

## SEVERE *CLOSTRIDIUM DIFFICILE* INFECTIONS. A SYSTEMATIC LITERATURE

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Received 2 March 2016; accepted 13 April 2016

### ABSTRACT

*Clostridium difficile* is a bacterium that has been brought to the attention of the medical community recently, as the number of infections related to it has increased dramatically. This is happening mainly because of the excessive and defective use of antibiotic therapy. The pathology of a *Clostridium Difficile* infection is very complex, as it ranges from easy symptoms like abdominal pain and diarrhea to severe complications, like toxic megacolon. The management of these infections has become even more difficult, as they are not appearing only in the hospital environment anymore, but also outside of it. The bacterium spreads through poor hands hygiene. Also, we don't have a clear strategy for overcoming an infection like this, so it gets even more difficult as most of the times the doctors need to rely only on their experience and knowledge to find ways of battling it. We would like to underline the research opportunities that are available in this domain as very few things are known about *Clostridium difficile* and also the crucial importance of research, as these infections are common and dangerous not only for patients, but for the medical staff and their families too.

**KEY WORDS:** *Clostridium difficile*, pseudocolitis, toxic megacolon, enterotoxin, cytotoxin

### INTRODUCTION

*Clostridium difficile* is a gram-positive, anaerobic, sporulated bacterium with a cosmopolitan character. Although it came to the attention of the medical world not long ago, the bacteria has been known since 1935 when it was discovered in the intestinal bacterial flora of newborns. Later, in 1978, toxin-producing *C. difficile* was identified as the causative agent of pseudomembranous colitis after tests on laboratory animals (Shimizu *et al.*, 2015). Initially, *C. difficile* infections were nosocomial, those acquired outside of the hospital being extremely rare. However, the *C. difficile* is highly resistant when sporulated and it can be found both in the hospital and outside it nowadays. The most exposed are hospitalized patients who spend a lot of time in the ICU (Intensive Care Unit) or surgery departments. The most common form of infection is spread by a fecal-oral route, through poor hygiene (Kazanowski *et al.*, 2013).

## MATERIALS AND METHODS

This article is a systematic review of other statistic articles which we identified in the literature as a result of searches by the specific medical search engine PubMed after the words "*Clostridium difficile*", "*Clostridium difficile* treatment", "surgical *Clostridium difficile*". Out of all appearances, only editorial articles published in the last 10 years were chosen. Pediatric themed articles and isolated clinical cases were left out. We tried to chose articles published by doctors and researchers from different areas of the world (Canada, USA, South America, Europe, Asia, Australia) to provide a more comprehensive analysis of infections with *C. difficile* and highlight the cosmopolitan character of the bacteria.

## RESULTS AND DISCUSSIONS

*Clostridium difficile* is a bacterium that is found in the commensal bacterial flora of 60% of newborns, 2-3% of the adult population and 40-50% of medical personnel (Furuya-Kanamori *et al.*, 2015).

**Epidemiology.** Infections with *C. difficile* have been occurring more often since the introduction of antibiotic therapy. Recently it was shown that patients exposed to certain classes of antibiotics such as clindamycin, fluoroquinolones, cephalosporins, penicillins, macrolides and sulfonamides have developed infections more often than those who have not made contact with them. The exaggerated global fondness of antibiotics has lately contributed in a significant way to the increasing number of infections (Cohen *et al.*, 2015). In terms of frequency of appearance, in Germany the incidence is about 15 cases per 100.000, while in North America it is up to 100 cases per 100.000. These values are getting bigger every year (Borody *et al.*, 2015).

**Risk factors.** We have identified a series of factors which predispose the appearance of a severe *C. difficile* - related infection: antibiotic therapy, age (>65 years old), long hospitalization periods, patients who are medicated with protein-pump inhibitors, chronic inflammatory intestinal diseases, immunosuppressed patients, those who have suffered recent surgical interventions, patients undergoing chemotherapy treatment. Although the spores of *C. difficile* are very resistant, even in the gastric acid environment, it seems that the vegetative state of the bacterium might be sensible to it. This is the reason why administering protein-pump inhibitors increases the risk of *C. difficile* - related infections, this aspect being confirmed by the high number of researches we have analyzed (Seltman, 2012; Lübbert *et al.*, 2014; Indra *et al.*, 2015).

**Diagnosis.** The most difficult part in detecting *C. difficile* in the stool samples received from patients is represented by the isolation of this bacteria from the commensal intestinal flora. Sometimes the sample contains few spores/bacteria and a very competent culture medium is needed in order to cultivate it, as the risk of obtaining a false-negative result is high.

In a study published in 2014 the authors have compared multiple culture media, both liquid and solid, in order to find out which is the most efficient in detecting the presence of *C. difficile* in stool samples from infected hamsters. The conclusion was that the non-enriched agar-medium CCEY (Cycliserin/ Cefoxithin with egg-yolk) was the one with the best results, as both sporulated and vegetative forms of *C. difficile* have been successfully cultivated on it. On this medium the cultures appear to be round, individualized, flat and grey. Also, on the ChromID medium (which is specific for cultivating the vegetative state of the bacterium) the cultures appear to be black. This happens because of a black pigment produced by the bacteria

when cultivated on it. ChromID does have the disadvantage that not all roots of *C. difficile* produce this pigment, situation which can lead to false-negative results due to confusions (Crowther & Wilcox, 2015).

In spite of all these technical difficulties, the identification of this bacteria in cultures still remains the most useful method for the diagnosis of a *C. difficile* -related infection, as it has the biggest specificity and sensibility altogether (Dantes *et al.*, 2015).

The main toxins produced by *C. difficile* are A and B, together with the recent discovered binary toxin produced by the very virulent strain of bacterium called 027 Ribotype. They act in a complex way, by intervening in the protein synthesis necessary for the cell's actin cytoskeleton. Without a proper cytoskeleton, the cells go through apoptosis. Even in these circumstances, there are also strains of *C. difficile* who do not produce any of these toxins. Because of this, it is very important not only to identify the bacteria in the patient's stool sample, but to demonstrate the presence of at least one aggressive toxin (Keller & Weber, 2014).

The immunoenzymatic detection tests for A and B toxins are the fastest. Even though their specificity can reach 95%, they have a smaller sensitivity and can sometimes offer false-negative results. Another possible way is the detection of GDH (glutamate-dehydrogenase) as a screening method for asymptomatic patients, and if the test is positive then continuing by making cultures. This method is still being researched because different results were obtained depending on the test kit used (Sayedy *et al.*, 2010).

Another possible diagnosis method is represented by genetic tests PCR (polymerase chain reaction) which seem to have both specificity and sensitivity at good levels (Burckhardt *et al.*, 2008).

**The main stages of the *C. difficile* infection** are: the stage of asymptomatic carrier (very serious and controversial in the same time because even though the infection does not manifest itself on these patients, they can still be an infection source for those around them), the diarrheal stage (patients can have up to 10-15 bowel movements a day along with a hydro-electrolytic imbalance and severe dehydration), colitis (the changes in the colon mucosa are visible through colonoscopy), pseudomembranous colitis (obvious changes in the intestinal mucosa which vary from superficial changes to necrosis and ulcerations), fulminant colitis (ulcerations, high mortality rate), enteritis, appendicitis (rarely), toxic megacolon (the most severe form, it is associated with a hyperinflation of the colon which can even lead to perforations) (Grünwald *et al.*, 2010; Baban *et al.*, 2013; Lübbert *et al.*, 2014; Alasmari *et al.*, 2014; Duke & Fardy, 2014).

Many of the *C. difficile* infections are found quickly and treated accordingly. Even though, a high number of patients get severe infections. 3-8% of all patients get to the stage of fulminant colitis. Many of them develop a toxic megacolon and 80% of those who reach this stage are in need of a total colectomy (Gough *et al.*, 2011; Hargreaves *et al.*, 2015; Furci *et al.*, 2015).

In what concerns the treatment, the ironic situation when an antibiotic-produced disease can be treated (at least at the beginning) with antibiotic treatment is very common. This is also the case of *C. difficile* infections, where the main treatment consists of Vancomycin or Metronidazol. Recently, Fidaxomycin was also approved as an option, but only in the USA. Also, Bacitracin can be administered per os. For recurrent infections though, the treatment is

completely different. It consists of transplanting stool samples from healthy patients. This form of treatment has a very high chance of success for 70-92% of all patients. The most difficult challenge for the doctors is when a *C. difficile* infection evolves to a severe stage. This rarely happens and has an unfavorable evolution from fulminant colitis to toxic megacolon. The main treatment in this case is certainly a surgical intervention. The problem in these situations is that there is no way of knowing when is the right time for surgery in order to increase the possibility that the patient will be kept in a safe zone with a maximum survival rate.

The studies bring arguments favoring early surgical interventions, bringing clear information from a statistic point of view that a surgical procedure done earlier has a higher chance of being successful with a more favorable prognostic for the patient than a late surgical approach. For infections surpassing the stage of fulminant colitis (few, but severe), the main treatment is the surgical one. The most frequent choice is a total colectomy with a permanent ileostomy, with the main purpose of decimating the bacteria population. Though, if viable colon portions were to be found, it is recommended to preserve them. So, with all these information around, there are some legitimate questions to be asked: should we practice an early total colectomy with favorable results regarding the infection, but a disaster for the patient's quality of life? Which is the perfect moment for adopting a surgical attitude? Regarding the quality of life, even though a digestive continuation is being tried through an ileo-reanastomoses, this procedure has had a favorable evolution in only 20% of the cases, as the studies show. Another problem that has determined us to consider this subject is summarized by the question: after a total colectomy, can a culture taken from the ileostomy be positive for *C. difficile*? The answer can be provided by the experience in the departments where we operate (The Anesthesia and Intensive Care Clinic and the General Surgical Clinic, both in the University Emergency Hospital Bucharest) and it is yes, we can find the *C. difficile* bacteria in the ileostomy after a total colectomy (Kassam et al., 2012; Hensgens et al., 2014; Kazanowski et al., 2014).

Another therapeutic method mentioned in our research is the minimally invasive technique – laparoscopy - associated with a lavage that contains Vancomycin. The studies that have evaluated in comparison both the radical surgical method – total colectomy - and the laparoscopy still bring arguments favoring the total colectomy as the main course of action (Swindells et al., 2010; Rodriguez-Pardo et al., 2013; McCune et al., 2014; Zhou et al., 2014; Korac et al., 2015).

## CONCLUSIONS

Diarrhea, as a symptom, can have multiple medical pathologies as a cause. The evaluation of a patient must be done systematically, taking into account other signs as well: abdominal cramps, fever, dehydration, hypotension or even sepsis. For a certain diagnosis of a *C. difficile* infection we need, besides the evidence of 3 bowel movements in 24 hours, a confirmation of the toxins produced by a toxin-producing bacteria in the stool sample taken from the patient. Also, suggestive imagistic data can be useful.

The infection with *C. difficile* is a very complicated pathology. When the patient reaches the stage of a severe infection any medical decision is very important and can directly influence the therapeutic success. It is tragic that in those moments we can only rely on the experience and thoughts of the doctors, as we don't have clear action criteria regarding these

infections that appear more and more often nowadays both in the hospital environment as well as outside.

One of the purposes of this article is to underline the research opportunities in this domain, as we have very little information about such an important subject.

Also, the importance of a good hands hygiene in the prophylaxis of *C. difficile* -related infections is worth mentioning, as the main pathway for these germs to spread is through dirty hands.

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