> In our protocol, patients with a birth weight between 750 and 1000 g were not included unless they were less than 26.0 weeks gestational age. Using the same prophylaxis protocol entry criteria for infants between 750 and 1000 g birth weight, 47 additional infants would have been targeted for fluconazole prophylaxis between 1 November 2005 and 31 October 2006. Nine infants in this group received prophylaxis based on the <26 completed weeks gestational age criteria, but 38 did not. Only one of these infants developed candidemia, which was uncomplicated and resolved after systemic treatment with fluconazole. This infant had a birth weight of 970 g and had a gestational age of 26 weeks and 6 days. A central line was placed at 4.5 weeks of life for persistent feeding intolerance. Fungal infection occurred at 8 weeks of life, a period not covered by the protocol.

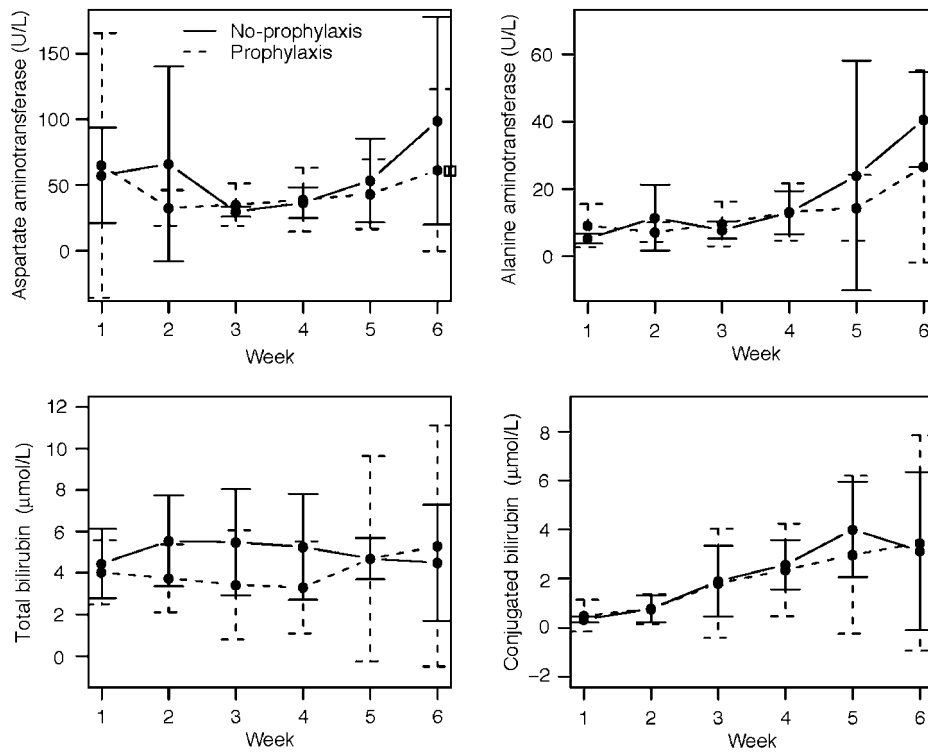
Therefore, the modified protocol avoided treatment of 38 infants with fluconazole without missing a preventable infection in the first 6 weeks of life, a period when ELBW infants are most susceptible to complications from invasive fungal infections.

#### Evaluation of undesired side effects

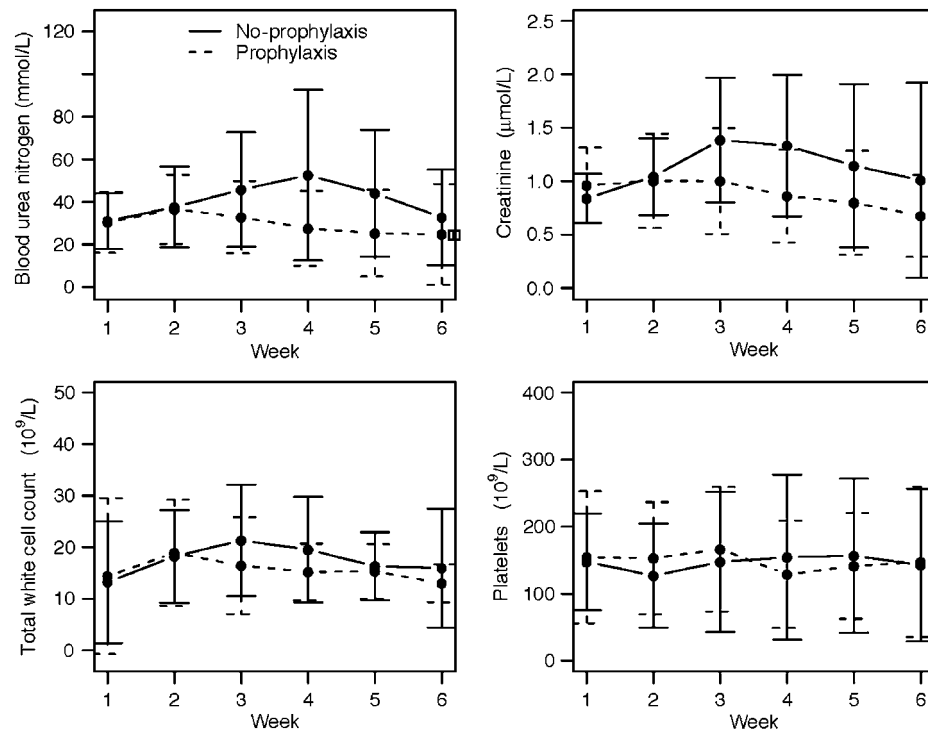
A recent study suggests that fluconazole prophylaxis may be associated with a higher risk for cholestasis in preterm infants <1000 g.<sup>16</sup> As part of our protocol, hepatic function tests (AST, ALT, total bilirubin and conjugated bilirubin), serum creatinine, BUN, platelets and complete blood count with differential were ordered weekly for patients receiving fluconazole prophylaxis. We compared the no-prophylaxis and prophylaxis groups to identify unwanted side effects associated with fluconazole prophylaxis and found no differences (Figures 1 and 2). Although laboratory tests to monitor for unwanted side effects of fluconazole coincided with weekly monitoring of TPN tolerance, we detected a small but statistically significant increase in the number of hepatic function tests performed in the prophylaxis group (162 versus 122). There was no statistically significant difference in the number of hematologic or renal function tests between the two groups.

#### Discussion

Results from several single-center studies and one multicenter trial suggest that fluconazole prophylaxis for high-risk preterm infants significantly lowers the incidence of invasive *Candida* infections.<sup>7,9–12,14,15,18</sup> In solid organ and bone marrow transplant patients, antifungal prophylaxis with fluconazole has been successfully used for years to prevent colonization and infection due to *Candida* species and markedly reduced the need for empiric amphotericin B therapy.<sup>19,20</sup> However, because of the lack of larger multicenter randomized trials and data on long-term



**Figure 1** Line plots with mean and standard deviations for each time point for hepatic function tests by no-prophylaxis (solid line) and prophylaxis (broken line) group. The upper error bars for alanine aminotransferase (2 weeks) for both groups are on top of each other.



**Figure 2** Line plots with mean and standard deviations for each time point for hematologic and renal function tests by no-prophylaxis (solid line) and prophylaxis (broken line) group. The lower error bars for creatinine (1 week) for both groups are on top of each other.

neurodevelopmental outcomes as well as concerns about unwanted side effects and development of *Candida* resistance, fluconazole prophylaxis in high-risk infants remains controversial.<sup>16,17,21–23</sup>

A fluconazole prophylaxis protocol for preterm infants did not exist in our NICU prior to Fall 2005. At that time, we reviewed the incidence and mortality of fungemia in high-risk infants in our unit and designed a targeted fluconazole prophylaxis protocol for infants at highest risk to prevent early death from fungemia. We predicted that implementation of such a protocol via the CPOE system would improve care provider compliance. After 1 year, we retrospectively reviewed the data and conclude that the fluconazole protocol for infants <26 weeks or <750 g admitted to the NICU within 5 days of life and requiring central access was safe and effective in preventing fungemia, although the overall mortality through hospital discharge in these highest risk infants was not affected. Limiting fluconazole prophylaxis to the highest risk infants less than 26 completed weeks gestation or less than 750 g reduced unnecessary drug exposure in larger ELBW infants. However, one infant with 970 g birth weight and central line access had uncomplicated candidemia at 8 weeks of life. Two infants in the prophylaxis group received fluconazole for 8 and 9 weeks, respectively. Therefore, eligible infants with remaining risk factors may benefit from extended fluconazole prophylaxis.

Our study has a number of limitations. One is the retrospective study design. Additionally, many changes have occurred with the standard of care in NICUs that may have also reduced the risk of systemic fungal infection.<sup>24</sup> Possibilities include more aggressive hand washing practices, decreased utilization of broad-spectrum antibiotics, TPN, H2 receptor blockers or corticosteroids, more intense glycemic control and limited use of invasive central catheterization. For instance, in our NICU, we adhere to infection control measures and discourage the use of H2 receptor blockers and third-generation cephalosporins in high-risk infants. The routine implementation of such measures may result in a more important reduction of systemic infections than fluconazole prophylaxis, though none of these associations has been subjected to a randomized control trial. Although statistically not significant, we did find a marked reduction in the use of third-generation cephalosporins between the two cohorts (Table 2).

A limitation of the methods used in this study is that results of pre-post studies can sometimes be explained by the statistical principle of regression to the mean. In addition, maturation effects are a threat to the validity of pre-post studies. These effects are related to the natural changes that occur with time. We tried to control for this phenomenon by choosing a historical control group from the same unit that experienced a very similar exposure 1 year prior to implementation of the fluconazole prophylaxis protocol. However, multiple confounding variables besides the ones collected could explain the different infection rates in the two periods.

We did not routinely monitor for fungal colonization and development of antifungal resistance. However, we did not observe

emergence of resistance in *Candida* isolates sent for fluconazole sensitivity and did not witness breakthrough infections during the prophylaxis period. Although emergence of antifungal resistance should be monitored, thus far *Candida* blood stream infections in NICUs with species other than *C. albicans* or *C. parapsilosis* are rare in contrast to adult surgical intensive care units.<sup>25</sup> Moreover, a recent analysis of the incidence of *Candida* bloodstream infections among ELBW infants in the United States between 1995 and 2004 reported no increase in infections by species that tend to demonstrate resistance to fluconazole (*Candida glabrata* or *Candida krusei*).<sup>24</sup> This is consistent with results from a recent study in adult patients suggesting that prior use of vancomycin or piperacillin-tazobactam, but not fluconazole, is associated with subsequent increase in nosocomial non-albicans candidemia.<sup>26</sup>

Fluconazole has an excellent safety profile in children<sup>27</sup> and we did not observe any untoward side effects in the fluconazole prophylaxis group, such as increases in conjugated bilirubin. This is in contrast to a study by Aghai *et al.*<sup>16</sup> who found a transient but significant increase in conjugated hyperbilirubinemia in the fluconazole prophylaxis group. One explanation for this difference could be that we used a twice weekly dosing protocol in contrast to the more frequent dosing protocol used by Aghai *et al.* Additionally, our study was not powered to detect statistically significant differences in this specific outcome. However, given the large standard deviations, very large sample sizes of this small subgroup of highest risk infants would be needed to detect differences, if they exist.

In conclusion, the fluconazole prophylaxis protocol adopted at our institution was safe and effective in infants <26 weeks and <750 g admitted to the NICU within 5 days of life requiring central access. No adverse effects were seen. In addition, limiting prophylaxis to this subgroup of highest risk infants reduced unnecessary exposure to fluconazole. To our knowledge, this study is the first evaluation of a computerized standardized order set in pediatrics or more specifically the NICU. We found that a targeted fluconazole prophylaxis admission order set within the CPOE system assured correct dosing and established a >90% provider compliance.

More multicenter, randomized controlled trials comparing the dosage, efficacy and safety of fluconazole or other antifungal agents for neonatal fungal prophylaxis are needed. Until then, the use of antifungal prophylaxis in these patients should be accompanied by a careful risk/benefit evaluation and should be implemented only in specific populations that are at highest risk. Careful evaluation and monitoring is needed to ensure compliance with suggested protocols, safety, efficacy and resistance patterns.

### Acknowledgments

We thank Steven Steele, RN, for his assistance in data retrieval for this study. We thank Russell Waitman, PhD and the Vanderbilt WizOrder Team for their

continued CPOE support as well as William Walsh, MD and Judy Aschner, MD, for review of the manuscript and helpful discussions. This study has been acknowledged by the Vanderbilt Infection Prevention (VIP) award to one of the authors (JHW).

## References

- 1 Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA *et al*. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. *Pediatrics* 2002; **110**: 285–291.
- 2 Feja KN, Wu F, Roberts K, Loughrey M, Nesin M, Larson E *et al*. Risk factors for candidemia in critically ill infants: a matched case-control study. *J Pediatr* 2005; **147**: 156–161.
- 3 Saiman L, Ludington E, Pfaller M, Rangel-Frausto S, Wiblin RT, Dawson J *et al*. Risk factors for candidemia in Neonatal Intensive Care Unit patients. The National Epidemiology of Mycosis Survey Study Group. *Pediatr Infect Dis J* 2000; **19**: 319–324.
- 4 Benjamin Jr DK, Ross K, McKinney Jr RE, Benjamin DK, Auten R, Fisher RG. When to suspect fungal infection in neonates: a clinical comparison of *Candida albicans* and *Candida parapsilosis* fungemia with coagulase-negative staphylococcal bacteremia. *Pediatrics* 2000; **106**: 712–718.
- 5 Baley JE, Kliegman RM, Boxerbaum B, Fanaroff AA. Fungal colonization in the very low birth weight infant. *Pediatrics* 1986; **78**: 225–232.
- 6 Saiman L, Ludington E, Dawson JD, Patterson JE, Rangel-Frausto S, Wiblin RT *et al*. Risk factors for *Candida* species colonization of neonatal intensive care unit patients. *Pediatr Infect Dis J* 2001; **20**: 1119–1124.
- 7 Kaufman D, Kaufman D, Boyle R, Hazen KC, Patrie JT, Robinson M *et al*. Fluconazole prophylaxis against fungal colonization and infection in preterm infants. *N Engl J Med* 2001; **345**: 1660–1666.
- 8 Smith PB, Morgan J, Benjamin JD, Fridkin SK, Sanza LT, Harrison LH *et al*. Excess costs of hospital care associated with neonatal candidemia. *Pediatr Infect Dis J* 2007; **26**: 197–200.
- 9 Kaufman D, Boyle R, Hazen KC, Patrie JT, Robinson M, Grossman LB. Twice weekly fluconazole prophylaxis for prevention of invasive *Candida* infection in high-risk infants of <1000 grams birth weight. *J Pediatr* 2005; **147**: 172–179.
- 10 Healy CM, Baker CJ, Zaccaria E, Campbell JR. Impact of fluconazole prophylaxis on incidence and outcome of invasive candidiasis in a neonatal intensive care unit. *J Pediatr* 2005; **147**: 166–171.
- 11 Bertini G, Perugi S, Dani C, Filippi L, Pratesi S, Rubaltelli FF. Fluconazole prophylaxis prevents invasive fungal infection in high-risk, very low birth weight infants. *J Pediatr* 2005; **147**: 162–165.
- 12 Manzoni P, Arisio R, Mostert M, Leonessa M, Farina D, Latino MA *et al*. Prophylactic fluconazole is effective in preventing fungal colonization and fungal systemic infections in preterm neonates: a single-center, 6-year, retrospective cohort study. *Pediatrics* 2006; **117**: e22–e32.
- 13 McCrossan BA, McHenry E, O'Neil F, Ong G, Sweet DG. Selective fluconazole prophylaxis in high risk babies to reduce invasive fungal infection. *Arch Dis Child Fetal Neonatal Ed* 2007; **92**: F454–F458.
- 14 Uko S, Soghier LM, Vega M, Marsh J, Reinersman GT, Herring L *et al*. Targeted short-term fluconazole prophylaxis among very low birth weight and extremely low birth weight infants. *Pediatrics* 2006; **117**: 1243–1252.
- 15 Manzoni P, Stolli I, Pugni L, Decembrino L, Magnani C, Vetrano G *et al*. A multicenter, randomized trial of prophylactic fluconazole in preterm neonates. *N Engl J Med* 2007; **356**: 2483–2495.
- 16 Aghai ZH, Mudduluru M, Nakhla TA, Amendolia B, Longo D, Kemble N *et al*. Fluconazole prophylaxis in extremely low birth weight infants: association with cholestasis. *J Perinatol* 2006; **26**: 550–555.
- 17 McGuire W, Clerihew L, Austin N. Prophylactic intravenous antifungal agents to prevent mortality and morbidity in very low birth weight infants. *Cochrane Database Syst Rev* 2004; (1): CD003850.
- 18 Martinez Sesmero JM, Farfan Sedano FJ, Molina Garcia T, Brussi MM, Sanchez-Rubio Ferrandez J, Diez Fernandez R *et al*. Fungal chemoprophylaxis with fluconazole in preterm infants. *Pharm World Sci* 2005; **27**: 475–477.
- 19 Alangaden G, Chandrasekar PH, Bailey E, Khaliq Y. Antifungal prophylaxis with low-dose fluconazole during bone marrow transplantation. The Bone Marrow Transplantation Team. *Bone Marrow Transplant* 1994; **14**: 919–924.
- 20 Playford EG, Webster AC, Sorell TC, Craig JC. Antifungal agents for preventing fungal infections in solid organ transplant recipients. *Cochrane Database Syst Rev* 2004; (3): CD004291.
- 21 Burwell IA, Kaufman D, Blakely J, Stoll BJ, Fridkin SK. Antifungal prophylaxis to prevent neonatal candidiasis: a survey of perinatal physician practices. *Pediatrics* 2006; **118**: e1019–e1026.
- 22 Long SS, Stevenson DK. Reducing *Candida* infections during neonatal intensive care: management choices, infection control, and fluconazole prophylaxis. *J Pediatr* 2005; **147**: 135–141.
- 23 Fanaroff AA. Fluconazole for the prevention of fungal infections: get ready, get set, caution. *Pediatrics* 2006; **117**: 214–215.
- 24 Fridkin SK, Kaufman D, Edwards JR, Shetty S, Horan T. Changing incidence of *Candida* bloodstream infections among NICU patients in the United States: 1995–2004. *Pediatrics* 2006; **117**: 1680–1687.
- 25 Rangel-Frausto MS, Wiblin T, Blumberg HM, Saiman L, Patterson J, Rinaldi M *et al*. National epidemiology of mycoses survey (NEMIS): variations in rates of bloodstream infections due to *Candida* species in seven surgical intensive care units and six neonatal intensive care units. *Clin Infect Dis* 1999; **29**: 253–258.
- 26 Lin MY, Carmeli Y, Zumsteg J, Flores EL, Tolentino J, Sreeramouju P *et al*. Prior antimicrobial therapy and risk for hospital-acquired *Candida glabrata* and *Candida krusei* fungemia: a case-case-control study. *Antimicrob Agents Chemother* 2005; **49**: 4555–4560.
- 27 Novelli V, Holzel H. Safety and tolerability of fluconazole in children. *Antimicrob Agents Chemother* 1999; **43**: 1955–1960.