Fluconazole in NICU Not Linked to Resistance

BY DIANA MAHONEY
New England Bureau

TORONTO — Fluconazole prophylaxis for invasive candidiasis in extremely low-birth-weight infants is not associated with the emergence of fluconazole-resistant *Candida* species, Dr. C. Mary Healy said at the annual meeting of the Infectious Diseases Society of America.

In infants weighing less than 1,000 g at birth, 42 days of fluconazole prophylaxis (FP) has been shown to reduce *Candida* colonization and invasive candidiasis, "but the possibility that [this regimen] could lead to a resistant *Candida* species is an ongoing concern," said Dr. Healy of Baylor College of Medicine in Houston. "The worry is that FP will cause overgrowth and infection by inherently less susceptible species, particularly *C. glabrata*."

To evaluate the impact of FP on the incidence of invasive candidiasis (IC), as well as IC-related mortality and fluconazole susceptibility of *Candida* isolates, Dr. Healy and her colleagues reviewed data from the neonatal intensive care unit (NICU) at the Women's Hospital of Texas in Houston for infants treated both before and after the implementation of an FP strategy in 2002. For the purposes of this investigation, IC was defined as the presence of a *Candida* species isolated from blood or cerebrospinal fluid in NICU infants.

Since April 2002, as per hospital protocol, extremely low-birth-weight infants younger than 5 days in the NICU of the Women's Hospital of Texas have been eligible to receive intravenous FP at a dose of 3 mg/kg for 6 weeks on a dosing schedule that varies by age: every third day for the first 3 weeks, every second day for the subsequent 2 weeks, and daily for the final 2 weeks, said Dr. Healy.

Using pharmacy and electronic records, Dr. Healy and her colleagues reviewed the demographic, clinical, and laboratory data for all of the NICU infants of any birth weight during the first 4 years of FP implementation and compared it with that of infants who were in the NICU in 2000-2001, before the use of FP.

Between April 2002 and March 2006, 362 extremely low-birth-weight infants in the hospital's NICU received FP, along with 47 infants with a body weight greater than 1,000 g who were started on the preventive therapy at the discretion of the neonatologist. The median body weight of the 409 infants was 775 g, the median gestation was 26 weeks, and the median dose they received was 13 mg/kg over 29 days.

Twenty-nine percent of those infants receiving FP completed the 6-week protocol. Fifty-nine percent discontinued the therapy because IV access was no longer needed, 7% died from non IC-related causes, 2% transferred to other hospitals, 2% had breakthrough infections, and 1% had transient elevation of liver transaminases, which resolved when FP was discontinued, Dr. Healy reported.

Comparing infants who developed IC during the pre- and post-FP time periods showed 19 cases in 2000-2001 and 22 cases in 2002-2006. "Infants [who developed IC] during the FP period were of significantly greater gestational age and had significantly higher birth weight than those who developed it before FP," said Dr. Healy. "There was also a strong trend toward them being older, although this did not reach significance." There was no difference in prenatal or perinatal complications, nor were there differences in complications of prematurity.

Among the risk factors for infection in both groups, "there was a strong trend toward more antibiotic use, longer duration of infant vascular catheters, and longer duration of TPN [total parenteral nutrition] in the FP period, but the only risk factor that reaches statistical significance was the use of H_2 blockers," said Dr. Healy.

With respect to potential resistance, "our findings are reassuring," said Dr. Healy. "The IC species distribution remained stable both before and after FP implementation. In the IC cases prior to FP, *C. albicans* was identified in 14 infants, *C. parapsilosis* in 3, *C. tropicalis* in 1, and *C. glabrata* in 1. After FP, the species distribution was *C. albicans* in 13 infants, *C. parapsilosis* in 6, *C. tropicalis* in 1, and *C. glabrata* in 2. "It's particularly reassuring that *C. glabrata* is no more common now than it was before FP," she said.

Similarly, the minimum inhibitory concentrations (MICs) for fluconazole were consistent.

Dr. Healy reported having no conflicts of interest related to this presentation. ■