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# EDITORIAL

# Why prevent Invasive *Candida* Infections?

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In the Journal, Weitkamp *et al*. describe their approach to the application of fluconazole prophylaxis to high-risk preterm infants to prevent invasive *Candida* infections (ICIs). This group examined their incidence of ICI, and instituted prophylaxis at a cutoff for ICI based on gestational age and birth weight, and reported a significant decrease in ICI, elimination of *Candida*-related mortality and a reduction in empiric antifungal use. This paper gives insight into the application of this evidence-based therapy to neonatal intensive care units (NICUs).

## Why prevent ICI?

There are nearly 30 000 preterm infants $<1000$ g and/or $\leqslant 27$ weeks gestation born each year in the United States (National Vital Statistics, Center of Disease Control and Prevention-CDC, 2004), translating into approximately 2000 to 3000 ICI, 200 to 400 *Candida*-related deaths and 900 to 1200 infants developing neurodevelopmental impairment (NDI) associated with ICI.[1,2]

Prevention of ICI is critical as NDI or death occurs in 73% of infected infants $<1000$ g.[3] NDI occurred in 57% of survivors with bloodstream or cerebrospinal fluid (CSF) ICI and *Candida* bloodstream infections have the highest associated NDI compared to other infections (Figure 1).[4] In this analysis, prompt or empiric therapy did not decrease NDI in these patients.

In infants $<1000$ g with ICI, mortality rates range from 26 to 66% of the control patients in the prophylaxis studies.[5–13] There is a marked difference in mortality between infants $<1000$ g and larger infants. A recent analysis using ICD-9 codes reported a crude mortality rate of 26% with ICI compared to 13% for other infants $<1000$ g, and for infants $>1000$ g with ICI, mortality was 2% compared to 0.4% among infants without candidiasis.[1,14,15]

In additional to the morbidity and mortality, two recent case-controlled studies have examined the effect of ICI on cost of hospitalization and length of hospital stay.[14,15] They are limited in being based on ICD-9 codes which often may not be coded for all ICI. The mean increase in hospital costs was $39 045 for infants $<1000$ g with no difference in length of stay, and for infants $\geqslant 1000$ g $122 302 with an additional length of stay of 16 days.[15]

## Prophylaxis

The efficacy and safety of fluconazole prophylaxis in preterm infants has been reported in over 2400 patients from four randomized controlled trials[5–8] and five retrospective studies[9–13] without any significant adverse effects or emergence of resistance. Meta-analysis of these studies demonstrates that fluconazole prophylaxis reduced the risk of developing ICI in high-risk infants $<1000$ g by 91% (odds ratio (OR), 0.09; 95% confidence interval (CI), 0.04 to 0.24; $P=0.0004$) and all infants $<1500$ g by 85% (OR, 0.15; 95% CI, 0.08 to 0.26; $P<0.0001$). *Candida*-related mortality was decreased by 96% (OR, 0.04; 95% CI, 0.01, 0.31; $P=0.0055$) and overall mortality rate by 25% (11% in the fluconazole-treated infants compared with 16.3% in the control patients) (OR, 0.75; 95% CI, 0.58 to 0.97; $P=0.029$). Healy *et al*.[9] also reported the elimination of *Candida*-related mortality in any patient in their NICU when fluconazole prophylaxis was targeted to infants $<1000$ g.

Fluconazole prophylaxis is extremely cost effective. Uko *et al*.[12] examined the cost with fluconazole prophylaxis and showed a significant cost benefit of $516 702 over 18 months in their NICU. At our institution, pharmacy costs of one dose are $18 (M Buck, PharmD, personal communication), making the cost of the average time of prophylaxis of 4 to 6 weeks (8 to 12 doses) between $144 and 216 per patient.

## Resistance and safety

Some of the issues related to prophylaxis include side effects and resistance. In bone marrow transplant patients, fluconazole prophylaxis has decreased both ICI and mortality while fungal resistance remains low around 5%.[16] Neonatal prophylaxis studies have not reported a significant change or emergence of resistant species over the course of prophylaxis, during the study periods of 2 to 3 years, or over a 5-year period encompassing two studies.[5,7] Furthermore, there was no emergence or increase in the incidence of colonization or infection due to *Candida glabrata* or *Candida krusei* reported in any studies as well as a recent single center analysis of 10 years (4 years prior to and 6 years post-fluconazole prophylaxis).[17]

Fluconazole prophylaxis at higher doses $\geqslant 6\,\mathrm{mg\,kg^{-1}}$ and frequency may be associated with the development of *C. parapsilosis* resistance.[18,19] This finding suggests that it may be important to focus fluconazole prophylaxis use in only select high-risk NICU patients and primarily for prophylaxis and a different antifungal for treatment or empiric therapy, such as amphotericin B when able, as this will limit overall fungal exposure to fluconazole and possibly prevent the emergence of resistance.

This study did not demonstrate any side effects, including the incidence of cholestasis, which is consistent with results from the randomized controlled studies. One of the retrospective studies reported a higher incidence of cholestasis in the fluconazole prophylaxis patients that was transient with no difference at discharge while another retrospective study demonstrated a lower incidence of cholestasis.[12,13] Since there were no significant differences in direct bilirubin or liver enzymes in the four randomized placebo-controlled trials, it may be that in the one retrospective study other factors present during the study period increased the likelihood of cholestasis.

## What is the incidence and severity of ICI in your NICU?

Most studies only report bloodstream infections, and fail to account for meningitis, urinary tract infections (of which one-third have renal abscess involvement) and sterile body fluids such as peritoneal infections complicating NEC and focal bowel perforations. Furthermore, some cases are missed as meningitis is likely underreported due to lack of CSF data at the time of sepsis evaluations, some cases are not detected until autopsy (which often does not occur) and *Candida* pneumonia is difficult to definitively diagnose.[20]

This paper demonstrates the importance of examining ICI incidence in each NICU as many flaws exist when solely relying on the literature for incidence. This NICU reported that their rate of *Candida* bloodstream infections was 6.8%, while the rate of all ICI was 10% for infants $<1000$ g. In the largest analysis from 132 NICUs, the median rate of *Candida* bloodstream infections was 7.5% in infants $<1000$ g, and similar to this study results, the incidence of all ICI would be approximately 4% higher when including meningitis and urine tract infections.[1,21]

Gestational age has a more linear relationship to ICI compared to birth weight and captures the highest-risk patients.[22–24] For example, examining growth charts, a 24-week gestation infant could be between 468 to 940 g (3rd to 97th percentiles).[25] As this study demonstrated, by examining the incidence of ICI by each gestational age and birth weight, they were able to see where the rates in their population fell to zero. Table 1 illustrates an infectious control approach for each NICU to analyze their incidence of ICI with infection-related mortality and NDI.

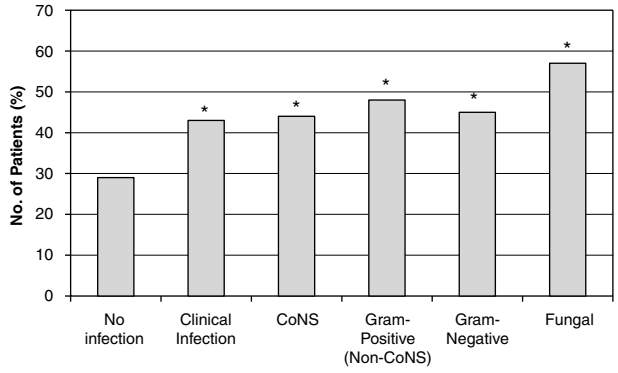


**Figure 1** Neurodevelopmental impairment and bloodstream infection in infants $<1000$ g.[4] *$P \leqslant 0.001$ compared to no infection group.

## Who should receive antifungal prophylaxis?

The question many have raised is, who would benefit from receiving antifungal prophylaxis? Several factors should go into that decision including incidence, mortality and NDI.

(1) Targeted prophylaxis should be given to all infants $<1000$ g and/or $\leqslant 27$ weeks while they require intravenous (IV) access (peripheral or central) starting on day 1 up to 6 weeks of life. This subpopulation of preterm infants has high mortality and NDI, and this approach has demonstrated efficacy and safety without the emergence of resistance in randomized controlled trials, while eliminating *Candida*-related mortality.

**Table 1** Invasive *Candida* infection (ICI ) surveillance chart

| *Gestational age* | *All ICI (%)* | *Mortality* | *NDI* | *Bloodstream infections (%)* | *UTI (%)* | *Meningitis (%)* | *Other*(%)* |
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Abbreviations: ICI, invasive *Candida* infections; NDI, neurodevelopmental impairment; UTI, urinary tract infections.
NDI (one or more of the following: PDI or MDI $<70$, cerebral palsy, blindness and deafness).
*Other infections (peritoneal and/or other sterile body fluid).

(2) Even in a NICU with overall low rates of ICI (<2%), infants ⩽26 weeks are likely high-risk and would benefit from prophylaxis. Incidence and outcomes by gestational age should be examined and tracked (Table 1). ICI can be analyzed by filling out Table 1 at institutions with low rates to determine the gestational age range in which ICI does occur and to identify those infants who should receive prophylaxis. There is likely a gestational age cutoff wherein ICI falls to zero. If NICUs do not have neurodevelopmental outcome data, prophylactic treatment of high-risk infants <1000 g or ⩽27 weeks should strongly be considered as treatment of documented infections does not always prevent the NDI and mortality of these infections.[3,4]
(3) NICUs with high rates in infants 1000 to 1500 g may choose prophylaxis in these infants. A targeted approach to infants with a central venous catheter (CVC) or on antibiotics for >3 days has been used in retrospective studies.[10,12]

## Dosage and schedule

The dosage used in this study was 3 mg kg$^{-1}$ intravenously twice a week until IV access (peripheral or central) was no longer needed. This study safely extended prophylaxis beyond 6 weeks continuing up to 9 weeks in those infants who required IV access longer. Manzoni *et al*.[8] in their multicenter randomized clinical trials (RCT) demonstrated that 3 or 6 mg kg$^{-1}$ are equally effective. However, dosing with 3 mg kg$^{-1}$ is preferable for the following two reasons: (1) drug concentrations in the skin, lung and mucous membranes are greater than plasma levels (therefore larger doses may be unnecessary), (2) the use of higher doses may foster development fungal resistance. Furthermore, the goal of prophylaxis is to use the lowest effective dose (usually 50% of treatment dose). In a recently published RCT, twice weekly dosing was as effective in preventing infection as more frequent dosing.[7] Therefore, 3 mg kg$^{-1}$ given twice a week is the optimal dosing schedule, maximizing efficacy, safety and cost.

The computerized system order entry system designed to not miss any potential patients was used in this study for quality improvement. In addition, we administer fluconazole prophylaxis twice weekly on the same days, every Tuesday and Friday, at a specified time (for example, 10:00), which further reduces pharmacy costs and limits medication errors.

Pediatrics has led the way in infectious disease prevention and now we can alleviate one cause of nosocomial infection in preterm infants and prevention should be instituted in every NICU. With single center and multicenter randomized controlled studies and a meta-analysis demonstrating a 91% decrease in ICI in infants <1000 g, fluconazole prophylaxis should be targeted to this group of infants <1000 g or ⩽27 weeks due to the high mortality and NDI. The prevention of ICI in extremely preterm infants also eliminates *Candida* as a cause of mortality and NDI in these vulnerable hosts.

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