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Review Article

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Clostridium difficile in Children: To Treat or Not to Treat?

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Clostridium difficile infection has been increasing since 2000 in children and in adults. Frequent antibiotics use, co-morbidity, and the development of hypervirulent strains have increased the risk of infection. Despite the high carriage rates of *C. difficile*, infants rarely develop clinical infection. Discontinuing antibiotics and supportive management usually leads to resolution of disease. Antibiotics use should be stratified depending on the patient's age and severity of the disease.

Key Words: *Clostridium difficile*, Child, Anti-bacterial agents

EPIDEMIOLOGY AND PATHOGENESIS

Clostridium difficile is a gram-positive, spore forming bacterium usually spread through the fecal-oral route. It is non-invasive and presentation rages from asymptomatic carriage, to mild diarrhea, colitis, or pseudomembranous colitis caused by production of toxin A and B. *C. difficile* infection (CDI) is defined as the acute onset of diarrhea with documented toxigenic *C. difficile* or its toxin and no other cause for diarrhea. CDI increases morbidity and mortality, particularly in hospitalized patients. CDI has been increasing since 2000 in both hospitalized patients and the general community in Asia, Europe, and North America. In adult patients, CDI increased 4-fold in Canada [1]. In Korea, the prevalence was 1.7 per 1,000 hospitalized adult patients in 2004 and 2.7 per 1,000 hospitalized adult patients in 2008 [2]. In pediatric patients, the United States Healthcare Cost and Utilization Project Kids' Inpatient Database (HCUP-KID) reported 0.2% cases in hospitalized pediatric patients, and a significant increase from 3,565 cases in 1997 to 7,779 cases in 2006 [3].

The increase in CDI incidence is thought to be multifactorial, including increased antibiotic use such as cephalosporins and quinolone, an increasing elderly patient population, and the development of hypervirulent strains of *C. difficile* [4]. *C. difficile* colonizes in the intestine after disruption of normal intestinal microbiota. Frequent use of antibiotics increases the risk of colonization and toxin production by 2-16 fold [5]. Severe CDI is associated with hyper-

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virulent strains such as ribotype 027, North American pulsed-field gel electrophoresis type 1 (NAP1), and restriction endonuclease analysis B1. The NAP1 strain produces approximately 20-fold higher levels of toxins A and B due to a deletion in the toxin regulatory gene, tcdC [6]. Severe CDI outbreaks have been reported in Western countries, Japan and Korea. A fluoroquinolone-resistant strain of *C. difficile* (B1/NAP1/027) has been predominantly associated with these outbreaks [7]. In 2008, European multicountry surveillance attributed 4.1 per 10,000 patient-days per hospital to CDI, and identified 65 different ribotypes. Of the cases analyzed, 22% of patients had died and *C. difficile* contributed at least in part to 40% of deaths. Infection by polymerase chain reaction-ribotypes is associated with complicated disease outcome [8].

In 2010, the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America published clinical guidelines for CDI in adults [9]. They recommended metronidazole in mild to moderate disease, and vancomycin as a first-line therapy in severe disease. However, there are sparse data and guidelines for treatment of pediatric CDI.

CHARACTERISTICS OF *CLOSTRIDIUM DIFFICILE* IN CHILDREN

While the incidence of CDI in children also has been increasing, the severity of cases has not increased. In sharp contrast to adult data, HCUP-KID data reported no significant positive trends in mortality, rate of colectomy, or hospital days [3]. The percentage of NAP1 in pediatric CDI was 19.4% in a report [10], compared to more than 50% in adults. The relatively low incidence of hypervirulent strains might explain the observation that severe cases in children have not increased. On the other hand, asymptomatic colonization of *C. difficile* is common in early infancy, and it often occurs in the first week of life. The carrier rate is reported to be 1% to 84% in healthy newborns and infants [11,12], but it decreases to less than 5% by 8 years of age. The most likely source in infants is from environmental contamination rather than direct maternal infant transmission. Chang et al. [13] reported that the toxin positivity rate is significantly higher in the infants with persistent *C. difficile* colonization than in those with transient colonization (66.7% vs. 24.5%, p=0.001). Exclusive breast-milk feeding decreases the risk of persistent colonization compared to formula or mixed feeding. The susceptibility to *C. difficile* colonization might be because of the immaturity of the intestine and lack of protective intestinal microbiota [11]. Despite the high carriage rates, infants rarely develop clinical infection. The mechanisms for the resistance of infants to CDI are thought to be related to the immunoglobulin fractions of breast milk that inhibit the binding of toxin A to its intestinal receptor, and absence in the newborn gut of the intestinal receptor that binds *C. difficile* toxin A [11,14]. Risk factors of CDI in children are previous antibiotics use, and predisposing comorbidities. A recent study of pediatric CDI cases reported 92% of children with previous antibiotics use, 60% with immunosuppressive treatment, 39% with a malignancy or organ transplantation, and 13% with inflammatory bowel disease [15]. While previous proton pump inhibitor use is known to be associated with CDI in adults [16], the association with CDI in children is not established.

DIAGNOSIS OF CDI IN CHILDREN

Guidelines for diagnosis recommend that only stools from patients with diarrhea should be tested for *C. difficile* and tests for cure should not be performed [1]. Endoscopic examination is not commonly recommended except in special cases. Toxigenic cultures and cytotoxin assays are the gold standard for CDI diagnosis. Nucleic acid amplification tests for toxin genes are superior to the toxin A and B enzyme immunoassay (EIA) tests. Although the EIA test is highly specific, it is not highly sensitive in adults. *C. difficile* culture is not recommended because only the toxigenic organisms cause disease. Use of EIA in pediatric patients showed similar results, although, Toltzis et al. [17] reported a positive predictive value of 64% in children. Children with

false-positive EIA results were significantly younger than those with true-positive tests. El Feghaly et al. [15] reported that 24% of children with CDI had a concomitant viral co-infection and reported that norovirus genogroup 2 was the most common virus. Detection of *C. difficile* toxin in stool may not be the causative agent in children with diarrhea, particularly in young children. Stool examination for *C. difficile* in infants should be limited.

TREATMENT

The use of antibiotics is not recommended in case of asymptomatic colonization with *C. difficile*. Eradication of *C. difficile* was attempted in one hospital to eliminate a potential reservoir for nosocomial outbreaks, but metronidazole was ineffective and vancomycin was only of temporary effect [18].

General considerations for treatment of children with CDI include correction of fluid and electrolyte imbalances in addition to examination of the patient's medical record for any history of antibiotics and proton pump inhibitor use. Opiates for pain control increase risk of ileus or toxic megacolon. Antimotility agents such as loperamide should be avoided.

The treatment of CDI in children is based on data from clinical trials in adults. Mild to moderate disease is defined as diarrhea (<6 stools/day) without signs of systemic toxicity. Fever is usually absent. Severe colitis is defined as frequent diarrhea (>6 stools/day) with severe abdominal pain and fever. Marked leukocytosis and azotemia may be observed. Children with fulminant colitis show the most extreme manifestations such as hypotension, rising lactic acid levels, shock, and complete ileus or toxic megacolon. For children with moderate or severe disease, data-supported empirical antibiotic treatment should be started as soon as the diagnosis of CDI is suspected. Oral metronidazole at 30 mg/kg/day in 4 divided doses for 10-14 days is recommended in mild-to-moderate disease. For severe colitis, oral vancomycin at 40 mg/kg/day in 4 divided doses for 10-14 days is recommended. If necessary, subsequent adjuvant therapy with intravenous metronidazole and vancomycin retention enema (adult dose 0.5-1.0 g in 100 mL of normal saline every 4-12 hours) may be considered [19].

In adult patients, metronidazole and vancomycin showed an initial high cure rate of 76-90% in 2007 [20]. Since then, the rate of treatment failure and disease relapse with the use of metronidazole has increased. NAP1 isolates may have reduced susceptibility to metronidazole [7]. Jardin et al. [21] compared treatment patterns and outcome of adult patients before and after implementation of severity-based CDI guidelines. After implementation of guidelines, the use of oral vancomycin was increased and the increased use was associated with decreased rates of refractory CDI.

Based on recent observational data, 53-63% of children with CDI are treated with metronidazole, and use of oral vancomycin in children varies from 3.5-30% [19]. In a recent study, 27% of children with CDI were not treated with antibiotics, and the majority (42%) were treated with metronidazole, though 74% of children had severe colitis [22]. The American Association of Pediatrics recommends discontinuation of antibiotics as the first step in treating CDI, which may suffice in most instances [23]. Algorithm for CDI in children is suggested in Fig. 1.

Probiotics could be started with antibiotic therapy to prevent antibiotic-associated diarrhea in children. The use of high-dose probiotics (5 billion CFU/day) appears to be effective with the number needed to treat to prevent 1 case of diarrhea of 7 (95% confidence interval, 6-10) [24]. Studies of the effect of probiotics in the treatment of CDI are limited. In recurrent or severe CDI, fecal microbiota transplantation might be effective. Donor-acquired feces are implanted into the gastrointestinal tract of the patient via a nasoduodenal catheters, retention enema, duodenoscopy or colonoscopy. van Nood et al. [25] reported 81% resolution of recurrent CDI after the first infusion of feces in a small group of patients. Normal bowel flora serve as a defense mechanism against pathogenic organisms and may result in the elimination of *C. difficile* spores.

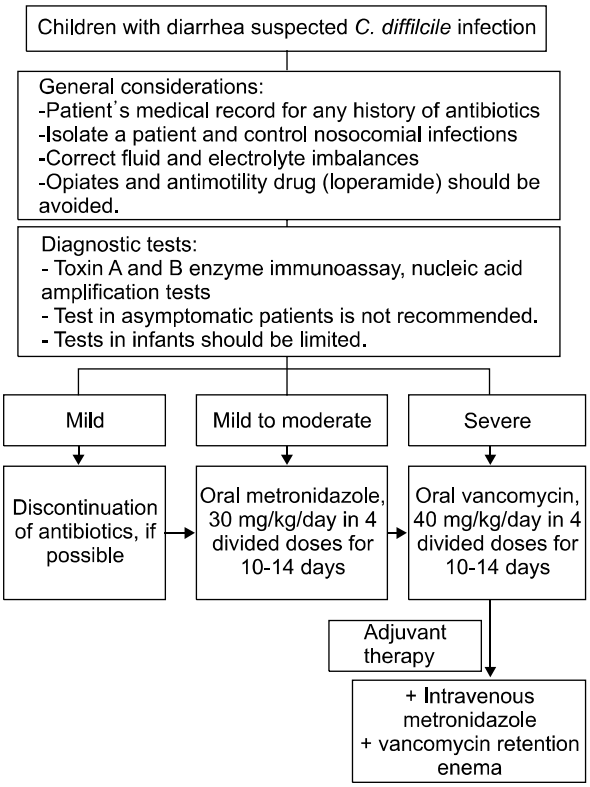

Fig. 1. Algorithm for management of children with unexplained diarrhea suspected *Clostridium difficile* infection.

CONCLUSION

Cases of CDI in children are different from those in adults. Despite the high carriage rates of *C. difficile*, infants rarely develop clinical infection. Antibiotics should be stratified depending on the patient's age and case severity. Genetic epidemiology of hypervirulent strains may be helpful in pediatric patients with CDI.

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