



***Clostridioides difficile* Toxin Positivity in a Hospitalized Baby with Diarrhea: How Should the Evaluation and Management Be?**

Hastanede Yatan ve İshali Gelişen Küçük Bebekte *Clostridioides difficile* Toksini Pozitifliği: Değerlendirme ve Yönetim Nasıl Olmalıdır?

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Question: *Clostridioides difficile* Toxin Positivity in a Hospitalized Baby with Diarrhea: How Should the Evaluation and Management Be? **Sinem İrez, MD, Kasım Bozgeyik, MD, Ceren Can, MD**

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On the 8th day of hospitalization in a six-month-old hospitalized baby, vomiting and mild fever begin. One day later, profuse watery diarrhea develops 5-7 times a day. Two infants in the ward had similar acute gastroenteritis complaints at similar times. *Clostridioides difficile* toxin is positive in the stool of the baby who was treated with cefotaxime vancomycin with the diagnosis of pneumonia and parapneumonic effusion. Vomiting passes and diarrhea decreases significantly in the three-day period until the available test result.

In this patient:

- 1) Can *C. difficile* infection (CDI) develop while taking IV vancomycin? (Sinem İrez, MD)
- 2) Is treatment required for CDI, and if so, what should be the optimal management? (Kasım Bozgeyik, MD)
- 3) Is it necessary to look for control *C. difficile* toxin, and if necessary, when? (Ceren Can, MD)

Answer (Fatma Dilşad Aksoy, MD; Mustafa Kemal Hacimustafaoğlu, MD)

Introduction and general information: *Clostridioides difficile* is an anaerobic, gram-positive, spore-forming bacterium that causes disease via its toxins. *C. difficile* rapidly transform into a spore form with a durable and infective capacity in the environment (such as perianal, soil, home or hospital environment, patient or hand and skin surfaces of contacted person). Spores are very resistant to outdoor conditions. They can survive for months on hospital surfaces. *C. difficile* causes acute gastroenteritis through toxin A (enterotoxin) and toxin B (cytotoxin). Toxin-free types (non-toxicogenic *C. difficile*) do not cause disease. In fact, gastrointestinal (GIS) colonization with non-toxicogenic types may provide protection against *C. difficile* infection (CDI) that develops with toxicogenic types (1,2).

C. difficile can cause antibiotic-associated diarrhea and is the most important cause of antibiotic-associated diarrhea. In

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this respect, in clinical practice, CDI; considered as antibiotic-associated diarrhea. CDI is more common in adults than children. *C. difficile* can cause community-acquired or hospital-acquired antibiotic-associated diarrhea. Antibiotic use is the most important risk factor for both community-acquired and hospital-acquired CDI, and may develop during antibiotic use or up to 10 weeks after antibiotic discontinuation. For CDI, other risk factors include; use of proton pump inhibitors, GI feeding tubes (such as gastrostomy, jejunostomy), malignancy, transplantation, inflammatory bowel disease, cystic fibrosis, Hirschprung's disease, structural and post-operative bowel diseases. Both CDI (symptomatic) and asymptomatic colonization rates were found to be higher in risk groups (1).

C. difficile colonization in the infants and children: Toxicogenic (or non-toxicogenic) *C. difficile* colonization is common during the first year of life. Colonization usually lasts for several months, but can sometimes take much longer (a year or more). In addition, in colonized cases, there may be a transition between toxicogenic and non-toxicogenic types over time (3-6). In a meta-analysis, 95 observational studies (approximately 20,000 asymptomatic pediatric cases) over a 30-year period between 1990 and 2020; *C. difficile* (toxicogenic and non-toxicogenic) colonization rates were evaluated (6). Total colonization (toxicogenic and non-toxicogenic) rates were found 15% (95% CI, 7-25%) at <7 days, peaked 41% (95% CI, 32-50%) at 6-12 months, decreased again after one year, and 12% (95% CI, 7-18%) at 5-18 years. Toxicogenic *C. difficile* rates were found 3% (95% CI, 1-5%) at 1-3 months, peaked at 6-12 months as 14% (95% CI, 8-21%), and decreased again 6% (95% CI, 2-11%) at age >5 years (6). Hospital-acquired acquisition is important in the development of colonization in hospitalized newborns and infants, and the colonization rate increases as the length of hospital stay increases (3).

Newborns and infants <1 year of age are frequently colonized even with the toxicogenic *C. difficile* types, however, they rarely experience symptomatic disease (1,5). The exact reason for this is not known (7). In newborns and small infants, the lack of receptors to which CD toxin binds or weakly binding may be a factor. Toxin not binded to the intestinal epithelium; diarrhea (toxin A; via enterotoxin) and enterocyte damage (toxin B; via cytotoxin) cannot be developed. In addition, the presence of antibodies to toxins A and B; prevents the development of clinical signs. The presence of antibodies against toxins has been demonstrated in asymptomatic colonized infants (8).

Colonized infants and children may transmit the agent to others (adults and other children), and may cause infection (especially in the presence of risk factors) or colonization after transmission (9). In addition, colonized patients can also infect the hospital environment if infection control measures are not followed properly. Therefore, it is important to apply infection

control measures (predominantly hand washing) for *C. difficile* in the management of the hospitalized asymptomatic/colonized patients.

Clinical findings in CDI: Acute onset, mild to moderate diarrhea (watery and profuse) is the most common finding in CDI, especially in a child receiving antibiotics (or within 10 weeks of antibiotic discontinuation). Fever and cramping pain in the lower abdomen are common. On physical examination, there may be tenderness in the lower abdomen. Sometimes there may be vomiting. Presence of significant systemic findings (such as fever, chills, severe abdominal pain, tenderness, distension), blood in stool (macroscopic or laboratory based), significant leukocytosis ($\geq 15,000$), elevated creatinine, hypoalbuminemia (<2.5 gr/dL), presence of pseudomembranous enterocolitis, consider serious CDI. Presence of ileus, toxic megacolon, hypotension or shock suggest fulminant disease (1,10). The presence of overt or occult blood in the stool and the presence of leukocytes in the stool support CDI, but these laboratory findings (for each) are seen in about a quarter of the cases (10-15). Detection of *C. difficile* toxin (CDT; toxin A and/or toxin B) in the stool of a child with symptoms consistent with CDI is the most commonly used test for diagnosing CDI infection. This test is inexpensive and can be resulted in a short time (11).

If there is symptomatic CDI, there is indication for treatment (oral vancomycin, or oral/iv metronidazole). In severe cases who cannot take it orally, vancomycin can be given rectally (as a retention enema) (16). Since intravenous vancomycin is not secreted effectively into the colonic mucosa, it is not effective in the treatment of CDI. So, intravenous vancomycin should not be given for CDI treatment (16).

In regard of this general information, the answers to the questions can be briefly summarized as follows;

1) Can CDI develop while taking IV vancomycin? Vancomycin is given orally in the treatment of CDI (10 mg/kg/dose, po, routinely maximum 125 mg/dose, or maximum 500 mg/dose in fulminant disease). Oral vancomycin is not absorbed from the GI tract and achieves effective concentrations in the target site (mainly the colon). IV vancomycin is not effective because it is not secreted to reach effective concentrations in the colonic mucosa. Therefore, iv vancomycin is not expected to have a preventive (or curative) effect from CDI.

2) Does this patient require treatment for CDI, and if so, what should be the optimal management? As noted above, asymptomatic *C. difficile* colonization is common in newborns and infants <1 year old. Colonization rate is most common especially between 6-12 months (mean 41% colonization rate). In addition, hospitalization and/or antibiotic use increase the frequency of colonization. Although, symptomatic CDI requires treatment, in regard of colonization (including toxin-producing *C. difficile* types), there is no indication for treatment. Tak-

ing into account the high colonization rates, some clinicians do not routinely order CDT at <1 year of age (and there may be co-incidence with other causes of acute gastroenteritis). It is important to determine whether the acute gastroenteritis in this patient is due to CDI or colonization. Fever, diarrhea and lower abdominal pain predominate in CDI, however, vomiting is not very common. Acute gastroenteritis in this patient and other patients with in the same ward, can consider the other etiologies (especially rotavirus, norovirus and other viral agents) as the causative agent of acute gastroenteritis (co-incidence with CDT positivity?). In addition, the improvement of the clinical picture until the CDT result is available can be considered as a factor deterring the diagnosis of symptomatic CDI.

Briefly, although antibiotic use is a risk factor, the possibility of acute gastroenteritis due to CDI is low in this patient. In addition, Existing CDT positivity can most likely be interpreted as colonization (toxicogenic *C. difficile*), and it would be appropriate to monitor the patient without prescribing CDI therapy.

3) Is control CD toxin required in this patient, and when should it be checked? *C. difficile* colonization in infants can last for months, sometimes longer. Therefore, there is no indication for routine control CDT in colonized cases. In addition, in symptomatic CDI, control CDT is not recommended after optimal treatment. Because even after successful treatment, colonization with toxin-producing strains may continue for some time (17).

Other causes of acute gastroenteritis should be investigated in the patient in question and appropriate optimal management should be performed. In addition, a colonized patient (as with CDI) can contaminate the hospital environment, health workers and other patients. In this respect, hospital infection control measures (such as contact isolation, and especially hand washing) for *C. difficile* should be applied meticulously. It should be kept in mind that alcohol-based hand disinfectants are not effective against *C. difficile* spores, and hand washing practice should be kept in mind when entering and leaving the patient's room. The same is true for the caregiver (e.g. mother or caregiver person) of the baby. Since detergents containing quaternary ammonium are not effective against spores, patient room (including bathroom, toilet etc.) should be cleaned with disinfectants containing chlorine (approximately 5000 ppm chlorine, or 1 part bleach to 10 parts water) during hospitalization (daily cleaning) and room cleaning after discharge.

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