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Targeted Short-Term Fluconazole Prophylaxis Among Very Low Birth Weight and Extremely Low Birth Weight Infants

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ABSTRACT

OBJECTIVES. To assess whether targeted short-term fluconazole prophylaxis reduces late-onset (>3 days of age) invasive fungal infection (IFI) among very low birth weight infants and extremely low birth weight (ELBW) infants and to assess mortality rates, toxicity, and costs associated with this intervention.

METHODS. An observational study of 2 subsequent epochs of inborn infants with birth weight of <1500 g or gestational age of <32 weeks, 1 before (control) and 1 after (fluconazole) initiation of routine targeted fluconazole prophylaxis in March 2003, was performed. Targeted fluconazole (3 mg/kg) prophylaxis was administered to infants for whom a decision was made to administer broad-spectrum antibiotics for >3 days.

RESULTS. IFI was observed for 13 (6.3%) of 206 infants in the control epoch and 2 (1.1%) of 178 in the fluconazole epoch, with a common odds ratio of 0.166. Logistic regression analysis taking into account all published factors (except for fungal colonization) showed that the fluconazole epoch was associated significantly with lower IFI rates. We observed no change in late (>3 days) mortality rates (11 of 206 infants in the control epoch vs 8 of 178 infants in the prophylaxis epoch). The mortality rate for ELBW infants with IFI was low (15%) in our study. Fluconazole was administered to 81% of ELBW infants, who received a median of 8 doses, and 41% of larger infants, who received a median of 5 doses. The intervention was cost-effective, and the effective number needed to treat to prevent 1 IFI was 10.

CONCLUSIONS. This study suggests that targeted short-course fluconazole prophylaxis in very low birth weight and ELBW infants may be efficacious and cost effective.
Fungal sepsis or other invasive fungal infection (IFI) occurs for 2% to 4% of very low birth weight (VLBW) infants (birth weight [BW]: <1500 g) and 10% of extremely low BW (ELBW) infants (BW: <1000 g). Factors associated with late (>3 days of age) IFI among neonates in at least some multivariate analyses include low gestational age (GA) (GA <28 weeks, especially <25 weeks), ELBW, severe illness at birth, duration of antibiotic administration, use of third-generation cephalosporins and carbapenems, central line, umbilical venous catheter in place for >7 days, mechanical ventilation, intravenous parenteral nutrition for >5 days, intravenous lipid infusion for >7 days, fungal colonization, time to full enteral feeding containing breast milk of >2 weeks, use of histamine receptor subtype 2 antagonists, necrotizing enterocolitis (NEC), bowel perforation, and thrombocytopenia. It is important to note the tremendous variability in risk factors among studies. Empirical therapy pending culture results may be justified if the infant meets specific criteria, because of high attributable mortality rates (21–32%), acute and long-term neurodevelopmental morbidity associated with IFI, and lack of specificity of clinical presentation. A study of a Norwegian national cohort of extremely premature infants showed that late-onset sepsis was associated with high Clinical Risk Index for Infants (CRIB) scores, an umbilical venous catheter in situ for 7 days, and time of achievement of full enteral feeding with human breast milk, with an adjusted relative risk (RR) of 3.7 (95% confidence interval [CI]: 2.0–6.9) for late-onset sepsis if full enteral feeding (with the infant’s own mother’s milk or banked breast milk) was not established within the second week of life. Fungal sepsis was observed for all 5 deaths among 19 infants with NEC or perforation in that study. Data from the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network NICUs showed that center differences in Candida IFI rates (ranging from 2.4% to 20.4% among ELBW infants) were at least in part related to a strong association between candidemia among ELBW infants and prolonged antibiotic administration.

Prophylaxis of IFI has been proposed for several populations at risk, including neutropenic patients with cancer, patients with HIV, solid-organ transplant recipients, critically ill surgical patients, patients with chronic granulomatous disease, patients with previous invasive mycosis who need additional immunosuppression, and VLBW infants. One medication used commonly for prophylaxis is fluconazole. It is a fungal enzyme, compared with the mammalian enzyme. A survey showed that 34% of neonatologists in the United States routinely used some kind of antifungal prophylaxis, most often (66%) fluconazole.

Crude data obtained from our NICU database (L.M.S.) showed that the frequency of late IFI (defined as developing among patients surviving after 3 days of life) among VLBW infants was significantly greater at Weiler Hospital from September 1, 1998, to August 31, 2000, than in the NICHD network, in the absence of fungal prophylaxis. Early neonatal death occurred for 10 (5.9%) of 170 patients at Weiler Hospital, compared with 741 (10.7%) of 6956 patients in the NICHD network (P = .061). Late IFI developed for 17 (10.6%) of 160 patients at Weiler Hospital, compared with 160 (2.6%) of 6215 patients in the NICHD network. Although this difference reached statistical significance (P = 4 × 10^-5, χ^2 analysis), our late IFI rate was within the range (2.4–20.4%) observed for late candidemia among centers in the NICHD network.

These data were confirmed in a multivariate analysis that compared our data with those of the Vermont Oxford Neonatal Network for the 3-year period from 2002 to 2005. The adjusted odds ratio (OR) for IFI among VLBW infants (specifically, 501–1500 g), obtained as a standardized ratio (observed/expected), was 2.67 (95% CI: 1.91–3.42). Therefore, for a period of 4 years between 1998 and 2002, we had a frequency of IFI among these infants that was 2 to 4 times greater than expected. In March 2003, evidence-based analysis with the critically appraised topic method included a review of our own data and the Cochrane review by McGuire et al. On the basis of this analysis, all faculty members in the section of neonatology at Weiler Hospital and the quality improvement committee decided to initiate routine fluconazole prophylaxis. The purpose of this article is to report our experience with targeted fluconazole prophylaxis.

METHODS
Inclusion and Exclusion Criteria
We included all inborn infants with GA of <32 weeks or BW of <1500 g. Early-onset IFI, defined as a blood culture or spinal tap sample positive for fungus before 72 hours of life, was excluded from the analysis (see below).

Study Epochs
During the first (control) epoch (January 1, 2001, through December 31, 2002; n = 206 infants), we did not use fluconazole prophylaxis. During the second (fluconazole) epoch (July 1, 2003, through December 30, 2004; n = 178 infants), targeted fluconazole prophylaxis was used for all infants with GA of <32 weeks or BW of <1500 g.

Targeted Fluconazole Prophylaxis
We selected targeted fluconazole prophylaxis during periods of antibiotic administration of >3 consecutive days, thereby targeting high-risk patients while minimizing the duration of exposure to fluconazole. Fluconazole was administered intravenously over 30 minutes at a
dose of 3 mg/kg, at intervals ranging between every third day and every day, depending on postmenstrual age.20 Fluconazole administration was stopped if levels of both transaminases were >150 IU/L or if the direct bilirubin level was >5 mg/dL, and the interval of administration was adjusted for patients with renal failure.

Patients with suspected IFI (thrombocytopenia, tracheal yeast colonization, or cutaneous yeast infection associated with clinical deterioration) received a blood culture, urine culture, and spinal tap and received amphotericin (or any appropriate medication for the infection) for 5 days, pending culture results. Those with proven IFI received amphotericin (or any appropriate medication, on the basis of sensitivity, end-organ damage, and response to therapy) for ≥3 weeks.

Outcome Variables
The primary outcome variable was IFI, defined as a blood, cerebrospinal fluid, or urine culture positive for fungus. Evidence for end-organ damage was assessed routinely with cultures as just described, with head and abdomen ultrasound scans for assessment of the possibility of ventriculitis, brain abscess, or renal or hepato-splenic disease, and with echocardiograms and eye examinations for assessment of possible endophthalmitis.21

Secondary outcomes variables were secondary analysis of IFI, mortality rates, type of fungus, morbidity and specific mortality rates for IFI, toxicity (including maximal direct bilirubin and transaminase levels), cost analysis, and percentage of resistant strains among infected patients during the second epoch. Cost analysis was performed with the following variables: (1) cost of a premixed bag of fluconazole ($14.66), which can be used for a few doses if >1 infant in the NICU requires treatment at the same time; (2) cost of 1 day of hospitalization in a NICU ($3000); and (3) length of stay (LOS) and morbidity and mortality rates in our study.

Sample Size and Statistical Analyses
Statistical analyses of the primary outcome variable were performed with the intention-to-treat approach (ie, belonging to the fluconazole epoch versus the control epoch, regardless of whether the patient received fluconazole effectively). We used SPSS version 13 software (SPSS, Chicago, IL), 2-tailed tests, and P < .05 as the criterion for statistical significance. We performed a Cochran-Mantel-Haenszel $\chi^2$ analysis to assess the effect attributable to epoch, taking into account groups of BW (≥1000 g versus <1000 g).

Next, we performed a logistic regression analysis to test whether belonging to the fluconazole epoch reduced the odds of late IFI. In the first model, we entered all factors reported previously (except for fungal colonization, which was not available to us because surveillance fungal cultures were not obtained routinely in our NICU). To assess which variables were significant in our study, we removed, one by one, variables with the highest $P$ values until all variables had $P$ values of <.05. We checked the adequacy of the model with the Hosmer-Lemeshow goodness-of-fit statistic. We combined NEC and perforation, as well as GA groups of 23 to 24 and 25 to 27 weeks, into a single variable, to avoid collinearity. To test whether changes in infection control could in part explain changes in IFI rates, we used another model that included the numbers of episodes of proven bacterial sepsis (ie, with ≥1 positive blood or cerebrospinal fluid culture) and of clinical sepsis.

Sample size analysis was performed with Sample Power software (SPSS), with the assumption of a baseline (before introduction of fluconazole prophylaxis) IFI rate of 10%. With $\chi^2$ analysis, a $P$ value of .05, and a power of 0.80, we would need 138 patients in each epoch to detect an 80% reduction in the frequency of outcome (as reported in a systematic review of randomized trials of fluconazole prophylaxis among low BW infants),14 with 184 patients in each epoch being needed to reach a power of 90%.

Secondary Outcomes
We used $\chi^2$ analysis (Fisher’s exact test or Cochran-Mantel-Haenszel test) for dichotomous variables and Student’s $t$ test, analysis of variance, or Mann-Whitney test with exact probability for other variables. For variables skewed to the right for which a logarithmic transformation was either impossible (range included 0) or did not yield a Gaussian distribution, we used both the Mann-Whitney test and $\chi^2$ analysis. Values are presented as median (with interquartile range [IQR] or range) or mean ± SD.

Protection of Human Subjects
Fluconazole is not approved by the Food and Drug Administration for neonatal use, including prophylaxis of neonatal IFI. Initiation of fluconazole prophylaxis in our NICU was based on an observational quality improvement project and was not undertaken with the goal of obtaining approval of this drug for neonatal use. Therefore, we did not obtain an investigational new drug application. A recent survey showed that approximately one third of the neonatologists in the United States use routine antifungal prophylaxis for ELBW infants.10 Chart review for the multivariate analysis was conducted with approval from the Montefiore Medical Center institutional review board.

RESULTS
Demographic and Patient Characteristics
There was no significant difference in GA or BW between the 2 epochs (Table 1). CRIB scores, number of episodes of clinical sepsis and bacterial sepsis, and total duration of antibiotic therapy were lower in the second epoch than in the first epoch, and the frequency of NEC tended to increase during the second epoch. The percent-
age of infants with bacterial sepsis was significantly lower during the second epoch than during the first epoch, with a common OR of 0.581 (95% CI: 0.357–0.945; *P*/H11005 .028, Cochran test, adjusting for BW [<1 kg versus ≥1 kg]).

**Primary Outcome Variable**

**IFI Rates**

Late-onset IFI was observed for 15 infants, at a median age of 25 days (range: 7–94 days) (Tables 2–4). The frequency of IFI in the first epoch was significantly related to BW, ie, 0 of 30 patients of <1500 g, 2 (2.1%) of 95 patients of 1000 to 1499 g, and 4 (9.5%) of 749 to 999 g, and 7 (17.9%) of 750 g (<1 kg versus ≥1 kg). IFI was observed for 13 (6.3%) of 206 infants in the control epoch, compared with 2 (1.1%) of 178 in the second (fluconazole) epoch, with a common OR of 0.166 (95% CI: 0.033–0.709; *P*/H11005 .007, Cochran test, adjusting for BW [<1 kg versus ≥1 kg]).

**IFI Versus Published Factors**

Logistic regression taking into account all published variables (except for fungal colonization) showed that the

### TABLE 1  Demographic Features and Characteristics of Infants With GA of < 32 Weeks or BW of < 1500 g During the Control and Fluconazole Epochs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 206)</th>
<th>Fluconazole (n = 178)</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>BW, mean ± SD, g</td>
<td>1128 ± 377</td>
<td>1185 ± 408</td>
<td>NS</td>
</tr>
<tr>
<td>GA, mean ± SD, wk</td>
<td>28.4 ± 2.7</td>
<td>28.6 ± 3.1</td>
<td>NS</td>
</tr>
<tr>
<td>Male, %</td>
<td>52</td>
<td>48</td>
<td>NS</td>
</tr>
<tr>
<td>Hispanic, %</td>
<td>32</td>
<td>34</td>
<td>NS</td>
</tr>
<tr>
<td>Black, %</td>
<td>50</td>
<td>46</td>
<td>NS</td>
</tr>
<tr>
<td>White, %</td>
<td>14</td>
<td>17</td>
<td>NS</td>
</tr>
<tr>
<td>Asian, %</td>
<td>4</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Other race, %</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>CRIB score, median (IQR; range)</td>
<td>2 (1–6; 0–24)</td>
<td>1 (0–4; 0–18)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Bacterial sepsis episodes, median (IQR; range), no.</td>
<td>0 (0–1; 0–3)</td>
<td>0 (0–0; 0–3)</td>
<td>.040</td>
</tr>
<tr>
<td>Clinical sepsis episodes per patient, median (IQR; range), no.</td>
<td>1 (1–2; 0–6)</td>
<td>1 (1–2; 0–6)</td>
<td>.004</td>
</tr>
<tr>
<td>Duration of antibiotic therapy, median (IQR; range), d</td>
<td>8 (6–23; 0–87)</td>
<td>7 (3–22; 0–110)</td>
<td>.030</td>
</tr>
<tr>
<td>Duration of umbilical venous line, median (IQR; range), d</td>
<td>8 (0–9; 0–25)</td>
<td>0 (0–6; 0–30)</td>
<td>NS</td>
</tr>
<tr>
<td>Death during the first 3 d, no. (%)</td>
<td>8 (4)</td>
<td>9 (5)</td>
<td>NS</td>
</tr>
<tr>
<td>Death after the first 3 d, no. (%)</td>
<td>11 (5)</td>
<td>8 (4)</td>
<td>NS</td>
</tr>
<tr>
<td>NEC (modified Bell stage II or more), no. (%)</td>
<td>15 (7)</td>
<td>22 (12)</td>
<td>NS</td>
</tr>
<tr>
<td>Bowel perforation, no. (%)</td>
<td>7 (2)</td>
<td>7 (2)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS indicates not significant.

* Cochran-Mantel-Haenszel test, adjusting for BW.

### TABLE 2  Fungal Prevention and Infection Among Infants With GA of < 32 Weeks or BW of < 1500 g During the Control and Fluconazole Epochs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 206)</th>
<th>Fluconazole (n = 178)</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who received fluconazole prophylaxis, no. (%)</td>
<td>91 (51)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Doses of fluconazole (all infants), median (IQR; range), no.</td>
<td>1 (0–6; 0–60)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Doses of fluconazole (infants who received fluconazole), median (IQR; range), no.</td>
<td>6 (3–11; 2–60)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>IFI after the first 3 d, no. (%)</td>
<td>13 (6)</td>
<td>2 (1)</td>
<td>.007</td>
</tr>
<tr>
<td>Days on amphotericin, median (IQR; range), no.</td>
<td>0 (0.4; 0–54)</td>
<td>0 (0.0; 0–30)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Clinical fungal sepsis episodes per patients, median (IQR; range), no.</td>
<td>0 (0.0; 0–5)</td>
<td>0 (0.0; 0–1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Patients with direct bilirubin level of &gt; 5 mg/dL, no. (%)</td>
<td>24 (12)</td>
<td>8 (4)</td>
<td>.015</td>
</tr>
<tr>
<td>Maximal direct bilirubin level, median (IQR; range), mg/dL</td>
<td>0.9 (0.7–1.2; 0.2–21.2)</td>
<td>0.6 (0.5–1.0; 0.0–19.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Patients with SGOT level of &gt; 150 IU/L, no. (%)</td>
<td>18 (11)</td>
<td>7 (4)</td>
<td>.021</td>
</tr>
<tr>
<td>Maximal SGOT level, median (IQR; range), IU/L</td>
<td>34 (27.15–392)</td>
<td>30 (18–47; 0–811)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Patients with SGPT level of &gt; 150 IU/L, no. (%)</td>
<td>3 (2)</td>
<td>3 (2)</td>
<td>NS</td>
</tr>
<tr>
<td>Maximal SGPT level, median (IQR; range), IU/L</td>
<td>11 (9–18; 3–217)</td>
<td>10 (6–17; 0–239)</td>
<td>.007</td>
</tr>
<tr>
<td>Patients with both SGOT and SGPT levels of &gt; 150 IU/L, no. (%)</td>
<td>3 (2)</td>
<td>3 (2)</td>
<td>NS</td>
</tr>
<tr>
<td>Candida parapsilosis, no. (%) of patients</td>
<td>9/13 (69)</td>
<td>0/2 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Candida albicans, no. (%)</td>
<td>4/13 (31%)</td>
<td>1/2 (50)</td>
<td></td>
</tr>
<tr>
<td>Candida lusitaniae, no. (%)</td>
<td>0/13 (0)</td>
<td>1/2 (50)</td>
<td></td>
</tr>
<tr>
<td>Age at time of diagnosis of IFI, median (IQR; range), d</td>
<td>25 (11.5–38.5; 7–94)</td>
<td>22.5 (21–24; 21–24)</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of antibiotics at diagnosis, median (IQR; range), d</td>
<td>13 (7–32.5; 0–41)</td>
<td>22.5 (21–24; 21–24)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Many variables had a non-gaussian distribution, which was skewed to the right (see text for details). NA indicates not applicable; NS, not significant; SGOT, alanine aminotransferase; SGPT, aspartate aminotransferase.

* Cochran-Mantel-Haenszel test, adjusting for BW.

In addition, 1 patient had 2 episodes of IFI with *C. albicans* and another patient had simultaneously *C. parapsilosis* in the blood and *C. albicans* in the urine.
Multivariate Analysis of IFI Designed to Assess Whether There Was an Association Between Fluconazole Epoch and IFI

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoch (fluconazole versus control)</td>
<td>0.142 (0.025–0.806)</td>
<td>.028</td>
</tr>
<tr>
<td>GA of 23–27 wk versus ≥28 wk</td>
<td>3.511 (0.496–24.830)</td>
<td>.208</td>
</tr>
<tr>
<td>BW of &lt;1000 g</td>
<td>1.713 (0.206–14.228)</td>
<td>.618</td>
</tr>
<tr>
<td>CRB score</td>
<td>0.977 (0.817–1.171)</td>
<td>.813</td>
</tr>
<tr>
<td>Exposure to third-generation cephalosporin or carbapenem</td>
<td>0.149 (0.010–2.217)</td>
<td>.167</td>
</tr>
<tr>
<td>Total duration of antibiotic therapy</td>
<td>1.025 (0.989–1.062)</td>
<td>.175</td>
</tr>
<tr>
<td>Administration of histamine receptor subtype 2 antagonist</td>
<td>1.083 (0.196–5.978)</td>
<td>.927</td>
</tr>
<tr>
<td>NEC (modified Bell stage II or III) or intestinal perforation</td>
<td>3.970 (0.966–16.322)</td>
<td>.056</td>
</tr>
<tr>
<td>Time from birth to full enteral feeding containing breast milk of &gt;2 wk</td>
<td>4 × 10^3 (0–∞)</td>
<td>.995</td>
</tr>
<tr>
<td>Central line</td>
<td>0.349 (0.015–7.918)</td>
<td>.509</td>
</tr>
<tr>
<td>Artificial ventilation</td>
<td>4 × 10^3 (0–∞)</td>
<td>.994</td>
</tr>
<tr>
<td>Umbilical venous line placement for &gt;7 d</td>
<td>0.809 (0.191–3.418)</td>
<td>.773</td>
</tr>
<tr>
<td>Total parenteral nutrition for &gt;5 d</td>
<td>9 × 10^3 (0–∞)</td>
<td>.997</td>
</tr>
<tr>
<td>Intravenous lipid administration for &gt;7 d</td>
<td>0.121 (0.005–2.656)</td>
<td>.180</td>
</tr>
<tr>
<td>Model including only the variables that reached significance in our study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epoch (fluconazole versus control)</td>
<td>0.113 (0.022–0.577)</td>
<td>.009</td>
</tr>
<tr>
<td>Total duration of antibiotic therapy</td>
<td>1.030 (1.000–1.061)</td>
<td>.047</td>
</tr>
<tr>
<td>NEC (stage II or III) or intestinal perforation</td>
<td>4.764 (1.191–19.056)</td>
<td>.027</td>
</tr>
<tr>
<td>GA of 23–27 wk versus ≥28 wk</td>
<td>6.407 (1.241–33.064)</td>
<td>.027</td>
</tr>
</tbody>
</table>

Logistic regression analysis was performed by entering all factors shown in previous studies to be associated with IFI (except for fungal colonization).

### Secondary Outcome Variables

#### Mortality Rate

Fluconazole prophylaxis was not associated with any change in late (>3 days) mortality rates, ie, 11 (5.3%) of 206 patients in the control epoch and 8 (4.5%) of 178 patients in the fluconazole epoch (common OR: 0.795; 95% CI: 0.301–2.102; P = .644, Cochran test) or in total mortality rates, ie, 19 (9.2%) of 206 patients in the control epoch and 17 (9.6%) of 178 patients in the fluconazole epoch (common OR: 0.988; 95% CI: 0.473–2.066; P = .975).

#### Description of IFI

Among the 15 infected infants, 14 had positive blood cultures, 2 had positive urine cultures, 1 had a positive peritoneal culture, and 1 had a positive tracheal culture. All infants had thrombocytopenia but none had ventriculitis, endophthalmitis, endocarditis, or ultrasonographic evidence of fungal infection of the kidney or hepatosplenic abscess. One infant in the control epoch had 2 episodes of IFI with *Candida albicans*, 1 had *C albicans* only in the urine, and another 1 had simultaneously *Candida parapsilosis* in the blood and *C albicans* in the urine. Strains included *C albicans* (n = 7; 5 infants plus 1 infant with 2 episodes of IFI and 1 with *C albicans* in the urine and *C parapsilosis* in the blood), *C parapsilosis* (n = 9), and *Candida lusitaniae* (n = 1) (Table 2). Two ELBW infants with IFI died in the control epoch, 1 at day of IFI decreased during the fluconazole epoch, with an adjusted OR of 0.142 (95% CI: 0.025–0.806; P = .028; n = 384) (Table 3). After removal of all variables with P > .05 from this model, 4 variables had an independent association with IFI, ie, fluconazole epoch (adjusted OR: 0.113; 95% CI: 0.022–0.577; P = .009), NEC or perforation, total duration of antibiotic therapy, and GA of 23 to 27 weeks (Table 3).

### IFI Versus Infection Control

The numbers of cases of bacterial sepsis and clinical sepsis were entered into and kept in the model (n = 384) while other nonsignificant variables were removed (Table 4). Total duration of antibiotic therapy was removed for collinearity. Only 3 variables reached statistical significance, ie, fluconazole epoch, NEC or perforation, and GA of 23 to 27 weeks. The adjusted OR for IFI in the fluconazole epoch was 0.133 (95% CI: 0.023–0.762; P = .023).
9 after 2 days of amphotericin treatment (C albicans) and 1 on day 65 after 47 days of amphotericin treatment (C parapsilosis). The mortality rate for ELBW infants with IFI was low (15%) in our study, compared with previous reports (37–40%), presumably because of predominance of C parapsilosis in our study (9 of 15 patients, 60%; 9 of 17 isolates, 53%). The median duration of amphotericin therapy was 29 days (range: 2–54 days). All patients but 1 had received a third-generation cephalosporin, carbapenem, or both before the IFI, and the total duration of antibiotic treatment before IFI was 18.5 days (range: 0–41 days).

Cost Analysis
During the 18-month second epoch, we administered a total of 775 doses of fluconazole to 91 infants (51%) in the whole group (total cost: $11 361.50), including 566 doses to 68 ELBW infants (81%) (total cost: $8297.56) and 209 doses to 110 larger infants (41%) (total cost: $3063.94). Among ELBW infants who received fluconazole effectively, the median was 8 doses (IQR: 4–15 doses); among larger infants, the median was 5 doses (IQR: 3–8.5 doses). Among patients who survived >3 days (n = 365), there was no significant difference in LOS between the control and fluconazole epochs, after adjustment for BW and CRIB score. The LOS for patients with IFI was longer than that for patients without IFI, with a contrast estimate of 24.7 days (95% CI: 10.9–38.6 days; P = .001, after adjustment for BW and CRIB score), yielding an additional cost of 25 × $3000 = $75 000 for each IFI. The possible impact of fluconazole was estimated by comparing the rates of IFI between the 2 epochs in 2 BW subgroups. Among ELBW infants, the rate of IFI decreased during the fluconazole epoch (11 of 81 infants in the control epoch versus 2 of 68 infants in the fluconazole epoch; OR: 0.19; 95% CI: 0.04–0.90; P = .04); among infants of >1-kg BW, the rate did not change significantly (2 of 125 infants in the control epoch versus 0 of 110 infants in the fluconazole epoch: OR: 0.22; 95% CI: 0.01–4.71; not significant). The number needed to treat (NNT) (number of patients exposed to fluconazole to prevent 1 IFI) was estimated from the OR. The effective NNT values, calculated by multiplying the NNT by the proportion of those receiving fluconazole (51% for the whole group and 81% among ELBW infants), were 10 (95% CI: 8–35) and 8 (95% CI: 6–70), respectively. The estimated net savings were $663 638 (95% CI: $72 724–$1 291 388, taking into account the CIs for effective NNT values and for LOS contrast) for the whole group and $516 702 (95% CI: $17 862–1 072 502) for ELBW infants.

Toxicity and Emergence of Resistance
The frequencies of serum direct bilirubin levels of >5 mg/dL and of aspartate aminotransferase levels of >150 IU/L were significantly lower in the fluconazole epoch than in the control epoch (Table 2). Maximal direct bilirubin and transaminase levels were lower during the second epoch than during the first epoch (Table 2). The minimal inhibitory concentration (MIC) for fluconazole was available for 1 infected patient during the first epoch (C albicans, 0.25 μg/mL) and for 2 infected patients during the second epoch (C albicans, 1 μg/mL; C lusitaniae, 4.8 μg/mL). All strains were sensitive to amphotericin B.

DISCUSSION
Fluconazole is the most commonly (66%) used medication for fungal prophylaxis among ELBW infants. Although other prophylactic strategies have been used (eg, oral administration of antifungal agents such as nystatin, miconazole, or fluconazole), the numbers of subjects assigned randomly were much too small to allow any recommendation. In any case, a strategy based entirely on enteral prophylaxis might have limited use for high-risk ELBW infants, who are the ones with limited or no food intake.

The systematic review by McGuire et al showed that continuous fluconazole prophylaxis for 4 to 6 weeks reduces the risk for IFI among VLBW and ELBW infants. The systematic review included 3 single-site, randomized trials, in which 214 VLBW or ELBW infants were assigned randomly to receive either a 4- to 6-week course of fluconazole as prophylaxis against IFI or placebo. Altogether, fluconazole reduced significantly the risk for fungal colonization (RR: 0.45; 95% CI: 0.29–0.72) (without affecting triazole resistance), fungal sepsis (RR: 0.20; 95% CI: 0.07–0.64), and death (RR: 0.44; 95% CI: 0.21–0.91). However both McGuire et al in their systematic review and Neely and Schreiber in their editorial raised serious concerns about possible routine use of fluconazole prophylaxis, including (1) potential risks, such as development of fungal resistance, toxicity of fluconazole, and interference with the metabolism of other medications, and (2) cost. Kicklighter et al assigned randomly 103 VLBW infants, within the first 3 days of life, to receive either intravenously administered (enterally administered when the infant was receiving full enteral feeding) fluconazole (6 mg/kg) or placebo, administered every 72 hours during the first 7 days of life and then every 24 hours until day 28, to assess the effect of fluconazole on fungal colonization. Kaufman et al assigned randomly 100 ELBW infants who were either intubated or had a central venous catheter present in the first 5 days of life to receive either 3 mg/kg fluconazole or placebo every third day for the first 2 weeks, every other day during the third and fourth weeks, and every day during the fifth and sixth weeks. Cabrera et al assigned randomly 11 VLBW infants with fungal colonization to receive either 6 mg/kg fluconazole or placebo, given intravenously until intravenous access was no longer otherwise required. Death before hospital discharge, as reported in 2 of these tri-
als,23,24 occurred for 29 of 203 infants. Only the trial by Kaufman et al24 showed a significant reduction in fungal sepsis rate. Kaufman et al22 recently completed another randomized trial, which showed that twice-weekly administration of fluconazole for 6 weeks among high-risk ELBW infants yielded results that were similar to those achieved with the previous schedule; the authors observed no development of resistance to fluconazole among 81 patients during a 24-month period. Two studies with a before/after study design similar to our study, 1 with ELBW infants and 1 with VLBW infants, were published recently.28,29 Both studies showed significant efficacy of fluconazole prophylaxis in IFI; 1 showed a significant decrease in mortality rate, whereas the other showed a trend toward an increase in IFI rate among larger, more mature infants not exposed to fluconazole prophylaxis.28

The OR of IFI associated with the fluconazole epoch in our study was similar to the OR associated with the 4- to 6-week course in randomized, controlled trials reported by McGuire et al14 (OR: 0.18; 95% CI: 0.06–0.59). Targeted short-term fluconazole therapy may be as efficacious in reducing the risk of IFI as a 4- to 6-week continuous course but exposes only 51% of all infants and 80% of ELBW infants to fluconazole, for a shorter time. In our study, the median number of doses was 6 among infants of <1500 g or <32 weeks who received the medication effectively and the median was 8 among ELBW infants who received fluconazole, compared with 23 or 24 doses in the original studies by Kicklighter et al23 and Kaufman et al.24 12 doses in the recent trial by Kaufman et al,27 25 doses in the study by Healy et al,28 and 23 doses of 6 mg/kg in the study by Bertini et al.29 Therefore, targeted short-term fluconazole therapy, by reducing exposure and cost but not efficacy, is an attractive alternative, especially in the context of inter-NICU variability in rates of IFI.

We found no effect of fluconazole prophylaxis on mortality rates, in contrast to the systematic review by McGuire et al14 and the study by Healy et al.28 This may be explained by 2 factors. First, because most deaths in the study by Kicklighter et al23 were observed among patients who did not have IFI, direct causality of fluconazole prophylaxis in any trend of mortality rates is questionable; therefore, any effect of fluconazole on mortality rates in the review by McGuire et al,14 although statistically significant, must be considered with caution. Second, the mortality rate among ELBW infants with IFI was low (14%) in our study, compared with previous reports (37–40%),4 presumably because of predominance (60%) of C parapsilosis in our study. The neonatal mortality rate resulting from invasive infections with C parapsilosis was one half that for C albicans (9 of 42 patients, 21%; vs 27 of 63 patients, 43%),30,31 which reflects its low virulence.32 The 2 strains are equally sensitive to fluconazole.30 In contrast, in the study by Kaufman et al,24 C parapsilosis accounted for only 44.6% of the strains in the placebo group. Another putative factor could be a difference in the use of empiric amphotericin therapy between the study by Kaufman et al24 and our study. The report on empiric amphotericin therapy was published by Benjamin et al21 in 2003, ie, after the initiation of the randomized trial by Kaufman et al24 and after completion of our control epoch. Nevertheless, in our study, use of amphotericin B among VLBW infants decreased, rather than increased, during the fluconazole epoch. Finally, systematic reviews of fluconazole prophylaxis for a large number of patients with cancer and patients with solid-organ transplants showed reductions in IFI rates but no effect on mortality rates.12,13

Our study has several limitations. The first is that this is a small, single-site, retrospective study with historical controls. The standard method to assess whether fluconazole prophylaxis meets all of the criteria for prophylactic antimicrobial therapy26 is a multicenter, double-blind, randomized, controlled trial. The reason why we selected a before/after design for our study is described above; the high rate of IFI in our NICU led to a quality improvement decision to start fluconazole prophylaxis, and this study is an analysis of the efficacy and toxicity of this intervention. We selected a compromise between the desire to reduce IFI rates and the fear of toxicity with use of a 4- to 6-week course for all infants. In this retrospective study, to control for possible bias and confounding variables, we conducted a logistic regression analysis with all published significant factors for IFI. We realized that, with such a design, it was possible that ongoing attempts at limiting nosocomial infections might have reduced the rates of all infections, not only IFI. Therefore, we compared changes in rates of bacterial infections and IFI from the control epoch to the fluconazole epoch. There was a statistically significant, although small, difference in CRIB scores, numbers of episodes of bacterial sepsis and of clinical sepsis, and duration of antibiotic therapy between the first and second epochs. We found that fluconazole prophylaxis was associated with halving of the rate of bacterial infections and a sixfold reduction in the rate of IFI. Furthermore, the number of bacterial infections was not an independent factor for IFI in multivariate analysis in our study. The second limitation of our study is the lack of control for fungal colonization. Fungal colonization was reported as a significant factor for IFI in most23 but not all14,33 studies. Another limitation of our study is the lack of certitude about the absence of adverse effects such as toxicity, medication interference, and emergence of resistant organisms, because of the small sample size, retrospective design, and lack of assessment of fungal colonization. Among 562 children (from 12 clinical studies),34 58 (10.3%) reported 80 treatment-related adverse effects, affecting the gastrointestinal tract (7.7%), skin (1.2%), or liver/biliary system (0.5%); 18 patients
(3.2%) discontinued treatment because of primarily gastrointestinal tract symptoms, and 2% to 5% had transiently elevated liver enzyme levels. Fluconazole inhibits 2 cytochrome P-450 reactions, ie, CYP3A4 and CYP2C9, thereby potentially reducing the metabolism of many medications.\textsuperscript{35,36}

In our study, MIC data were available for only 3 strains, none of which showed an unusual sensitivity pattern. We searched the literature for randomized trials reporting the rate of resistance associated with fluconazole prophylaxis in other age groups. Our meta-analysis showed a control event rate among patients with cancer or HIV infection of 15.5% (36 of 233 patients) and suggested that prolonged fluconazole administration\textsuperscript{37–39} might increase the risk of resistance to 24.1% (47 of 195 patients), with a RR of 2.03 (95% CI: 1.40–2.95); however, the sample size yielded a power of only 65%. In a population-based study, only 1.2% of \textit{C albicans} (the most frequent fungus infecting neonates) isolates were resistant to fluconazole (MIC of >64 \text{\mu}g/mL), compared with 7% of \textit{Candida glabrata} isolates and 6% of \textit{Candida tropicalis} isolates.\textsuperscript{40} The sample size in the systematic review by McGuire et al\textsuperscript{14} (total \textit{N} = 214) was quite insufficient for detection of a doubling of resistance; the power was only 9%, even if a baseline resistance rate of 1% was assumed. Importantly, at the Karolinska Institute, resistance of \textit{C parapsilosis} emerged after 12 years of fluconazole use (1990–2001), after \textasciitilde1200 VLBW infants were exposed to fluconazole.\textsuperscript{41} The experience at the Karolinska Institute had 3 phases, ie, a long period with lack of resistance and low MIC for several years, a 2-year period with appearance of fungi with intermediate MIC (16–32 \text{\mu}g/mL), and a third period with complete resistance. In contrast, resistance may occur after prophylaxis as short as 2 weeks.\textsuperscript{42} Triazole resistance may develop in a stepwise manner\textsuperscript{41,43} and may result through \textasciitilde1 of the following mechanisms, ie, (1) a relative increase in \textit{Candida} species with intrinsic resistance, (2) mutations in the gene encoding theazole target, lanosterol demethylease (\textit{ERG11}), or increased expression of \textit{ERG11} and genes encoding multidrug efflux pumps, thereby lowering intracellular drug levels, or (3) differential expression of essential genes (eg, \textit{ERG10P}) involved in ergosterol synthesis.\textsuperscript{41–53}

Our retrospective study suggests that targeted short-course fluconazole prophylaxis (only during periods of antibiotic therapy of \textasciitilde3 days and limited to VLBW infants) might be as efficacious as a 4- to 6-week course in reducing the risk of IFI but would expose fewer infants to a shorter fluconazole course (except for those at highest risk for IFI) and might be cost-effective. Our initial protocol included all infants with BW of \textless1500 g or GA of \textless32 weeks. Detailed analysis of risk factors for IFI in our own unit allowed us to restrict fluconazole administration to infants with a GA of \textless29 weeks in January 2005. In our study, the estimated effective NNT value for ELBW infants was 8, and cost analysis results were favorable to prophylaxis. However, risk factors for IFI seemed to vary greatly among centers. For instance, in the studies by Kaufman et al\textsuperscript{24,27} entry criteria for prophylaxis included not only a BW of \textless1 kg but also central catheter insertion or intubation. In contrast, Feja et al\textsuperscript{8} reported recently that, among 45 infants with IFI, 3 had a BW of \textless1000 g but did not have central catheters or intubation and 23 had a BW of \textgreater1 kg but had other risk factors, such as gastrointestinal pathologic conditions or previous bacterial sepsis.

Despite several studies showing efficacy of fluconazole prophylaxis for VLBW or ELBW infants, one major question to resolve is whether generalizing fluconazole prophylaxis may eventually enhance development of fungi resistant to azoles, as observed in some adult populations and in the NICU of the Karolinska Institute.\textsuperscript{41} In Denmark, including intrinsically resistant fungi, decreased susceptibility to fluconazole and/or itraconazole was detected in 32% of current bloodstream fungal isolates.\textsuperscript{44} Current data support the initiation of a multicenter trial\textsuperscript{55} to assess the efficacy, cost, toxicity, and potential risks of targeted fluconazole prophylaxis (including the risk of development of fluconazole resistance only after exposure of large numbers of patients)\textsuperscript{41} and neurodevelopmental follow-up results. The intervention should be targeted only to infants at high risk for IFI, on the basis of multivariate analysis in the network of participating institutions, and should involve random assignment to either targeted fluconazole prophylaxis or placebo. With the use of this targeted approach, units within a neonatal network with lower rates of bacterial infections or NEC would be expected to use less antibiotic therapy and thus to expose fewer infants to fluconazole and for shorter periods, thereby minimizing costs and risk for developing resistance to azoles.

Only limited pharmacokinetic data are available for the most immature ELBW infants.\textsuperscript{26,56–58} In adults, fluconazole is excreted mostly unchanged in the urine, with only 11% as inactive metabolites, including a glucuronide and a fluconazole N-oxide. Fluconazole is a substrate for CYP3A4, which is regulated developmentally.\textsuperscript{59} Therefore, a multicenter trial should be preceded by or merged with a pharmacokinetic study to determine the appropriate dose and interval of administration at various levels of maturation of renal and liver function.

After this study was completed, 66 infants with GA of \textless32 weeks or BW of \textless1500 g, including 25 ELBW infants, were born at Weiler Hospital between January 1, 2005, and June 30, 2005. During this period, targeted fluconazole prophylaxis was limited to infants with a GA of \textless29 weeks, and no IFI was observed. Combined analysis of all data (2001–2005), ie, 13 (6.3%) of 206 infants in the control epoch versus 2 (0.8%) of 244 infants in the fluconazole epoch, yielded a common OR of 0.113 (95% CI: 0.025–0.519; \textit{P} = .001).
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Targeted Short-Term Fluconazole Prophylaxis Among Very Low Birth Weight and Extremely Low Birth Weight Infants

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