Antibiotics Linked to Necrotizing Enterocolitis

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Prolonged empirical antibiotic therapy is associated with an increased risk of necrotizing enterocolitis and death in extremely low-birth-weight infants, results of a retrospective study found.

Although the study couldn't prove causality, it did link antibiotics use with a 46% increased risk of death among these already vulnerable newborns, Dr. C. Michael Cotten and his colleagues reported (Pediatrics 2009;123:58-66).

Dr. Cotten of Duke University, Durham, N.C., and the coauthors did not propose any changes to clinical practice. However, they said, broad-spectrum antibiotic treatment in the absence of proven sepsis "may not be benign."

The real problem, Dr. Richard Polin said in an interview, is how to identify which infants actually do have a bacterial infection and need the antibiotics therapy.

"It's very difficult to diagnose sepsis in these babies," said Dr. Polin, director of neonatology at the Morgan Stanley Children's Hospital of New York–Presbyterian Hospital. "There is no test to identify them, other than a positive blood culture, and that is an imperfect test because the volume of blood needed for a reliable diagnosis isn't always available. If we did develop a sensitive assay that would allow us to differentiate septic from nonseptic babies, we could keep them on antibiotics for shorter times. But until that happens, the best advice is to stop antibiotics as early as possible if you are reasonably sure that the infant is not septic."

The study examined the rates of necrotizing enterocolitis (NEC), death, and the combination of both in a group of 4,039 extremely low-birth-weight (ELBW) babies who received initial empirical antibiotic treatment during the first few days of life, despite a sterile blood culture. Most (2,147; 53%) received prolonged therapy, defined as at least 5 days of treatment. The most commonly prescribed regimen was a combination of ampicillin and gentamicin (83% of the study population).

Overall, 11% of the group (440) developed NEC; of these, 46% had NEC of Bell stage 2a, 2b, or 3a, and 54% had NEC of Bell stage 3b. Sixteen percent of the study group (658) died after postnatal day 5, while 23% (919) developed the composite outcome of NEC or death. Compared with infants who developed neither outcome, significantly more of those with the composite outcome had received prolonged antibiotic therapy (61% vs. 51%).

After adjusting for Apgar score, race, and gestational age, the investigators found a 4% increase in the combined risk of NEC or death with each additional day of initial empirical antibiotic treatment.

The increase was more striking when the results were examined separately, with about a 7% increase in the risk of NEC alone and a 16% increase in the risk of death alone for each additional treatment day.

The number needed to harm with prolonged antibiotic treatment for death alone was 21; for NEC alone, 54; and for the combination outcome, 22. Changing the definition of "prolonged" therapy from 5 or more days to 4 or more days did not change the risks, the authors commented. Sicker infants were at even higher risk. When the analysis considered only the newborns who were intubated for the first 7 postnatal days, the number needed to harm with prolonged empirical antibiotic therapy was 14 for NEC or death, 16 for death alone, and 25 for NEC alone.

Dr. Cotten and associates speculated that the link between antibiotic use and poor outcomes may be related to interference with the natural process of gut colonization.

"This colonization, at least in animal models, seems to contribute to physiologic development of the intestine, immunologic development, and absorbance of nutrients," they said.

They also noted that antibiotics may suppress normal flora, allowing competing organisms, like yeasts and fungi, the chance to overgrow. ■