



August 2008: VOLUME 5, NUMBER 12

Neonatal Fungal Chemoprophylaxis

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In this Issue...

Our treatment successes in newborn care have led to a growing population of surviving very low birth weight (VLBW) babies who are at high risk of nosocomial infection. Invasive fungal infection, particularly with *Candida* species, is being diagnosed more frequently. Increased mortality and worse long-term neurological outcomes are found in babies with invasive fungal infections compared with bacteraemia alone. While antifungal prophylaxis reduces the incidence of invasive fungal infection, there are concerns that widespread use of antifungals may increase the emergence of resistant strains.

In this issue we review the research that argues both for and against routine antifungal prophylaxis with fluconazole for VLBW babies in NICU.



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Dr. Sweet has no relevant financial relationships to disclose.

Dr. McCrossan has no relevant financial relationships to disclose.

Unlabeled/Unapproved Uses

The author has indicated that there will be no reference to unlabeled or unapproved uses of drugs or products in the presentation.

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LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

- Discuss the epidemiology of neonatal fungal infection
- Describe the benefits and risks of routine antifungal prophylaxis for very low birth weight babies (VLBW)
- List the additional risk factors for fungal sepsis in VLBW infants

AUGUST PODCAST



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COMMENTARY

Invasive fungal infection affects about 3 - 6% of very low birth weight (VLBW) babies; however, some estimates place the risk even higher in those with a birthweight less than 1 kg.¹ Invasive fungal infection has a much higher mortality than bacteraemia and a higher rate of adverse neurodevelopmental outcome.²

In addition to generalized measures for reducing nosocomial sepsis, clinicians have attempted to further reduce the risk of fungal infection by using prophylactic antifungals including nystatin, miconazole, and fluconazole. In the first small randomized trial in 1988, oral nystatin was shown to reduce invasive fungal infection. However the study was not sufficiently powered to show any effect on mortality or long-term outcome.³ In 1992, a larger study of oral miconazole gel versus placebo found no difference in the rates of invasive fungal infection.⁴ In more recent years, fluconazole prophylaxis has been shown to reduce the incidence of, and in some studies mortality from, invasive fungal infection. The earliest publications (Kicklighter et al. reviewed in this issue) showed that prophylactic fluconazole could reduce rectal colonization with *Candida* species by a third without any significant short term side effects.⁵ Subsequently (and reviewed herein), it was shown that prophylactic administration of 3mg/kg of fluconazole for the first 6 weeks of life to babies <1000g resulted in a reduction in invasive fungal infection from 20% to zero.¹ Four randomized trials have now been completed and subjected to meta-analysis showing that fluconazole prophylaxis reduces invasive fungal infection (Relative Risk 0.23 95% CI 0.11 – 0.46). There was also a trend towards reduction in all causes of mortality, which failed to reach statistical significance (RR 0.61 95% CI 0.37 – 1.03).⁶

Despite these encouraging findings, neonatologists in the UK, USA, and Ireland have remained reserved about initiating widespread fluconazole prophylaxis.⁷⁻⁹ Although side effects are relatively uncommon, transient rises in liver transaminases have been

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observed and there are concerns about treating many to protect a few. The largest of the multicenter randomized trials (Manzoni et al. reviewed herein), reported a high incidence of fungal colonization (29%) and invasive fungal infection (13%) in the control arm; however, there was no observed difference in survival with prophylaxis using either 3 mg/kg or 6 mg/kg of fluconazole.¹⁰ The high infection rates seen in most of the randomized trials may reflect the particular case mix in the units involved in the studies. In contrast, the recent prospective survey from the UK by Clerihew et al. (reviewed herein) perhaps gives a better reflection of the true incidence of invasive fungal infection in VLBW babies which is closer to 1%.¹¹ This lower incidence rate means that if all VLBW babies were to receive fluconazole prophylaxis there would be one less case of invasive fungal infection for every 125 babies treated. Such widespread use raises concerns about the emergence of fluconazole resistance, although this has not been observed and reported in the studies thus far.

An alternative to routine fluconazole prophylaxis is to limit this treatment to babies perceived to be at very high risk of fungal infection. There are additional recognized risk factors for acquiring fungal sepsis, including: 3rd generation cephalosporin use, fungal colonization, prolonged broad-spectrum antibiotic use, total parenteral nutrition with lipids, endotracheal intubation, central venous catheter use, previous blood stream infection, and postnatal steroids.¹²⁻¹⁴ So far, the evidence to support a selective approach is limited to case control studies.^{15,16} These have shown that targeting babies at highest risk results in fewer babies receiving prophylaxis yet achieving a similar reduction in invasive fungal infection.

It is time to establish recommendations and guidelines, so that clinicians may be able to decide which neonates to offer prophylaxis to according to patient risk factors, the local risk of invasive fungal infection, and antifungal resistance profile.

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FLUCONAZOLE PROPHYLAXIS REDUCES *CANDIDA* COLONIZATION

Kicklighter SD, Springer SC, Cox T, Hulseley TC, Turner RB. **Fluconazole for prophylaxis against candidal rectal colonization in the very low birth weight infant.** *Pediatrics.* 2001;107(2):293-298.

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Kicklighter et al. reported the first study of fluconazole prophylaxis in neonates. One-hundred-three very low birth weight (VLBW) babies were enrolled within 72 hours postnatally to receive low dose fluconazole or saline placebo. The fluconazole (6mg/kg) was administered intravenously or enterally once intravenous access was discontinued. The dose was administered every 72 hours during the first week of life, then daily thereafter until 28 days of age. Liver function testing and rectal swabs for fungal culture were done at recruitment and on days 7, 14, and 28. The primary outcome was the effect of fluconazole prophylaxis on the presence of rectal *Candidal* colonization.

Fifty-three babies were randomized to the fluconazole prophylaxis group and 50 to the placebo group, with baseline characteristics and risk factors for invasive fungal infection similar for both groups. The investigators found a significant reduction in *Candida* colonization in the fluconazole prophylaxis group: 15% vs 46%, $p = 0.0005$. The age at which fungal colonization was most prevalent also differed: in the fluconazole group fungal colonization was most common at day 7, whereas in the placebo group colonization continued to increase, peaking at day 28. Two babies in each group developed invasive fungal infection. No clinically important adverse effects were observed with fluconazole prophylaxis and no babies were withdrawn from the study. Alanine aminotransferase levels were slightly higher in the fluconazole group at day 14 (mean ALT 18 vs 15 IU/mL), but this normalized by day 28 and was not considered clinically significant. The mean inhibitory concentration (MIC) of fluconazole for *Candida* species remained unchanged throughout the study, and there was no difference between the two groups. There was also no increase found in inherently resistant *Candida* species.

The authors concluded that fluconazole prophylaxis was safe and effective at reducing the incidence of rectal *Candidal* colonization in VLBW infants, and recommend further studies to assess the effectiveness at reducing invasive fungal infection.

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FLUCONAZOLE PROPHYLAXIS REDUCES INVASIVE CANDIDAL INFECTION IN PRETERM INFANTS

Kaufman D, Boyle R, Hazen KC, Patrie JT, Robinson M, Donowitz LG. **Fluconazole prophylaxis against fungal colonization and infection in preterm infants.** *N Engl J Med.* 2001;345(23):1660-1666.

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Manzoni P, Stolfi I, Pugni L, Decembrino L, Magnani C, Vetrano G, et al; Italian Task Force for the Study and Prevention of Neonatal Fungal Infections; Italian Society of Neonatology. **A multicenter, randomized trial of prophylactic fluconazole in preterm neonates.** *N Engl J Med.* 2007;356(24):2483-2495.

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Kaufman et al. published the first study evaluating the efficacy of fluconazole prophylaxis in preventing invasive fungal infection in a single center randomized placebo-controlled trial conducted over a 30-month period. Inclusion criteria were birth weight <1000g, presence of a central venous catheter or endotracheal tube (ETT), and enrollment within the first 5 days of life. Babies were excluded if there was evidence of hepatic impairment.

The treatment group received fluconazole 3mg/kg for up to 6 weeks, initially every 3rd day, then on alternate days, and then daily only until intravenous access was discontinued. Surveillance cultures were taken weekly from multiple non-invasive sites and blood cultures as clinically indicated. Liver function was monitored weekly. The primary outcomes were the rate of fungal colonization and the development of invasive fungal infection (positive culture in a normally sterile site).

Of 114 extremely low birth weight (ELBW) babies born during the study period, 100 were eligible for randomization (50 to each group). The investigators found a significant reduction in *Candida* colonization in the fluconazole prophylaxis group (22% vs 60%; $p = 0.002$), as well as a significant reduction in invasive fungal infection (0% vs 20%; $p = 0.008$). Eight of the 10 babies who developed invasive fungal infection were born colonized with *Candida*. There was 40% mortality in those babies with invasive fungal infection. The authors observed no changes in sensitivity to fluconazole during the study period, and found no evidence of emergence of other *Candida* species. No adverse events were described.

This study was the first to demonstrate a reduction in invasive fungal infection in pre-term infants using low-dose fluconazole prophylaxis. Although fewer babies died in the fluconazole prophylaxis group (8% vs 20%; $p = 0.22$), the study was not powered to detect a significant difference in mortality. Although the presence of a central venous catheter or ETT were used as inclusion criteria, this proved to be a superfluous detail, as only one ELBW baby was excluded on this basis.

The paper by Manzoni et al. reports on the largest randomized controlled trial of fluconazole prophylaxis to date. Eight Italian centers recruited VLBW babies less than 72 hours old, excluding only babies with evidence of liver failure. The study was designed to compare two fluconazole prophylaxis dosing regimens – fluconazole 6mg/kg (FP6) and 3mg/kg (FP3) – with placebo. The dose interval in both intervention groups was the same as in Kaufman's study (above) and fluconazole was continued for 30 days in babies with birth weight of 1.0-1.5 kg and 45 days in babies <1kg. The main outcome measures were fungal colonization, invasive fungal infection, mortality, adverse effects of fluconazole, and emergence of resistance. Multiple baseline and weekly non-invasive cultures were obtained for colonization surveillance, and liver function tests were performed weekly.

Of 363 eligible infants, 322 were randomized: 106 to placebo, 112 to FP6 and 104 to FP3. The investigators report a significant reduction in fungal colonization in the intervention groups (FP6 9.8%; FP3 7.7%; placebo 29.2%; $p < 0.001$), but no difference between the two different dosing regimens with respect to fungal colonization. There was a significant reduction in invasive fungal infection in both intervention groups (FP6 2.7%, $p = 0.005$; FP3 3.8%, $p = 0.02$ vs placebo 13.2%), but again no difference between the two intervention groups. Despite the large reduction in invasive fungal infection, there was no



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reduction in all-cause mortality (FP6 8%; FP3 8.7%; Placebo 9.4%). Once colonized, fluconazole prophylaxis did not alter the conversion to invasive fungal infection. There were no reported adverse effects and no evidence of resistant *Candida* strains emerging or change in MIC.

This study confirms that fluconazole 3mg/kg has similar efficacy to a 6mg/kg dosing regime, and that fluconazole prophylaxis reduces the incidence of invasive fungal infection in VLBW babies. However, the authors concede that the study was underpowered to detect differences in mortality (NOTE: **1100 patients would be required to detect differences in mortality**). In addition, the incidence of invasive fungal infection in the placebo arm was much higher than would be expected for this population.

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FLUCONAZOLE PROPHYLAXIS AND SURVIVAL

Clerihew L, Austin N, McGuire W. **Systemic antifungal prophylaxis for very low birth weight infants: systematic review.** *Arch Dis Child Fetal Neonatal Ed.* 2008;93(3):F198-200. Epub 2007 Sept 3.

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The Cochrane review authors, reporting on fluconazole prophylaxis in VLBW babies, published a recent systematic review of the randomized controlled trials up to July 2007. Four randomized controlled trials (including the Kaufman and Manzoni studies described above) were analyzed involving 536 VLBW babies. All of the trials compared fluconazole prophylaxis with placebo and were of good methodological quality. The principal outcomes of the trials were the incidence of fungal colonization and invasive fungal infection. Three studies reported resistance patterns of fungi and one study documented neurodevelopmental outcomes.

The meta-analysis showed that invasive fungal infection is reduced with fluconazole prophylaxis (RR 0.23 95% CI 0.11-0.46). While there was no significant difference found in mortality in individual studies or on meta-analysis (RR 0.61 95% CI (0.37 - 1.03)), the trend towards reduction in mortality is encouraging. There was no significant change in the mean inhibitory concentration of fluconazole in fungal isolates in any of the studies or the meta-analysis. In the one study reporting developmental outcome, there was no significant difference in the modified Gessell test or in motor and sensory impairment at a median age of 16 months. Using the meta-analysis data, the authors calculated that for every 9 babies treated with fluconazole prophylaxis there would be one less case of invasive fungal infection. However, the authors caution that the incidence of invasive fungal infection in the placebo groups was high (13% – 16%) and the number needed to treat (NNT) would increase with decreasing incidence of fungal infection rates.

The authors conclude that the available data are reassuring, but cautioned that the actual incidence of invasive fungal infection is much lower and would result in a larger number of babies needing treatment to achieve benefit. Data from further trials is needed to provide a more precise estimate of the effects on mortality. The authors suggested that further trials of systemic fluconazole prophylaxis should be restricted to babies at higher risk, such as those <1000g with additional risk factors such as prolonged broad spectrum antibiotic use.

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INCIDENCE OF INVASIVE FUNGAL INFECTION IN VLBW BABIES

Clerihew L, Lamagni TL, Brocklehurst P, McGuire W. **Invasive fungal infection in very low birthweight infants: national prospective surveillance study.** *Arch Dis Child Fetal Neonatal Ed.* 2006;91(3):F188-192.

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In 2006, Clerihew et al. reported a national prospective surveillance survey of all cases of invasive fungal infection in babies less than 3 months old born in the UK during a 12 month period. Invasive fungal infection was defined as the presence of one or more of the following features:

- culture of fungus from a sterile site including blood
- central venous catheter tip
- urine (supra-pubic aspirate or catheter)
- cerebrospinal fluid
- bone/joint aspirate
- peritoneal/pleural fluid
- ophthalmologic findings
- fungal balls on ultrasound scan of kidneys
- an autopsy diagnosis of invasive fungal infection

Data were collected from 3 independent nationwide sources, including directly contacting every paediatrician in the UK monthly through the British Pediatric Surveillance Unit, as well as reports from microbiology laboratories reporting to the Communicable Disease Surveillance Center, and fungal isolates from infants referred to the UK Mycology Reference Laboratory.

A 92% response rate was achieved. During the study period, 9425 VLBW and 3837 extremely low birth weight (ELBW) babies were born in the UK. There were 94 cases of invasive fungal infection reported. All affected babies were VLBW, with 86% being ELBW. The estimated incidence in VLBW babies was 1% (10 per 1000 live-born; 95% CI: 8 – 12 per 1000). The estimated incidence in ELBW babies was 2% (21.1 per 1000 live-born; 95% CI: 16.5 – 25.7 per 1000). The median (range) gestation and weight of affected babies was 25 (23 – 32) weeks and 720 (420 – 1460) grams. Forty-one percent of VLBW babies with invasive fungal infection died.

Approximately 95% of affected babies had a central venous line in situ and were in receipt of mechanical ventilation, with total parenteral nutrition (TPN) and antibiotics likely representing the usual problems associated with extreme prematurity rather than independently predicting risk of fungal infection. Reassuringly, 93% of isolates were *Candida* species, with only one case resistant to standard antifungal agents (*C. glabrata*). Thirty-five percent of babies with invasive fungal infection were previously colonized and 38% had received antifungal prophylaxis (mostly nystatin). Almost 80% of affected babies were treated with amphotericin B and 46% with fluconazole. In 7 cases antifungal therapy was discontinued due to possible drug toxicity.

This study is valuable in that it is the first to present almost complete, prospective, nationwide data on babies with invasive fungal infection. Clerihew et al. suggest that the true incidence in VLBW babies is closer to 1% rather than the 5 – 15% reported in randomized trials. This has major implications when considering routine fluconazole prophylaxis. The number-needed-to-treat (NNT) to prevent one case of invasive fungal infection is shifted from 9 babies (*Cochrane Review*) to 125 VLBW and 45 ELBW babies. However, the authors acknowledge that some cases may have been missed, especially in

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those patients receiving antifungal prophylaxis. The authors felt that ascertainment bias was unlikely due to the comprehensive nature of the survey and comment that the higher incidence of invasive fungal infection reported in other studies may reflect the subgroup of patients cared for in tertiary units (where babies tend to be sicker). For clinicians working in tertiary neonatal units where the incidence of fungal infection is high, patients are likely to achieve the most benefit from fluconazole prophylaxis.

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RISK FACTORS FOR INVASIVE FUNGAL INFECTION IN VLBW BABIES

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(4):319-324.

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This prospective, multi-center cohort study conducted over a two-year period is the largest of several studies describing the risk factors associated with invasive fungal infection. The aims were to determine whether *Candida* strains colonizing the gastro-intestinal tract caused bloodstream infection (BSI) and to evaluate the possible associated risk factors.

During the study period, there were 2,847 admissions with 35 cases of *Candida* BSI (1.2%). The incidence in VLBW and ELBW babies was 3.1% and 5.5%, respectively. Forty-five percent of babies with *Candida* BSI had preceding rectal colonization. Univariate analysis identified risk factors strongly associated with *Candida* BSI and a multivariate regression analysis was performed, with the following factors found to be significantly associated with *Candida* BSI (after controlling for birthweight and abdominal surgery):

- shock ($p = 0.001$)
- central venous catheter ($p = 0.004$)
- endotracheal intubation
- Apgar score <5 at 5 minutes
- TPN
- intravascular lipids
- H2 antagonists
- administration of more than 2 courses of antibiotics

On univariate analysis, rectal colonization was strongly related to *Candida* BSI (OR = 2.97, $p = 0.002$), but not on multivariate analysis (OR = 1.71, $p = 0.21$). Several potential risk factors were found **NOT** to be associated with *Candida* BSI included: maternal antibiotics, prolonged rupture of membranes, vaginal delivery, gender, or postnatal steroid use. Interestingly, despite being strongly correlated with birth weight, gestational age <32 weeks remained an independent risk factor. The authors postulate that the immune status of a baby may be linked more closely with gestation than birth weight.

This study is useful, but only includes *Candida* BSI, potentially missing other babies with invasive fungal infection. The authors conclude that antifungal prophylaxis should be limited to very high-risk preterm babies.

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SELECTIVE FLUCONAZOLE PROPHYLAXIS FOR BABIES WITH ADDITIONAL RISK FACTORS FOR INVASIVE FUNGAL INFECTION

McCrossan BA, McHenry E, O'Neill 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(6):F454-458.

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The impact of fluconazole prophylaxis on *Candida* colonization and invasive fungal infection in VLBW babies is now well established, and most authors concur that clinicians should be trying to select babies who are most at risk for further study. In an attempt to strike a balance between universal prophylaxis, which raises the risk of resistance, versus no treatment while waiting for further evidence, some units have adopted prophylaxis policies based on selecting babies with additional risk factors. McCrossan et al. present one such retrospective case-control study, describing their experience following the introduction of a highly selective fluconazole prophylaxis guideline. Babies were eligible for prophylaxis if they were VLBW and fulfilled one of the following additional criteria: fungal colonization and the presence of a central venous catheter; treatment with 3rd generation cephalosporin; total duration of systemic antibiotics greater than 10 consecutive days. The decision to commence prophylaxis was at the discretion of the attending neonatologist. The dosing schedule was fluconazole 6mg/kg for 3 weeks, either intravenously or orally, with decreasing dosing interval as described previously in the Kaufman study. The aim of the study was to evaluate the impact of selective fluconazole prophylaxis on the incidence of invasive fungal infection and emergence of fluconazole resistance.

One hundred twenty-one VLBW babies were born in the year before the guideline was implemented, and 107 were born after; data were available in 110 and 102 charts respectively. Using the specified criteria, 33/110 and 31/102 babies were eligible for fluconazole prophylaxis in the periods before and after guideline implementation. Eighteen percent (6/33) of eligible babies developed culture-proven invasive fungal infection in the before group, compared with none after the guideline was implemented ($p=0.03$). One baby developed "probable" invasive fungal infection in the post-guideline implementation period (culture negative but critically ill with the appearance of fungal balls on ultrasound of the renal tracts). During both study periods all *Candida* isolates remained fully susceptible to fluconazole.

This study demonstrated that introduction of a highly selective fluconazole prophylaxis policy within a tertiary-level NICU limited fluconazole use to only 30% of VLBW babies but appeared to have significantly reduced invasive fungal infection. The results should be interpreted with caution, given that this was not a randomized controlled trial; however these data give clinicians an idea about a possible means of avoiding universal prophylaxis given the concerns about the emergence of resistant *Candida* species.

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eNewsletter: The Johns Hopkins University School of Medicine designates this educational activity for a maximum of 1.0 *AMA PRA Category 1 Credit(s)*TM. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Podcast: The Johns Hopkins University School of Medicine designates this educational activity for a maximum of 0.5 *AMA PRA Category 1 Credit(s)*TM. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Nurses

eNewsletter: This 1.0 contact hour Educational Activity is provided by The Institute for Johns Hopkins Nursing. Each newsletter carries a maximum of 1.0 contact hours.

Podcast: This 0.5 contact hour Educational Activity is provided by The Institute for Johns Hopkins Nursing. Each podcast carries a maximum of 0.5 contact hours.

Respiratory Therapists

For United States: [Visit this page](#) to confirm that your state will accept the CE Credits gained through this program.

For Canada: [Visit this page](#) to confirm that your province will accept the CE Credits gained through this program.

Post-Test — [back to top](#)

To take the post-test for eNeonatal Review you will need to visit [The Johns Hopkins University School of Medicine's CME website](#) or [The Institute for Johns Hopkins Nursing](#). If you have already registered for another Hopkins CME program at these sites, simply enter the requested information when prompted. Otherwise, complete the registration form to begin the testing process. A passing grade of 70% or higher on the post-test/evaluation is required to receive CME/CNE credit.

Statement of Responsibility — [back to top](#)

The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing take responsibility for the content, quality, and scientific integrity of this CME/CNE activity.

Intended Audience — [back to top](#)

This activity has been developed for neonatologists, NICU nurses and respiratory therapists working with neonatal patients. There are no fees or prerequisites for this activity.

Learning Objectives — [back to top](#)

At the conclusion of this activity, participants should be able to:

- Discuss the epidemiology of neonatal fungal infection
- Describe the benefits and risks of routine antifungal prophylaxis for very low birth weight babies (VLBW)
- List the additional risk factors for fungal sepsis in VLBW infants

Internet CME/CNE Policy — [back to top](#)

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Step 4.

Print out your certificate.

PHYSICIAN
POST-TEST

NURSE
POST-TEST

Respiratory Therapists

[Visit this page](#) to confirm that your state will accept the CE Credits gained through this program or click on the link below to go directly to the post-test.

RESPIRATORY
THERAPIST
POST-TEST

Faculty Disclosure — [back to top](#)

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- **Edward E. Lawson, MD** has indicated a financial relationship of grant/research support from the National Institute of Health (NIH). He also receives financial/material support from Nature Publishing Group as the Editor of the *Journal of Perinatology*.
- **Christoph U. Lehmann, MD** has received grant support from the Agency for Healthcare Research and Quality and the Thomas Wilson Sanitarium of Children of Baltimore City.
- **Lawrence M. Noguee, MD** has received grant support from the NIH.
- **Mary Terhaar, DNSc, RN** has indicated no financial relationship with commercial supporters.

[Guest Authors Disclosures](#)

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