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Clostridium difficile Diarrheal Disease in Children

ABSTRACT & COMMENTARY

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THE DIAGNOSIS OF *C. difficile*-RELATED DISEASE (CDD) IN CHILDREN IS CONtroversial, as recently reviewed.[1] Do children < 1 year old actually develop diarrhea due to *C. difficile*? What should be the patient age cutoff below which laboratories should reject any stools for *C. difficile* testing? How will the new state-of-the-art molecular tests influence the interpretation of results in children?

The situation for rejecting stools for *C. difficile* testing from children < 2 years old is similar to the reasoning used by microbiologists to reject sputum containing too many squamous epithelial cells (originating from upper airway secretions) for culture. Even if a potential pathogen is recovered in culture from a sputum containing > 10 squamous epithelial cells per low power field, as enumerated on Gram stain, the involvement of that pathogen in lower lung disease cannot be unequivocally determined. The isolate could be colonizing the upper airway without contributing to the patient's pneumonia at all. The laboratory cannot come to any conclusion; therefore, to avoid inappropriate interpretations, it chooses not to perform the test.[2] This rejection criterion is actually a requirement for laboratory accreditation by the College of American Pathologists. Diagnosis of *C. difficile* disease in young children is equally difficult because of the large number of asymptomatic infants who carry toxin-producing and non-toxin-producing strains in their feces.[3,4] The commercial molecular tests all have an FDA-required two year age limitation below which test results have not been validated, as stated in their product inserts (Prodesse, Milwaukee, WI; BD, Franklin Lakes, NJ; Cepheid, Sunnyvale, CA). In the future, perhaps the age cutoff for accepting stool for testing should be lowered to one year for reasons outlined below.

Epidemiological studies report incidences of asymptomatic colonization that vary from 50%-90% immediately after birth, with an average of 50% during the first year, falling to around 3%-6% during the second year.[1,3,8] Studies looking for the organism in newborns on a daily basis found colonization rates as high as 52%, tracked to acquisition from the environment, not from the mothers.[3,9] Although not reported in all studies, it seems that acquisition of *C. difficile* in newborns was not associated with gastrointestinal symptoms, but the percentage of strains producing toxin varies among studies.[3,6] Some studies even showed that children with *C. difficile* had a lower incidence of diarrhea than non-colonized controls.[7] However, colonized children can serve as a source of disease in others.[10,11] Reading these numerous studies linking colonization to the environment in the hospital suggests to me that effective disinfection (using bleach or more aggressive techniques) and assiduous infection control practices for newborn nurseries and NICUs might significantly decrease colonization rates in infants and, perhaps, lower disease rates in associated adults. Could at least some of our growing epidemic of CDD be traced to an uncontained reservoir in our pediatric facilities?

Why some infants carrying fecal toxigenic *C. difficile* do not become ill is still a mystery, but a pattern is emerging. Hospital discharge records from 22 children's hospitals in the United States were surveyed to determine the incidence of *C. difficile*-associated disease reported in children age 1-18.[12] A rise from 2.6 to 4.0 cases per 1,000 admissions was seen from 2001 to 2006, even when numbers of test requests were evaluated. This study, as well as others to be reviewed, noted that 67% of the CDD seen in children was associated with chronic underlying conditions.

Children < 1 year of age, and particularly those with complicating gastrointestinal conditions, clearly can develop CDD. *C. difficile*-associated gastroenteritis in patients with Hirschsprung's disease, inflammatory bowel disease, and necrotizing enterocolitis has been studied.[13,14] Back in 1986, workers showed that *C. difficile* could be found in stool cultures from Hirschsprung's syndromic children < 3 years old with colitis (77%) significantly more often than in normal children with or without diarrhea.[15] A group in Canada surveyed 200 children > 1 year old with *C. difficile*-associated diarrhea over a three-year period, basing their diagnosis on cell-culture cytotoxicity. They found a high proportion of the patients had Crohn's disease, chemotherapy treatment, immunotherapy and/or antibiotics post-transplantation, or immunodeficiency.[16] In total, 74.5% of the patients had received antibiotics and 55% had healthcare exposure in the preceding month, although these risks are not universally observed.

Pascarella et al studied *C. difficile* in association with pediatric inflammatory bowel disease (IBD), including Crohn's disease, ulcerative colitis, and colitis of indeterminate cause, as determined by radiology, histopathology, endoscopy, and clinical criteria.[17] *C. difficile* toxin was detected by a lateral flow enzyme immunoassay for toxins A and B in 24.7% of the 81

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patients with IBD and only 8.9% of the 112 without IBD. Unlike other studies, association of *C. difficile* colonization and pre-existing risk factors (antibiotic exposure, immunosuppression, chemotherapeutic agents, proton-pump inhibitors) was not seen. Of course, given the relative insensitivity of toxin assays, the prevalence of toxigenic *C. difficile* in both populations is likely to have been underestimated.[18]

The incidence of CDD in children without confounding comorbidities has been low, but outbreaks in day-care centers, for example, have been identified.[11] A study from Taiwan suggests that serious complications of CDD in children (average age 26 months) is also rare. Over the course of a year, 20 children developed toxic megacolon at their institution.[19] Pathogens were isolated from the stools of 13 patients, 12 Salmonella and only one *C. difficile*. Along with the rise of 027/NAP1/BI strain in the U.S. and Europe, however, infections in children may also be increasing.[8] The regular risk factors, including treatment with antibiotics and healthcare exposure, are not as common as would be expected.[20]

Although the results of some epidemiological studies in children appear compelling on the surface, they are usually marred by failure to explore potential other causes of diarrhea, including rotavirus, in the majority of cases. However, a group from the United Kingdom did use electron microscopy to detect viruses, along with routine tests for bacteria and parasites, to examine stools from children < 2 years old admitted to the hospital for gastrointestinal symptoms.[21] In addition, 390 infants and 118 controls were tested for *C. difficile* by both culture and cell culture cytotoxicity neutralization assay. Half of the children with gastroenteritis and one-third of the controls carried *C. difficile* in their feces. Only 19 (4.9%) of the children with gastroenteritis and 2.5% of the controls from whom *C. difficile* was isolated also had cytotoxin detected. Thirteen of these 19 patients had another fecal pathogen, usually an enteric virus, detected along with *C. difficile*. The control group was actually more likely to have received recent antibiotic treatment. Ellis and others concluded that *C. difficile* was a pathogen in their children with gastroenteritis; however their data alone, particularly regarding the role of the co-pathogens, do not support such a definitive conclusion. Other reports may provide support for their conclusion, however. Workers from Finland reported on the association of CDD and viral gastroenteritis, suggesting that virus infection may exacerbate the effects of toxin.[22] New epidemiologic studies of *C. difficile* utilizing the best molecular tests, complete studies for other stool pathogens (such as a microarray platform), and thorough clinical evaluations will be needed to fully determine the role of *C. difficile* in gastroenteritis of children and infants.

In summary, *C. difficile* is clearly extending its pathogenic reach into lower age groups. The organism is more likely to be a pathogen in children with comorbidities, with Hirschsprung's disease demonstrating the most convincing association. Laboratories may wish to validate their tests and then lower the age to one year below which samples should be rejected, and microbiologists should continue to insist that specimens not be tested if they are not clearly diarrhea (take the shape of the container, more than three loose stools per day) unless the diagnosis of toxic megacolon is suggested. ■

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Paired Malaria Infections in France

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Source: Pomares-Estran C, et al. *Malaria Journal* 2009;8:202-204.

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AUTOCHTHONOUS CASES OF MALARIA ARE RARELY reported in areas non-endemic for malaria — and generally occur within or near international airports. This curious report documents a young Parisian couple traveling around France on vacation in August 2008, who both developed fever, vertigo, and nausea, prompting a trip to the emergency room in Saint Raphael on the French Riviera. The man was hospitalized for a day and then discharged with no clear diagnosis. Within a day, both became progressively ill, returning to the ER for further care. Routine blood cell counts demonstrated thrombocytopenia, which prompted blood smears, surprisingly revealing intraerythrocytic parasites consistent with *P. falciparum* in both young people.

Parasite DNA extracted from blood samples was examined for four genetic loci, demonstrating the two isolates were identical.

The couple had no history of travel outside of France, and no history of transfusion, needle sharing, or intravenous drug use. Their vacation had brought them within eight miles of the Charles de Gaulle airport in Paris, and then up to Normandy, where the temperatures were 18°C (too cold to support Anopheles spp.), and then on to the French Riviera, where they fell ill. An intensive environmental search identified no other risk factors for malaria, and no Anopheles mosquitoes were found in any area visited by the couple. The only possible conclusion, stated Health Authorities, was that an isolated mosquito roaming outside of Charles de Gaulle airport bit both young people.

As an ID Fellow years ago, phone calls from the lab reporting malaria parasites on a blood smear, done for purposes of a manual cell count, were infrequent. But, such detection was important and often resolved some of the more puzzling cases of fever in patients without clear risk factors for malaria. With the universal use of automated cell counts, we seldom hear about such cases. ■

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert*, *Clinical Oncology Alert*, *Critical Care Alert*, *Hospital Medicine Alert, Infectious Disease Alert*, *Internal Medicine Alert*, *Neurology Alert*, *OB/GYN Clinical Alert*, *Primary Care Reports*, *Travel Medicine Advisor*.

Niacin Beats Ezetimibe Head to Head

In this issue: *Statin and niacin increase HDL-C, omeprazole reduces effectiveness of clopidogrel, darbepoetin increases risk of stroke, statins decrease risk of gallstone disease, FDA Actions.*

Statin plus niacin or ezetimibe?

Raising HDL-cholesterol (HDL-C) with niacin plus a statin is superior to lowering LDL-cholesterol (LDL-C) with ezetimibe plus statin in reversing atherosclerosis according to the widely reported ARBITER trial published on-line in the *New England Journal of Medicine* in November and simultaneously reported at the American Heart Association meeting in Orlando, FL. The trial enrolled more than 200 patients with coronary heart disease or a coronary heart disease equivalent who were receiving long-term statin therapy with an LDL-C < 100 mg/dL along with an HDL-C < 50 mg/dL for men or 55 mg/dL for women. The patients were randomly assigned to receive extended-release niacin (target is 2000 mg/day) or ezetimibe (10 mg/day). The primary endpoint was the difference in change from baseline in mean and maximal carotid intima-media thickness after 14 months. The trial was terminated early in July of 2009. Both drugs were effective in their roles — the mean HDL-C in the niacin group increased by 18.4% over the 14-month study period ($P < 0.001$) and the mean LDL-C level in the ezetimibe group decreased by 19.2% ($P < 0.001$). Niacin significantly reduced LDL-C and triglycerides as well, while ezetimibe lead to a reduction in HDL-C and triglycerides. Niacin was superior to ezetimibe in reducing the primary endpoint, leading to a reduction of both mean ($P = 0.001$) and maximal carotid intima-media thickness ($P \leq 0.001$ for all comparisons). Paradoxically, greater reductions in LDL-C seen with ezetimibe were significantly associated with increases in the carotid intima-media thickness. The incidence of major cardiovascular events was also lower in the niacin group than in the ezetimibe group (1% vs 5%; $P = 0.04$ by the chi square test) (published on-line at: www.nejm.org; Nov. 15, 2009).

The study has received enormous attention not only because of the primary endpoint, but also because of the significant reduction in major adverse cardiac events in the niacin group, even though the numbers were quite small. At least one editorialist laments the early termination of the study and feels that it is impossible to make recommendations regarding the "adjuvant agent of choice" based on the small numbers (The HALTS Trial — Halting Atherosclerosis or Halted Too Early; published on-line at: www.nejm.org; Nov. 15, 2009). Still, this study provides enough evidence to consider adding niacin to a statin in patients who are at risk of or have low HDL-C. It also deals another blow to ezetimibe (Zetia®) and its partner drug ezetimibe/simvastatin (Vytorin®).

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

Omeprazole's effect on clopidogrel

The FDA has issued a warning regarding the combination of clopidogrel (Plavix®) with omeprazole (Prilosec®) citing new data that suggest that the combination reduces clopidogrel's effectiveness by about half. Studies reported in 2009 suggested that omeprazole may block clopidogrel's conversion to its active metabolite via CYP2C19, an enzyme that is inhibited by omeprazole. New studies requested by the FDA from the manufacturers confirm a significant interaction between the two drugs, which can significantly hinder clopidogrel's ability to prevent platelet aggregation in patients at risk for heart disease. Omeprazole and clopidogrel are commonly prescribed together to prevent GI bleeding. At this time it is unclear whether this interaction extends to other proton pump inhibitors, although physicians are encouraged to avoid a combination of clopidogrel with esomeprazole (Nexium®, cimetidine (Tagamet®), and other drugs known to inhibit CYP2C19. The FDA is recommending that patients who need GI protection in conjunction with clopidogrel may safely use ranitidine (Zantac®), famotidine (Pepcid®), nizatidine (Axid®), or oral antacids.

Darbepoetin and risk of stroke

Darbepoetin alfa (Aranesp®) is commonly used in patients with chronic kidney disease and diabetes for the treatment of anemia. A new study suggests that the drug may be associated with increased risk of stroke in this patient population. More than 4000 patients with diabetes, chronic kidney disease, and anemia were randomly assigned to darbepoetin alfa to achieve a hemoglobin level of 13 g/dL or placebo with rescue darbepoetin alfa if hemoglobin levels dropped < 9 g/dL. The primary endpoints were the composite outcomes of death or cardiovascular event, and death or end-stage renal disease. After a follow up of 2.5 years, darbepoetin alfa was ineffective at preventing either primary outcome, and, more importantly, the rate of fatal or nonfatal stroke occurred almost twice as often in the treatment group (101 patients assigned to darbepoetin alfa vs 53 patients assigned to placebo; HR, 1.92; 95% confidence interval, 1.38-2.68; $P < 0.001$). The authors conclude that the use of darbepoetin alfa in patients with diabetes, chronic kidney disease, and moderate anemia who are not undergoing dialysis did not reduce the outcome of death, cardiovascular events, or renal events, but was associated with increased risk of stroke. For many "this risk will outweigh the potential benefits" of the drug (*N Engl J Med* 2009;361:2019-2032). Erythropoiesis-stimulating agents have come under fire in the treatment of cancer-associated anemia, and now in renal patients as well. As pointed out in an accompanying editorial, the risks and benefits of these agents must be weighed, namely an increased risk of stroke vs a perceived improvement in quality of life (*N Engl J Med* 2009; 361:2089-2090).

Statins and gallstone disease

Statins have been shown to reduce the risk of cardiovascular disease and death from all causes. Now another potential benefit is being reported: Statins may reduce gallstone disease. Utilizing a large patient database from the United Kingdom, researchers looked at the risk of developing gallstones followed by cholecystectomy in relation to exposure to lipid-lowering agents. The longer patients took statins, the lower the risk for gallstone disease, with patients who had filled 20 or more prescriptions noticing 36% reduction in risk (AOR, 0.64; 95% confidence interval, 0.59-0.70). The authors conclude that long-term use of statins is associated with a decrease risk of gallstones followed by cholecystectomy (*JAMA* 2009;302:2001-2007).

FDA Actions

The FDA has approved a new topical treatment for the treatment of post-herpetic neuralgia (PHN). The capsaicin 8% patch must be applied to the skin by a health care professional since placement may be quite painful, requiring the use of a local topical anesthetic. The patch is applied for one hour during which patients must be monitored, including observation for increases in blood pressure. The patches may be cut to conform to the area of pain and up to 4 patches may be used. The one-hour application is reported to provide up to 12 weeks of reduced pain from PHN. The capsaicin 8% patch will be manufactured by Lohmann Therapie-Systems and distributed by NeurogesX as Qutenza™.

The FDA has approved romidepsin for the treatment of cutaneous T-cell lymphoma in patients who received at least one prior systemic therapy. The drug is a histone deacetylase inhibitor, the first of a new class of antineoplastics. Romidepsin will be marketed as Istodax® by Gloucester Pharmaceuticals. ■

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