

Management of Recurrent *Clostridium Difficile Colitis* in Children - Intestinal Microbial Colonization (Fecal Microbiota Transplantation)

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Abstract

Clostridium difficile infection (CDI) is an intestinal condition, mostly occurring due to extended antimicrobial therapy but it can also be consequent to the host's immunodepression. Children can be asymptomatic carriers, especially toddlers below the age of two, where *Clostridium difficile* is more frequently encountered-in the saprophytic intestinal flora. However, there are cases of CDI in older children, predominantly in the aftermath of excessive administration of antibiotics or it can appear as a result of severe immunosuppressive affections (malignity due to chemotherapy, primary or acquired immunodeficiency- HIV/AIDS infection). These cases can have severe clinical forms (pseudomembranous colitis) whose onset can be represented by toxic phenomena and even death, due to the lack of proper treatment.

This material aims to present our clinical experience regarding the management of severe recurrent *Clostridium Difficile* Infection cases that required intestinal bacterial colonisation. This procedure is frequent in adults who do not respond to classic antimicrobial therapy. In children, few cases of faecal transplantation have been reported so far, as alternative therapy in the case of recurrent CDI, unresponsive to antimicrobial therapy. We present four clinical cases of paediatric *Clostridium difficile* where we applied intestinal bacterial colonisation with faecal microbiota transplantation from patients' next of kin (the child's mother or father). In three cases, we used the abovementioned technique after having applied the entire therapeutic protocol and after the onset of recurrences (metronidazole, vancomycin, prolonged course of vancomycin therapy with gradual dose reduction). All three cases of pseudomembranous colitis were consequent to prolonged administration of antibiotics, one of them being with congenital IgA, while the other two were immunocompetent children. Furthermore, we applied intestinal bacterial colonization in a CDI child with unspecified underlying congenital colitis that failed to be treated based on the classic therapeutic protocol due to multiple allergies (including to metronidazole and vancomycin).

In all cases, intestinal bacterial colonisation was administered without any incident, with favourable evolution, no reoccurrence and with a high success rate rendering the cases as a success. Thus, one may state that intestinal bacterial colonisation in children with *Clostridium Difficile* Infection is a therapeutic procedure that can be adopted by guidelines treating this affection, especially for those cases that are unresponsive to antibiotics but also for cases that reject classic therapy.

Keywords: Child; Recurrent *Clostridium Difficile*; Fecal Microbiota Transplantation

Abbreviations

CDI: *Clostridium Difficile* Infection; ESCMID: European Society of Clinical Microbiology and Infectious Diseases; FMT: Fecal Microbiota Transplantation; ID: Immunodepression

Introduction

Clostridium Difficile is mostly known as a saprophytic microorganism of the human intestinal flora. Records show that intestinal colonization with *Clostridium Difficile* occurs in adults approximately 2-3% compared to children where the percentage can reach as much as 70% (especially in children below two years of age) [4]. Certain toxigenic strains resulted from disequilibrium within the intestinal microbiota become pathogenic leading to a patient's development of a severe intestinal illness- pseudomembranous colitis. In adults, this condition is more frequent than in children, as in the former immunodepressive diseases are found more often - HIV/AIDS infection, oncological diseases, system impairments, diabetes, etc. but it can also be triggered by extended antimicrobial therapy [1]. In children, CDI symptomatic cases occur after antimicrobial therapy and, less frequent, as a consequence of chemotherapy applied for oncologic pathologies. However, paediatric cases of pseudomembranous colitis triggered by congenital or acquired immunodepression (HIV/AIDS) have also been described by literature [1,3]. Clinical CDI forms are more severe in adults than in children as they seldom present toxic evolution that may even lead to death [8]. Pseudomembranous colitis treatment is standardised, based on international guidelines and protocols [2,5].

In paediatrics, the therapeutic scheme is more limited as certain active antibiotics from the *Clostridium Difficile* toxigenic strains are contraindicated (tygecyline, fidaxomicine). Also, in adult cases, recurrent *Clostridium Difficile* infection - unresponsive to antimicrobial therapy- the experience with intestinal microbial colonization is more solid in adults than in children. There are few reports worldwide on intestinal microbial colonization in children. In this context, the National Institute for Infectious Diseases "Prof. Dr. Matei Bals", Bucharest has elaborated a standardised procedure for faecal transplantation in adults and children with pseudomembranous colitis, approved by the Ethical Committee [9].

Lately we have been facing an increase in the number of *Clostridium Difficile* infection cases in both adults and children often associated with infection recurrences which fits the estimates and reports of international specialists [6,7]. Possible explanations might be: excessive use of antibiotics (especially in children), broaden oncological therapy, namely more aggressive therapies that lower immunity levels (in adults) but also the medical professionals' ability to make a rapid diagnosis of this condition (rapid identification methods of toxigenic *Clostridium Difficile* strains - PCR) [10]. In addition, nosocomial cases of *Clostridium Difficile* Infection were reported, especially in wards with immobile patients who present multiple associated pathologies and co-morbidities or wards treating patients with immunodepression. Hence, one can conclude that CDI is a public health issue on the one hand, due to increased numbers of cases and their severity, with lethal potential and on the other due to its selection of immunocompromised patients, determined by significant intestinal microbiota impairment.

Objectives

The purpose of this paper is to describe several significant cases of recurrent paediatric *Clostridium Difficile* Infection from our clinical experience and to clearly define and delineate the transplantation site for faecal microbiota transplantation when managing similar cases.

Material and Methods

We deployed a retrospective study on *Clostridium Difficile* Infection cases in children, admitted on the Paediatric Clinical Ward IX in National Institute for Infectious Diseases "Prof. Dr. Matei Bals" during 2013-2016. We analysed the following data: age, sex, immune status and number of CDI relapses. Furthermore, we focused on the cases with multiple CDI relapses that ultimately required intestinal bacterial colonisation and their post-transplant evolution. *Clostridium Difficile* Infection diagnosis was established based on clinical criteria

(clinical aspect of pseudomembranous colitis) and confirmed by the laboratory data (toxigen *Clostridium Difficile* in the faeces: A/B toxin or polymerase chain reaction - PCR). Also, in addition to the etiological diagnosis we performed specific tests to set the disease's clinical stage: CBC (complete blood count), inflammatory tests, PCT-Q, biochemical assays and differential diagnosis: coproculture for specific viral germs, bacteria and fungi (*Rotavirus*, *Adenovirus*, *Norovirus*, *Salmonella*, *Shigella*, *Yersinia*, *Enteropathogenic E. Coli*, *Campylobacter*, *Candida* spp. etc). By laboratory and paraclinical investigations we ruled out other possible causes of non-infectious acute diarrheal disease (inflammatory bowel disease, intestinal malformations, metabolic impairment, etc).

The therapy for associated CDI colitis in children was selected following the recommendations of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID):

1. Conservatory attitude for asymptomatic cases;
2. Mild and average clinical forms - Metronidazole, oral 10 - 14 days. In case of intolerance, the first treatment line was Vancomycin;
3. Severe clinical forms- Vancomycin. In certain situations, combined therapy was applied: Vancomycin oral + Metronidazole i.v. and non-specific human immunoglobulin.

Antimicrobial therapy was doubled by systematic hygiene and disinfection measures, hygiene-dietary treatment (hydro-electrolytic and acid-base rebalancing), symptomatic drugs (anti-pyretic, non-steroidal anti-inflammatory drugs, anti-emetics, antispasmodic drugs, etc) as well as by oral administration of colonization flora- *Saccharomyces Boulardii* +/- oral doses of Rifaximin.

In case of relapse following the first treatment line with metronidazole, vancomycin was given for 14 days. At a second relapse, an extended vancomycin treatment scheme was applied: 14 days of the normal dose (30 mg/kg/day 3-4 doses), subsequent gradual dosing decrease from 7 to 7 days (7 days- 3 doses, 7 days- 2 doses, 7 days- one dose administered one day the following day no dose and, ultimately, one dose every two days for 7 days). After more than 3 relapses we proceeded to intestinal bacterial colonisation with fecal microbiota (fecal microbiota transplantation FMT). In one case alone, known with systemic mastocytosis and multiple drug allergies (including vancomycin and metronidazole) we adopted from the very beginning the intestinal bacterial colonization procedure.

The faecal microbiota transplantation procedure that registers limited experience among the paediatric clinical practice was applied in our institute based on a specially designed protocol that was developed leaving from data in literature and after being approved by the local Ethics Council. The transplant indication addresses those patients who registered three or more *Clostridium difficile* recurrent infections, who fail to respond to previously applied standardised therapies. Patients diagnosed with toxic megacolon, patients with immunosuppressive therapies (including corticotherapy), children aged below two do not qualify for this medical procedure.

Preparing the patient that will undergo fecal microbiota transplantation consists in:

- Interruption of antibiotic treatment 72 hours before the procedure;
- 12 hours prior to the procedure- total cleansing enema
- Fasting- 12 hours prior to the procedure
- Placement of the nasogastric tube. The procedure can be applied through enema but with a lower success rate.

The donor must be healthy, preferably a first-degree relative (the patient's mother or father), whose faeces sample undergoes specific screening (coproculture for *Shigella*, *Salmonella*, *Yersinia*, *E. Coli* O157:H, Ziehl-Neelsen Stain, *Cryptosporidium*, *Cyclospora*, *Isospora*, *Toxins A and B for C difficile*, PCR from the faeces for *Cl. Difficile*, faecal parasitology, stool *H. pylori* antigens) as well as serological screening (HIV, HTLV, VHA, VHB, VHC, TPHA).

The donor’s preparation begins 12 hours before the procedure and consists in administering light laxatives during the preceding evening. Fresh stool is used, obtained in the morning (the early hours) after dilution, homogenization and triple filtration-all performed in the Institute’s Microbiology Laboratory, under standard conditions of protection and level 2 biosafety. The administration is immediate, subsequent to the preparation process of the bacterial colonization product. The intestinal bacterial colonization product is inserted through a nasogastric tube. It is essential that the tube’s position to be as close as possible to the duodenum in order to avoid the product’s contact with gastric acid. After the procedure, the nasogastric tube is clipped for two hours, and then removed after six hours while the patient will undergo digestive rest for twelve hours. After this period, the meals will be normal without any restrictions. The patient is monitored for six months: at one week, one month, three months and 6 months after the procedure. If there are no signs of relapse during this 6-month interval the patient is considered cured.

Results and Discussion

Results

During the study period, we registered 33 *Clostridium Difficile* Infection cases in children. Thus, we noticed a 4.6 times increase in the annual number of these cases in 2016 compared to 2013 (Figure 1).

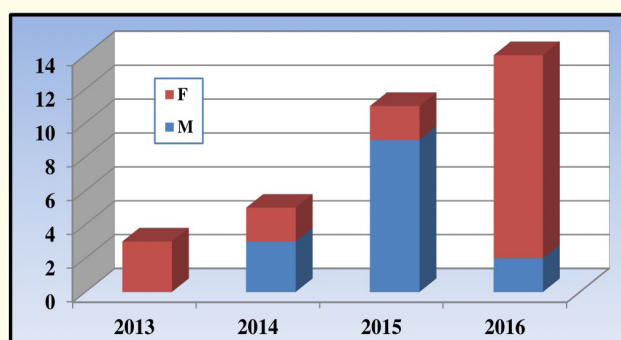


Figure 1: Distribution of CDI cases in children by years.

Most cases were recorded at the 1 - 4 age group, more than half of them (18/33) being female patients (54.4%- Figure 2). The majority of cases occurred in immunocompetent children (IC - 75.7%) subsiding as a consequence of prolonged antibiotic administration.

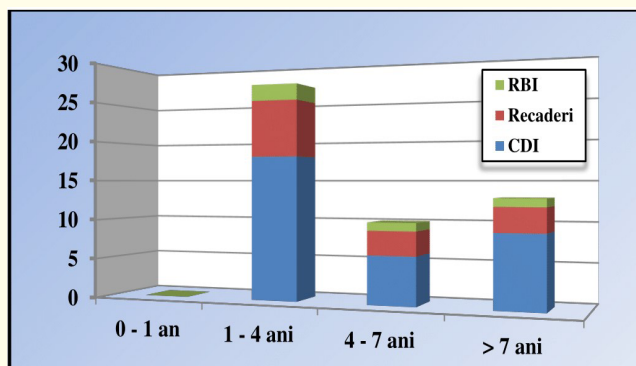


Figure 2: Distribution of cases by age group.

Among the patients with immunodepression (ID - 24,2%), two had Selective IgA deficiency and one presented Systemic mastocytosis (9,1% - ICD), while other five children had acquired immunodeficiency (15,1% - IDD) as a consequence of immunosuppressive therapies for various conditions (Acute Lymphoblastic Leukaemia ALL- two cases and one case of Hodgkin's disease, one hepatoblastoma, one autoimmune cholangitis) (Figure 3).

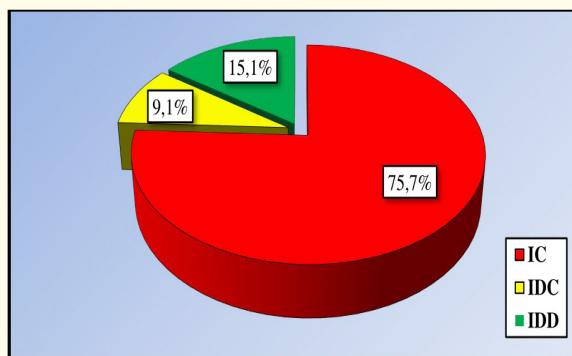


Figure 3: Distribution of cases by the patients' immune status.

39,4% of cases (13/33) presented one or more CDI relapses. As Graphic number three emphasises, most cases with relapses were in female patients 69,2% (9/13), more than half of them pertaining to the 1-4 age group (53,8%, 7/13). Sex distribution of cases with no relapse was equal (Figure 4).

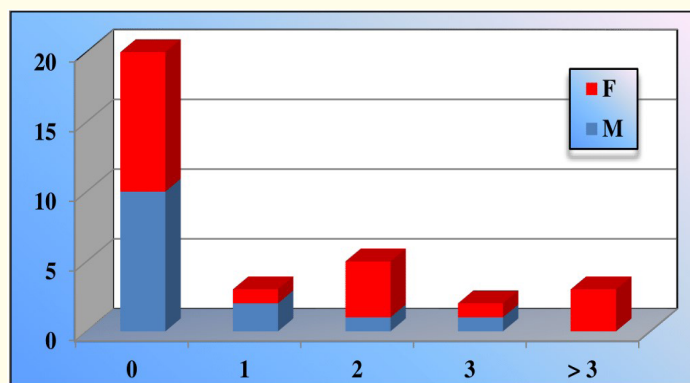


Figure 4: Distribution of cases by number of relapses and sex.

From the overall cases with more than three relapses, in three patients we applied faecal microbiota transplantation. Also, in one child we implemented this procedure from the very beginning without applying the standard treatment protocol as the patient presented multiple drug allergies. Three relapse cases that benefitted from the transplantation were female patients while the fourth was a male patient. In what concerns the age of patients that underwent faecal microbiota transplantation, it varies: 2, 3, 5 and 7 years of age. The immune status was low in two cases while other two cases were immunocompetent.

In all four cases, intestinal bacterial colonization was applied without incidents. In three cases the faecal microbiota donors were the patients' mothers while in one case the donor was the father. The product was inserted via a nasogastric tube and all case presented favourable post procedure evolution. Twelve hours after the transplantation, feeding was resumed and another 72 hours after, the patients were discharged in complete safety. Upon discharge, all children who experienced intestinal bacterial colonization were stable, with a good general condition, afebrile, no signs of pain, normal appetite and normal stools. The first faecal microbiota transplantation was carried out in March 2014, the second in December 2015 and the last two in July 2016. None of the cases had any *Clostridium Difficile* relapse, thus the first two being considered cured while the last two under monitoring.

Discussions

In the aftermath of our study on *Clostridium Difficile* Infection in children, we found that the most affected age group is 1 - 4 years, in immunocompetent children that were under excessive antimicrobial therapies. This aspect can also be explained by the fact that immunity acquired by the child from the mother disappears leaving way to intercurrent infections. Antibiotic administration, most times abusive (because the majority of infections at this age are viral) leads to disequilibrium in the intestinal flora and to the occurrence of pseudomembranous colitis. If predisposing factors are also of concern (congenital or acquired immunodepression) than CDI conditions are fulfilled. We haven't found a plausible explanation for frequent relapses in female patients more than in male patients but a larger study on an extended lot of patients should be deployed in order to see if this aspect carries a statistical significance. Our statistical data correspond to the ones in literature.

With regards to intestinal bacterial colonization in children, we can safely state that it represents a premiere in Romania, with only a few cases with this specific reported worldwide. Furthermore, our experience revealed that the procedure is safe and represents an effective treatment method for cases with recurrent CDI.

Among the top findings of our study we would like to stress that faecal microbiota transplantation can be applied regardless of the patient's age, even in immunosuppressed patients, patients with recurrent *Clostridium Difficile* Infection or even prior to the standard treatment. Intestinal bacterial colonization procedure is relatively easy to implement, with minimal risks, low costs and maximal efficacy.

Conclusion

The rate of *Clostridium Difficile* Infection rate is increasing in both immunocompetent children due to excessive or unjustified use of antibiotics as well as in immunosuppressed children (congenital or acquired immunodepression). The infection occurs more frequently in female patients, aged between 1 - 4 years.

A large number of cases present relapses (39,4%) which need extended therapeutic schemes, with a negative impact on the child and his family, from the standpoint of emotional balance, psychological, economical and social status. Faecal microbiota transplantation proved to be an efficient and safe treatment of paediatric CDI, in children with normal or low immune status.

The role and importance of intestinal bacterial recolonization as treatment option for *Clostridium Difficile* Infection in children continues to be a study theme that should be quantified and analysed further on.

Conflict of Interest

We declare no financial interest or any other conflict of interest.

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