American Academy of Pediatrics
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POLICY STATEMENT

Clostridium difficile Infection in Infants and Children

abstract

FREE

Infections caused by *Clostridium difficile* in hospitalized children are increasing. The recent publication of clinical practice guidelines for *C difficile* infection in adults did not address issues that are specific to children. The purpose of this policy statement is to provide the pediatrician with updated information and recommendations about *C difficile* infections affecting pediatric patients. *Pediatrics* 2013;131:196–200

COMMITTEE ON INFECTIOUS DISEASES

KEY WORDS

Clostridium difficile, *Clostridium difficile* infections, antibiotic-associated diarrhea

ABBREVIATIONS

CCCA—cell culture cytotoxicity assay
CDI—*Clostridium difficile* infection
EIA—enzyme immunoassay
FDA—Food and Drug Administration
NAAT—nucleic acid amplification test
NAP1—North American pulsed field type 1
PCR—polymerase chain reaction

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INTRODUCTION

Clostridium difficile is a spore-forming, obligate anaerobic, Gram-positive bacillus and is acquired from the environment or by the fecal-oral route. Toxins A and B are responsible for intestinal disease. *C difficile* is the most common cause of antimicrobial-associated diarrhea and is a common health care-associated pathogen. Clinical symptoms vary widely, from asymptomatic colonization to pseudomembranous colitis with bloody diarrhea, fever, and severe abdominal pain.

The incidence of *C difficile* infections (CDIs) among hospitalized children has been increasing across the United States since 1997.[1–3] Kim et al evaluated the annual incidence of *C difficile*–associated disease from 2001 to 2006 at 22 freestanding children's hospitals and found increases in the number of admissions (2.4 to 4.0/1000 admissions; $P = .04$) as well as the number of cases per patient-days in the hospital (4.4 to 6.5 cases/10 000 patient-days; $P = .06$).[1] Nylund et al evaluated data from 1997, 2000, 2003, and 2006 and demonstrated an increase in the number of CDIs, from 3565 cases in 1997 to 7779 cases in 2006 (total cases, 21 274; $P < .01$).[2] Zilberberg et al also demonstrated an increase of hospitalizations attributable to *C difficile*, from 7.24 to 12.80/10 000 hospitalizations.[3] The emergence of the epidemic strain of toxin-producing *C difficile* (North American pulsed field type 1 [NAP1]) in recent years may have changed the epidemiology in children. Published guidelines for managing CDI in adults affirm that there are gaps in the knowledge surrounding CDIs in infants and children.[4]

Disease in the Neonate/Infant/Young Child 0 to 3 Years of Age

Although testing of infants is not recommended, recent data have shown that 26% of children hospitalized with CDIs were infants younger than 1 year, and 5% were neonates.[1] What cannot be determined from these data are whether the rates of hospitalization for CDIs represent true disease or asymptomatic carriage.

The intestine of the newborn infant is sterile, but by 12 months of age, an infant's intestine has flora similar to that of an adult.[5] *C difficile* carriage rates average 37% for infants 0 to 1 month of age and 30% between 1 and 6 months of age.[5] Vaginal delivery, premature rupture of membranes, and previous administration of antimicrobial agents have little effect on carriage rates, but exposure to environments where *C difficile* is present (eg, ICUs) is important.[6–8] The organism has been recovered from the hands of hospital personnel, baby baths, oximeters, electronic thermometers, and hospital floors. Breastfed infants have lower carriage rates than do formula-fed infants (14% vs 30%, respectively).[9] At 6 to 12 months of age, approximately 14% of children are colonized with *C difficile*, and by 3 years of age, the rate is similar to that of nonhospitalized adults (0% to 3%).[5] Recognized risk factors for older children acquiring CDI included antimicrobial therapy, use of proton pump inhibitors, repeated enemas, use of diapers, prolonged nasogastric tube insertion, gastrostomy and jejunostomy tubes, underlying bowel disease, gastrointestinal tract surgery, renal insufficiency, and impaired humoral immunity. Carriage rates in hospitalized children and adults approximate 20%.[4] Many of these risk factors are common among hospitalized children; the presence of risk factors does not necessarily prove causation of CDI in an individual patient.

Clinical illness is rarely reported before 12 to 24 months of age. It is possible that neonates/infants may lack the cellular machinery to bind and process the toxins of *Clostridium* species.[10] There have been relatively few studies of *C difficile* with diarrhea that include control groups. In an emergency department treating children, 7% of patients with diarrhea and 15% of controls were colonized with *C difficile*.[11] In 2 studies of inpatients 0 to 2 years of age, 11% to 59% of patients with diarrhea and 24% to 33% of controls were colonized with *C difficile*.[12,13] Among inpatients 0 to 34 months of age, 21% of those with diarrhea and 33% of controls carried *C difficile*.[14] Among patients 0 to 12 years of age, 2.9% of outpatients, 4.6% of inpatients, and 6.6% of controls were colonized with *C difficile*.[15] In the setting of a high prevalence of asymptomatic carriage, detection of *C difficile* toxin cannot be assumed to be the causative agent for diarrhea in children before adolescence, particularly young children.[16]

The NAP1 Isolate of *C difficile*

The NAP1 strain of *C difficile* has been described as causing severe disease, including an increased incidence of symptomatic infection relative to colonization, recurrent disease, sepsis, toxic megacolon, bowel perforation, and mortality.[17] The NAP1 strain has entered the pediatric population at lower rates (10%–19% of *C difficile* isolates) than reported for adults (>50%).[18,19] NAP1-associated CDIs occur in children without exposure to health care facilities and/or to antimicrobial agents.[20,21] Whether the NAP1 strain is truly responsible for more severe disease in children requires further investigation. Newer strains of *C difficile* have also been isolated (eg, NAP7, NAP8), and their role in human disease has yet to be elucidated completely.[22] Detection of the NAP1 strain of *C difficile* is not possible in most laboratories and, in most situations, would not influence the clinical care of an individual patient.

DIAGNOSTIC TESTING

The diagnosis of *C difficile* disease is based on the presence of diarrhea and of *C difficile* toxins in a diarrheal stool specimen. Diarrhea is often defined as 3 or more stools that take the shape of their container in a 24-hour period. Because of a slow turnaround time, isolation of the organism from stool is not a clinically useful diagnostic test, nor is testing of stool from asymptomatic patients. The cell culture cytotoxicity assay (CCCA) has been replaced by more sensitive diagnostics. The most common testing method used today for *C difficile* toxins is the commercially available enzyme immunoassay (EIA), which detects toxins A and/or B. Mean test sensitivities range from 72% to 82%, with mean specificities of 97% to 98%, compared with the CCCA.[23] With low prevalence rates of disease in children, sensitivities and specificities such as these lead to an unacceptably low positive predictive value, thus limiting the usefulness of such testing.[11–15] Testing for glutamine dehydrogenase produced by *C difficile* should only be used as part of a 2-step algorithm with a confirmation of positive results by using either a toxin assay A/B EIA or a CCCA.[4]

Molecular assays using nucleic acid amplification tests (NAATs) are approved by the US Food and Drug Administration (FDA) and are now preferred by many laboratories. NAATs combine good sensitivity and specificity, have turnaround times comparable to EIAs, and are not required to be part of a 2- or 3-step algorithm.[24] In a recent study, the sensitivities of the real-time polymerase chain reaction (PCR) assay for toxin A/B compared with EIA for toxin A/B were superior (95% vs 35%, respectively), and the specificity was equal (100%).[25] With the use of the PCR, the positivity rates for stool samples doubled, from 7.9% to 8.3% with EIA to 14.9% to 18.1% with PCR, and the numbers of repeated samples decreased. Many children's hospitals are converting to NAAT technology to diagnose CDIs, but more data are needed before NAATs can be used routinely.[4]

Because carriage is so common, it is prudent to avoid routine testing for *C difficile* in children younger than 1 year. Testing for *C difficile* can be considered in children 1 to 3 years of age with diarrhea, but testing for other causes of diarrhea, particularly viral, is recommended first.[19] For children older than 3 years, testing can be performed in the same manner as for older children and adults. Endoscopic findings of pseudomembranes and hyperemic, friable rectal mucosa suggest pseudomembranous colitis and are sufficient to diagnose a CDI at any age.

A common mistake is to use EIAs and NAATs as tests of cure after treatment of CDIs. *C difficile*, its toxins, and genome are shed for long periods after resolution of diarrheal symptoms. None of the assays are licensed or recommended for tests of cure. Excretion of toxin approximates 13% to 24% at 2 weeks and 6% at 4 weeks after therapy.[26,27] Given that NAAT testing is more sensitive than toxin assays, an interval greater than 4 weeks since last testing should be used for testing with a recurrence.

TREATMENT

Discontinuation of antimicrobial agents is the first step in treating CDI and may suffice in most instances. For patients with moderate or severe disease, proper empirical antibiotic treatment should be started as soon as the diagnosis is suspected. Antiperistaltic medications should be avoided because they may obscure symptoms and precipitate complications, such as toxic megacolon. Although orally administered vancomycin is still the only agent approved by the US FDA for the treatment of CDI in children, it was replaced as the drug of choice in the 1990s in response to concerns over the emergence of vancomycin-resistant enterococcus. Metronidazole is currently the drug of choice for the initial treatment of children and adolescents with mild to moderate disease on the basis of efficacy, cost, and antimicrobial stewardship. Oral vancomycin or vancomycin administered by enema with or without intravenous metronidazole is indicated as initial therapy for patients with severe disease and for patients who do not respond to oral metronidazole.[4] Severe or fatal disease is more likely to occur in neutropenic children with leukemia, in children with intestinal stasis (eg, Hirschsprung disease), and in patients with inflammatory bowel disease. Prospective trials for therapy longer than 10 days have not been performed for either drug. Historically, metronidazole resistance in *C difficile* was rare, and there is no evidence that the new epidemic isolates, NAP1, is more resistant to metronidazole compared with the nonepidemic isolates. A recent randomized controlled trial evaluating a subgroup of patients with severe disease suggested that vancomycin treatment was superior to metronidazole even in patients infected with the NAP1 isolate.[28] Extrapolating these data to treatment with infants and children is difficult, and more data are required.

Up to 30% of patients treated for CDIs experience a recurrence after discontinuing therapy. Recurrences represent either relapse with the original isolate or reinfection with a new isolate. In clinical practice, the distinction cannot be made. Patients with a recurrence will usually respond to a second course of the same treatment. Metronidazole should not be used for the treatment of the second recurrence (third episode) or for chronic therapy (because of possible neurotoxicity[4]), and tapered or pulsed regimens of vancomycin are recommended for this situation. Vancomycin therapy is recommended in adults with the first recurrence if the patient has a white blood cell count of 15 000/μL or higher or has an increasing serum creatinine concentration, because they are at a higher risk of developing complications from CDI. No data exist for children. Other antimicrobial agents with activity against *C difficile* include nitazoxanide, fidaxomicin (FDA approved for treatment of CDI in adults in 2011), and rifaximin; criteria for optimal use of these drugs in children are unknown. Because there is a lack of controlled studies in children, probiotics are not recommended for either the prevention or the treatment of CDI. In rare instances, severely ill patients may require cecostomy for irrigation or a colectomy. Fecal transplantation (enteric administration of donor stool flora) is used anecdotally.[29]

CONTROL

Transmission is via the fecal-oral route, and CDI is transmitted to others by contact with the patient or the patients' contaminated environment. Control of *C difficile* in the environment is essential to the control of CDIs in health care facilities. People with *C difficile*–associated diarrhea should be placed in standard plus contact precautions for the duration of their diarrhea. Test of cure is not recommended; the patient may be removed from isolation once the diarrhea has resolved. Use of gloves is the best proven method for preventing patient-to-patient transmission via the hands of health care personnel. Hand-washing with soap and water is more effective for the removal of spores than is alcohol-based hand sanitizer. Germicidal wipes with 10% sodium hypochlorite are good adjuncts for cleaning the environment, especially in an outbreak situation.

RECOMMENDATIONS

1. Testing for *C difficile* colonization or toxin should only be performed in

children with diarrhea who meet the clinical and age-related conditions listed in the following recommendations.

2. Testing in infants (younger than 12 months of age) is complicated by a high rate of asymptomatic colonization. Testing of these infants should be limited to those with Hirschsprung disease or other severe motility disorders or in an outbreak situation. Alternative etiologies should be sought even in those with a positive test result for *C difficile*.
3. Testing in the second and third year of life is difficult to interpret; alternative etiologies should be sought. A positive test result indicates possible CDI.
4. A positive test result after the third year of life indicates probable CDI. Risk factors increasing the probability of CDI include antimicrobial therapy, use of proton pump inhibitors, underlying bowel disease, renal insufficiency, or impaired humoral immunity.
5. Endoscopic or histologic test results positive for pseudomembranous colitis indicate definite CDI.
6. Test of cure is not recommended. Testing for recurrences less than 4 weeks after initial testing is only useful when the results of repeat testing are negative.
7. Discontinuation of antimicrobial agents is the first step in treating CDI and may suffice in most instances. Antiperistaltic medications should be avoided.
8. When antimicrobial treatment is indicated for moderate disease, metronidazole (30 mg/kg/day in 4 divided doses, orally; maximum, 2 g/day) is the drug of choice for initial treatment of first episode of CDI and for first recurrence.
9. Oral vancomycin (40 mg/kg/day in 4 divided doses; maximum, 2 g/day), with or without metronidazole, is recommended for severe disease and second recurrence.
10. Use of gloves with symptomatic patients, washing of hands with soap and water, and environmental decontamination using chlorine products are key control measures. Contact isolation may be removed once the diarrhea has resolved.

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