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ID CONSULT

Clostridium difficile–Associated Disease

The evolving picture of *Clostridium difficile*–associated disease suggests that we may need to revise our traditional approach to the child with persistent diarrhea.

The increase in frequency and severity of health care–associated *Clostridium difficile*–associated disease (CDAD) in North America over the last several years is believed to be due in large part to a newer, more virulent strain first reported a little over a year ago (N. Engl. J. Med. 2005;353:2433-41, 2442-9)

At the same time, we've been seeing previously healthy patients without prior antimicrobial use, including children, become infected in the community. Of 23 community-acquired cases reported to the CDC from four states during May and June of 2005, 11 were in children less than 18 years of age (MMWR 2005;54:1201-5).

In a 3-year prospective study published in the fall of 2006, 7% of 1,626 stool samples from children who presented to an emergency department with diarrhea were positive for *C. difficile* toxin (Clin. Infect. Dis. 2006;43:807-13). It's not clear from the data whether this represents an increase, but we do know that it's a problem.

I think we need to consider the possibility of CDAD in any child—even those without prior antibiotic use—who has persistent diarrhea lasting more than 5 days, or very severe diarrhea of more than 8-10 stools a day. The data suggest that about 1 in 10 of these children will have stool assays positive for *C. difficile* toxin.

Some children with CDAD—perhaps 25%-35%—improve on their own within a week and may not need treatment. The ones whose condition does not resolve in a week are candidates for metronidazole therapy. About 15%-20% of those treated will fail. For them, the American Academy of Pediatrics advises a second course of metronidazole. For the 15%-20% who will fail or relapse a second time, oral vancomycin is recommended.

While you're waiting for the toxin assay to come back, I think it's a good idea to use probiotics such as *Lactobacillus GG* species or *Saccharomyces boulardii* as a preemptive strike, even before you know the pathogen. Data suggest that those "good bacteria" might be helpful in restoring balance in the flora and thus reduce symptoms due to a variety of diarrhea-causing organisms, including rotavirus and other viral agents as well as *C. difficile* (Am. J. Gastroenterol. 2006;101:812-22).

Because alcohol-based hand sanitizers aren't as effective at removing infectious *C. difficile* spores from contaminated hands, it's important to wash your hands with soap and water after examining children with prolonged diarrhea. However, until you know what the pathogen is, use of alcohol-based products also is recommended because they're better at eliminating other GI pathogens including the usual virus suspects. I will typically wash with soap and water first, dry my hands, then rub in the sanitizer as I'm walking away from the sink after seeing children with persistent diarrhea and an as-yet undefined pathogen.

The appearance of CDAD in previously healthy, community-dwelling individuals is a new and worrisome change. Until recently, antibiotic use was believed to be the nearly universal culprit that disrupted the natural gut flora and allowed *C. difficile* to flourish, leading to the presentations ranging from frequent diarrhea to the characteristic pseudomembranous colitis.

Now, however, it appears that in some children CDAD may be initially triggered by a common viral gastroenteritis—such as rotavirus, norovirus, or adenovirus—which lowers the colonic pH enough to prompt the normally-quiescent *C. difficile* to begin overproducing toxin.

This recent shift may be related to the newly described strain, which not only produces many times the usual amount of *C. difficile* toxins A and B, but also contains a mutation that leads to the production of an additional binary toxin that appears to be even more toxic to gut mucosa than are A and B. We don't fully understand the implications of this new strain. It is becoming clear, though, that it's not a temporary situation as we had hoped.

On the positive side, several ongoing trials offer some reason for optimism. A group at Baylor College of Medicine in Houston is now conducting National Institutes of Health–funded phase III trials of nitazoxanide in adults with CDAD. Nitazoxanide (Alinia, manufactured by Romark Laboratories L.C., Tampa, Fla.), which acts by interfering with anaerobic metabolic pathways, is already licensed for the treatment of parasitic diseases of the gastrointestinal tract, such as giardiasis, and has been used in millions of children worldwide. So far, the CDAD data look good.

A totally different approach to CDAD treatment is with a nonabsorbable polymer called tolevamer, manufactured by Genzyme Corp., Cambridge, Mass. It works by binding *C. difficile* toxins A and B. Because it's not an antibiotic, tolevamer would be expected to avoid the problems associated with antimicrobial treatment, including resistance. Phase II data suggested that it worked at least as well as vancomycin and was associated with less recurrence of diarrhea, although there was an increased risk for hyperkalemia (Clin. Infect. Dis. 2006;43:411-20). Genzyme expects to complete phase III trials this year. The agent has been given fast-track designation by the Food and Drug Administration, and the company anticipates commercial approval in 2008. ■

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Ultrasound Predicts Outcomes In CMV-Symptomatic Neonates

BY HEIDI SPLETE
Senior Writer

Cranial ultrasound scanning significantly predicted developmental outcomes in symptomatic newborns with cytomegalovirus, based on a study of 57 infants reported in the February issue of the Journal of Pediatrics.

To determine how well cranial ultrasound predicted clinical outcomes, two of the researchers reviewed the scans of the infants while blinded to the results (J. Pediatr. 2007;150:157-61). The ultrasound scans were taken during the first week of life and repeated weekly for the first month in cases of abnormal findings, and then repeated monthly until the infants were 6 months old.

Overall, 18 newborns had clinical and laboratory signs of cytomegalovirus (CMV) at birth, and 39 had no observable symptoms at birth. A total of 12 of the 57 (21%) infants had brain abnormalities that were visible on an ultrasound image. Ultrasound lesions were found in 10 of 18 (56%) newborns with clinical and laboratory symptoms, compared with 2 of 39 (5%) asymptomatic newborns.

None of the infants with normal ultrasound findings at birth had developed lesions at follow-up evaluations, and the negative predictive value of the ultrasound was 100% for motor delay and low developmental quotient and 93.3% for sensorineural hearing loss, Dr. Gina Ancora of the University of Bologna (Italy) and her colleagues wrote.

Data from evaluations at 12 months of age were available for 56 of 57 patients; one infant with visible ultrasound lesions had died of aortic thrombosis. Ten of the 11 remaining symptomatic newborns with abnormal ultrasound findings at birth developed at least one sequela, whereas none of the 8 newborns who were symptomatic but had normal ultrasound findings developed sequelae.

Similarly, only 3 of the 37 asymptomatic infants with no ultrasound abnormalities had poor outcomes at 12 months (sensorineural hearing loss), and 1 of 2 asymptomatic infants with abnormal ultrasound findings developed severe sequelae.

The presence of CMV symptoms at birth may not be enough to differentiate between children who will and will not develop lesions later, and ultrasound is a safe and easy diagnostic tool in this population, even for children in critical condition, the researchers wrote.

But the data were insufficient to make recommendations for ultrasound imaging in asymptomatic children, they said. ■

FDA Initiates Stricter Medical Glove Standards to Provide Better Barriers

The Food and Drug Administration has issued a final rule that would require medical glove makers to improve their products' ability to serve as a barrier against pathogens.

Manufacturers are being given 2 years to comply with the new regulations.

The goal is to reduce the risk of transmission of bloodborne pathogens such as HIV and hepatitis B, according to the FDA. While the agency can't quantify how many cases might be prevented with better barriers, it estimated that approximately 2.4 HIV infections occur each year due to "problems with the barrier protection properties of gloves used in health-care settings."

The FDA estimates that 140 health care workers are infected with the hepatitis B virus (HBV) on the job each year, primarily from percutaneous injuries. About a third, or 40 cases, may be due to glove defects, according to the agency.

There is less evidence that glove defects are associated with hepatitis C, said the agency, noting that most occupational exposures are from needle sticks.

The agency has inspected gloves—used for patient examinations and surgical procedures—since 1990. At that time, the International Organization for Standardization (ISO), ASTM International, and the FDA had the same standards for glove quality. A few years later, the ISO and ASTM began requiring higher standards.

The agency has allowed a defect rate of 4% for gloves used during patient exams and 2.5% for gloves used in surgery.

With more and more brands of gloves being marketed and sold, the agency hopes to maintain that defect rate. To do so means increasing the quality standards, said the agency.

The FDA estimates that about 2% of the 39.2 billion gloves currently marketed are defective—some 940 million gloves. There are more than 400 manufacturers, but the number of gloves made and sold is expected to vastly increase in the next 10 years. If standards were left at their current level, 10 years from now, some 1.2 billion defective gloves would be sold.

The agency said the benefits of higher standards will outweigh the costs. It will cost about $6.6 million a year, but will result in savings of about $15 million due to reduced need for blood screens and fewer infected health care workers.

—Alicia Ault