**Abstract**

Two case reports of children with muco-hemorrhagic diarrhea positive for *Clostridium difficile* introduce into the world of *Clostridium difficile* infection in the pediatric age. Epidemiological, clinical, and microbiological findings represent pieces of the puzzle of one of the most emerging infections at all the ages.

**Keywords:** *Clostridium difficile*, Children, Multifaceted infection

**Abbreviations**

CDI: *Clostridium Difficile* Infection, HA-CDI: Hospital Acquired *Clostridium Difficile* Infection, CA-CDI: Community Acquired *Clostridium Difficile* Infection, FMT: Faecal Microbiota Transplantation, IBD: Inflammatory Bowel Disease, PPI: Proton pump inhibitors

**Commentary**

Two children were referred to our Pediatric Gastroenterology Unit for muco-hemorrhagic diarrhea.

**Patient 1:**

The first one was a 13-month-old boy, with a medical history started since the third trimester of pregnancy when a moderate bilateral dilation of urinary tract was demonstrated at ultrasonography. After a normal delivery he underwent to recurrent episodes of urinary tract infections caused by *E.coli* and treated with amoxicillin when, at age of 6 months, a urinary cistography showed a 3rd degree bilateral vesicoureteral reflux. At 9 months of age, he developed fever, vomiting and diarrhoea, and he was treated with IV cephalosporin for pyelonephritis. Successively, a prophylactic therapy with amoxicillin was started. Two months later, when he was 1-year-old, he developed progressively irritability, feeding refusal, associated with failure to thrive; an urine analysis showed the presence of an infection by *E.coli* resistant to amoxicillin and IV cephalosporin therapy was administrated at home. After a few days of clinical improvement, the reappearance of symptoms suggested to refer the child to a Hospital, where gentamicin was added to treatment. Five days later, a picture of mild diarrhoea appeared, and stools analysis for common viral and bacterial pathogens, revealed the presence of Rotavirus infection. Three days later, diarrhoea increased with progressive appearance of mucous and blood, fever and worsening of general conditions. For this reason the child was referred to our Hospital, where he arrived febrile (39 degrees Celsius of temperature), with mild dehydration, dilated abdomen, 5 to 7 muco-hemorrhagic evacuations daily, and laboratory evidence of leukocytosis (16000/mmc), and raised serum CRP (9.1 mg/L; n.v. <0.5 mg/L). Urine, blood and faecal cultures were negative, but a search for toxigenic *Clostridium difficile* (CD) came back positive suggesting a presumptive diagnosis of *Clostridium difficile* infection (CDI). Discontinuation of cephalosporin and gentamicin and prompt administration of oral metronidazole (25-30 mg/kg/day qid x 10 days) induced an amelioration of clinical picture within 36 hours with complete remission after 3 days of such a treatment.

**Patient 2:**

The second patient was a 14-year-old girl, without any significant clinical history, who developed a severe diarrhoea with more than 8 loose stools for day with mucous and blood, fever and abdominal pain. Laboratory analysis showed anaemia (8.3 g/dl), thrombocytosis (580000/mmc), raised ESR (75 mm/hr) and CRP (7 mg/L; n.v. <0.5 mg/L), and the presence of toxigenic *C. difficile* in the stools. A treatment with metronidazole alone first and combined with IV later, didn’t improve the clinical picture. For this reason a systemic steroid therapy with methylprednisolone (1 mg/kg/day in 2 doses) was started and the patient was referred to our Division. At admission the clinical picture was very complicated, with radiologic evidence of dilation of the colon (Figure), suggesting the need to alert surgeons for possible colectomy. According with the ECCO guidelines for managing acute severe ulcerative colitis in children a rescue treatment with anti-TNFα resulted in a dramatic improvement and the patient was successively...
discharged after 10 days, with a diagnosis of severe ulcerative colitis in treatment with anti-TNFα and thiopurines.

Clostridium Difficile: Colonizer or Pathogen?

Human intestine is sterile at birth [1]. Successively a rapid bacterial colonization driven by the environment (vaginal flora, cutaneous flora) and mainly modulated by feeding (Human vs. Formula milk), occurrence of infections, antibiotics exposure, etc. happens [1]. Many different phyla of intestinal microbes, like Firmicutes and Bacteroidetes, as well as Clostridia develop as part of an extremely rich microbiota population where, during the first month Clostridium difficile is present in 50-70% of newborns [2]. In spite of the presence of CD, new-born’s rarely develop CD-associated diarrhea and, during the first year of life, gradually, eliminate Clostridium difficile from faeces, with only approximately 3% of children still harbouring the bacterium at 2 years of life. At the same time IgG-antitoxins increase suggesting that toxigenic strains are involved in colonization and that immune response is a key factor of the phenomenon of ecological succession and prevention of CDI in the adult age [2].

However, sometimes, the history has another course. It is the case of concomitant colonic diseases, or previous digestive surgery, or excessive exposure to health-care admissions, or disequilibrium of intestinal microflora caused by repeated antibiotic courses or immunosuppressive drugs [3,4]. In such conditions, rapid growth of Clostridium difficile may occur, and production of toxins A and/or B, as well as other less-known toxins, produces colonic epithelial injury leading to diarrhea, mainly mild to moderate, erosions with bloody diarrhea, up to pseudomembranous colitis with severe colonic and systemic impairment and death, which rarely occurs in children.

Case 1 describes an infant with hospital-acquired CDI, secondary to multiple antibiotic courses and responsive to specific treatment with oral vancomycin, which is the drug of choice in case of severe infection [5]. Hospitalization and exposure to multiple antibiotic classes may influence the development and severity of CDI4, as in this infant.

Case 2 describes a CD-associated onset of ulcerative colitis, in a child without any recent health-care exposure or antibiotic treatment. This is typical of community-associated CDI and the lack of response to and the lack of response to in this case is in keeping with Clostridium difficile as an innocent bystander or promoter of an idiopathic ulcerative colitis, as described in many retrospective and prospective studies in both children and adults with IBD [6,7].

Exploding or Rare Disease?

Many recent reports suggested that there is an increasing incidence of CDI infection in US and in Europe. Even if the burden of disease regards the adult age, a concomitant increase of number of hospitalizations, hospital length of stay, medical expenses, colectomy rate for CDI have been reported also in children [8,9]. In spite of this phenomenon, CDI infection is rarely severe at this age, and severity is strongly related to the presence of multiple antibiotic courses [4]. Other risk factors of CDI, as a particular age group, the presence of tube feedings, PPI use and abuse, intestinal surgery, have not been associated with a more severe course of disease [4].

Of interest, both hospital (HA) and community (CA) associated CDI are increasing [9], but while in HA-CDI the above mentioned risk factors are usually found, these factors are often lacking in CA-CDI [10], where the main determinant factor is the presence of comorbidities and among these of inflammatory bowel disease (IBD) [6-9].

Diagnosis of Clostridium Difficile Infection or Clostridium Difficile Colonization?

As the presence itself of Clostridium difficile in stools is not diagnostic of disease, we need to disambiguate two opposite situations, true infection or colonization [5]. The first mandatory finding we need for a diagnosis of CDI is the presence of diarrhea, especially if lasting more than 1 week and with characteristic of colitis (fever, mucous and blood in faeces). If diarrhoea is present, we have some factors of decreasing or increasing the risk to have CDI: among the first ones, age is the most important, exceptionally being CDI in healthy infants, rarely in children of 1-3 years of age, and possibly in older ones. However, if infants or small children have one or more of the already shown risk factors, and in particular a recent antibiotic exposure, CDI must be ruled out. There is not best laboratory test for diagnosis, because each method has its limitations. For this reason, a multistep approach, which first demonstrates the
presence of Clostridium difficile with high sensitivity and, in case of Clostridium difficile positivity, the toxigenicity (by EIA for toxins or more recently by PCR) of the strain, has been suggested and it is often applied [11].

When toxigenic Clostridium difficile is found in infants or children we have not the certainty that colonic disease is only due to CDI infection and not it is a superinfection, a trigger or an innocent bystander, as it may happens in case of IBD, as in case 2 of this paper. Only a prompt response to eradication treatment may answer to the question about the causative role of Clostridium difficile in such complex cases.

Treatment: To kill or to Antagonize?

The first risk factor for CDI is antibiotic exposure and administration of 3 antibiotic classes in the 30 days before infection was significantly associated with severe disease [4]. For this reason, it is curious that the mainstay of treatment of CDI is still antibiotic treatment (Table) [5,11]. However, to kill Clostridium difficile is not enough in 15-25% of children, as demonstrated by recurrence in such a proportion of patients. The most effective treatment should restore a physiological condition of Eubiosis, which antagonizes Clostridium difficile growth and toxins production. To this purpose, poor results have been obtained with probiotics, while faecal microbiota transplantation seems to be the best way to obtain the goal of eradication [12].

**Table**: Options of treatment for different forms of CDI, CDI: Clostridium difficile infection; FMT: Faecal microbiota transplantation.

<table>
<thead>
<tr>
<th>Clinical picture</th>
<th>Treatment</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Initial episode</td>
<td>Rehydration</td>
<td>Mandatory</td>
</tr>
<tr>
<td>Mild-to-moderate infection</td>
<td>Discontinuation of antimicrobial agents</td>
<td>Can be sufficient in mild cases</td>
</tr>
<tr>
<td>No administration of antiperistaltic medications</td>
<td>They may obscure symptoms and precipitate complications, such as toxic megacolon</td>
<td></td>
</tr>
<tr>
<td>Oral Metronidazole (25-30 mg/kg/day up to 500 mg qid) x 10-14 days</td>
<td>The least expensive drug for CDI for use in milder forms of disease; pharmacokinetics are not ideal with &gt;95% of drug absorbed from the upper gut</td>
<td></td>
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<tr>
<td>Severe infection or unresponsiveness to or intolerance of metronidazole</td>
<td>Oral Vancomycin (30-40 mg/kg/day qid) x 10-14 days or Vancomycin by enema x 14 days with or without iv Metronidazole (7.5 mg/kg 3 times a day)</td>
<td>Vancomycin therapy is recommended in adults as standard therapy for more severe forms of CDI; capsule form is expensive, compounding pharmacy to convert IV form for oral use</td>
</tr>
<tr>
<td>First recurrence</td>
<td>Oral Metronidazole (2nd course)</td>
<td>Metronidazole should not be used for the treatment of the second recurrence (third episode) or for chronic therapy (because of possible neurotoxicity)</td>
</tr>
<tr>
<td>Mild-to-moderate infection</td>
<td>Oral Vancomycin (30-40 mg/kg/day up to 125 mg qid) x 10-14 days or Vancomycin by enema x 14 days with or without iv Metronidazole (7.5 mg/kg 3 times a day)</td>
<td>Vancomycin therapy is recommended in adults 125 mg qid for 14 days 125 mg bid for 7 days 125 mg once daily for 7 days 125 mg every 2 days for 8 days (4 doses) 125 mg once every 3 days for 15 days (5 doses)</td>
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<tr>
<td>Second recurrence</td>
<td>Tapered or pulsed regimens of Vancomycin</td>
<td></td>
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<tr>
<td>Third recurrence</td>
<td>Oral Vancomycin followed by Rifaximin (20-30 mg/kg/d tid), oral Fidaxomicin (32 mg/kg/day up to 400 mg/day, bid for 10 days), FMT, Intravenous immune globulin (400 mg/kg dose repeated after 3 weeks up to 5 administrations)</td>
<td>Fidaxomicin is the most recently approved therapy with high cost and lower rates of recurrence. A Phase 3 trial in subjects aged ≥ 6 months to &lt; 18 years is ongoing</td>
</tr>
<tr>
<td>Other options for recurrent infection</td>
<td>Surgery</td>
<td>Colectomy should be considered in such patients</td>
</tr>
</tbody>
</table>

**References**


