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Fluconazole for the Prevention of Fungal Infections: Get Ready, Get Set, Caution

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DESPITE THE PROMISING data presented by Manzoni et al¹ in this month's *Pediatrics Electronic Pages*, there remains, in my opinion, insufficient evidence to recommend the routine use of fluconazole as a means of prophylaxis against systemic fungal infections in low birth weight infants. I wish the facts dictated otherwise. The search for means of preventing nosocomial infection has been at the forefront of the minds of clinicians since the emergence of the neonatal perinatal medicine discipline. Unfortunately, the history of this subspecialty is punctuated by the unanticipated disasters that followed well-meaning attempts to prevent infections in preterm infants. For example, in an effort to prevent nosocomial infections in preterm infants by administering a combination of penicillin and sulfonamides, Silverman² observed that more infants died as a result of kernicterus. He noted, "We cannot always make our patients better, but we can always make them worse!"² Other efforts to prevent infection have included the use of chloramphenicol (which produced the gray-infant syndrome), tetracyclines (which permanently stained teeth and bones), and pHisoHex baths (which resulted in cystic brain lesions). There have been successful programs of prophylaxis, including those for ophthalmia neonatorum (gonococcus), hepatitis, and, most recently, group B streptococcus. We are very cognizant that in neonatal-perinatal medicine the potentially long delay between the intervention and the detection of harmful effects may result in huge calamities. Definitive guidance for *Candida* prophylaxis and treatment is hindered by a lack of large, multicenter, randomized, controlled trials. Systemic prophylaxis is currently not recommended for any neonatal population.

There is no dispute that nosocomial infection is a significant problem. During their initial hospitalization,

>20% of very low birth weight (<1500 g) preterm infants experience a serious systemic infection.^{1,3,4} Despite the many advances in neonatal intensive care and introduction of new antimicrobial agents, mortality is as much as threefold higher for these infants who develop sepsis than their counterparts without sepsis during their hospitalization.⁴ In addition to the increased morbidity and mortality, together with the prolongation of hospitalization, hospital-acquired infections are associated with an increase in neurodevelopmental handicap.⁵

Fungal infections constitute an important component of these nosocomial infections. The incidence of candidiasis has risen in neonatal ICUs, and the mortality associated with systemic candidiasis may be as high as 20%.⁴ A better understanding of the incidence, diagnosis, clinical management, and prophylaxis is important for reducing morbidity and mortality. An integral component of this plan necessitates refinement of the molecular and adjunctive diagnostics so that colonization and invasive infection can be diagnosed earlier. Polymerase chain reaction techniques have demonstrated promise in neonatal patients⁶ and are being evaluated in a large prospective study by the National Institute of Child Health and Human Development Network, which also includes a β -glucan assay (β -D-glucan is a major component of the fungal cell wall) and gas chromatog-

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raphy mass spectrometry for D-arabinitol (D-arabinitol is a major metabolite of most *Candida* species).

An example of the application of polymerase chain reaction is the report from a nursery in Finland by Sarvikivi et al,⁷ who used genotyping with a complex DNA-fingerprinting probe to identify the emergence of a strain of *Candida parapsilosis* with decreasing sensitivity to fluconazole. This specific organism was responsible for cross infections that caused blood-stream infections in the NICU over a 12-year period. Thus, we have to be aware of the possible emergence of resistant strains of *Candida* species with the widespread introduction of fluconazole.

There is substantial evidence that fluconazole prophylaxis is effective in immunocompromised adults and infants, but few studies have addressed the problem in preterm infants. In the Cochrane review of this topic, Austin and Darlow³ identified only 3 eligible trials.⁸⁻¹⁰ They ultimately concluded that there is insufficient evidence to support the use of prophylactic oral antifungal agents in very low birth weight infants and recommended randomized, controlled trials to address this problem. We concur.

To these data sets we can now add the report from Manzoni et al,¹ and although I am encouraged by their numbers, my recommendation would be to wait for large, multicentered, randomized trials to reproduce their findings or results before embarking on a program of routine use of fluconazole in preterm infants. There of course must be supporting evidence that there are no harmful adverse effects or the emergence of resistant organisms. My enthusiasm for their outstanding outcomes is tempered by the fact that theirs is a single-center, retrospective, nonrandomized, intervention study with historical controls. This study design diminishes the weight of the evidence, which was that fluconazole significantly decreased the incidence of proven and presumed systemic fungal infections and avoided 1.9 expected deaths.

After reviewing the current state of our knowledge and evidence, you are at liberty to come to different conclusions. If you do, my plea is that you maintain careful records so that you can document the rates of colonization, the incidence of systemic infection, the organisms causing the infections, and the patterns of susceptibility to the antifungal agents.

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