

SPECIFIC FEATURES OF *CLOSTRIDIUM DIFFICILE* COLITIS IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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Abstract - Through its specific biological, epidemiological, diagnostic and infection management features, *Clostridium difficile* infection (CDI) can be considered a major health concern, especially in inflammatory bowel disease (IBD) patients. In this particular infection, many IBD risk factors are triggered due to bowel inflammation, antibiotics use, microbiota changes, immunosuppressive therapy use and surgical intervention. Thus, each IBD and diarrhea patient must be tested for CDI. Clinical features show different initial infectious stages such as mild, fulminate and refractory. It has been shown that CDI presents recurrent episodes. CDI treatment consists of metronidazole, vancomycin or fidaxomicin, as well as prophylactic measures. It was recently shown that antibiotic doses must be gradually reduced in order to avoid CDI relapses. Fecal transplantation, effective in CDI management, remains controversial in CDI patients with concurrent IBD.

Key words: *Clostridium difficile*; infection; inflammatory bowel disease; diarrhea; *Clostridium difficile* toxins

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INTRODUCTION

Clostridium difficile (CD) is a Gram-positive, spore-producing anaerobic bacillus that was first described in children's gastrointestinal flora (GIF). Due to its ability to form spores, there are many difficulties in biological eradication, high recurrent episode rates and long-lasting infection. *Clostridium difficile* colitis (CDC) rates are on the increase and thereby morbidity and mortality rates, especially for inpatients with or without IBD (Honda and Dubberke, 2014).

In the 1970s, CDI was associated with secondary type diarrhea, due to antibiotic use (Bartlett et

al., 2008). Several years later, CD toxins were highlighted in IBD relapse patients' feces (La Mont et al., 1980) and a CDC screening was introduced for all recurrent IBD patients (Bolton et al., 1982). Since then, CDI has been treated with oral administration of vancomycin, metronidazole or fidaxomicin, according to infection relapse type.

It is believed that IBD affects around 4 million patients worldwide. Because CDI is not a notifiable infection and because CDI prevalence is eight-fold greater in IBD patients compared to non-IBD (Ricciardi et al., 2009), it is extremely hard to calculate its exact incidence. Moreover, CDC has become a major public health issue due to its increasing in-

cidence as cited by Khana et al. (2010), displaying a fourfold increase in mortality rate than in the previous decade.

Pathological features of Clostridium difficile colitis in inflammatory bowel disease

IBD can be considered a multifactorial pathological condition based on abnormal immune responses to GIF in genetically predisposed patients (Xavier et al., 2007). It is well known that bowel inflammation and GIF changes during IBD can lead to CD colonization. CD colonization following CDI can be characterized by the presence of the two most common CD toxins, enterotoxin A and the more active cytotoxin B (Davies et al., 2011). Therefore, many CDI are found to return “A negative B positive” results rather than “A positive B negative”. Due to the absence of a specific occurrence pattern, both toxins’ presence must be tested.

Studies show the existence of a hypervirulent CD strain (NAP1/B1/O27) characterized by an increased ability to produce A and B toxins due to a supplemental binary toxin specific to this strain only (Loo et al., 2011).

Regarding the clinical forms of CDC in IBD, there have been identified four clinical forms of initial infection and two clinical forms of recurrent infection (Surawicz et al., 2013). These are initial infection forms and recurrent infection forms. Regarding the initial infection forms, mild or moderate disease is characterized by watery diarrhea (rarely bloody) and leukocytosis, normal albumin and creatinine serum concentrations; the severe disease is characterized by a decrease in albumin serum concentration, leukocytosis, anemia and high creatinine serum concentration due to severe diarrhea and dehydration; the fulminant or complicated disease is characterized by fever, vomiting, hypotension, abdominal distension and sudden interruption of diarrhea, severe leukocytosis, high lactate serum concentration and hypoalbuminemia; and finally the refractory disease presents no response to therapy and can exhibit ileus, toxic megacolon, perforation or obstruction identi-

fied by X-rays, CT or MRI scanning. In this case, a surgical approach is imperative.

Recurrent infection forms include same-strain recurrent infection and new-strain recurrent infection. In clinical practice, the only differentiation method between the two entities is a genetic-based strain identification test. Recurrent infection features are identical in IBD and non-IBD patients. However, initial and recurrent forms of CDI must be identified, as the medical therapy for the two of them is rather different (Surawicz et al., 2013).

Regarding the CDC prognosis in IBD, patients develop more severe forms of CDC. It has been shown that IBD patients affected by CDI need longer and more expensive medical care that brings a four-fold higher surgical treatment (Kariv et al., 2011) and a six-fold higher mortality compared to non-IBD CDI patients (Ananthakrishnan et al., 2009).

CDI risk factors in IBD

CDC is usually associated with age, prolonged inpatient stay, recent use of antibiotics, comorbidity provided by immunosuppressant therapy and increasing hypervirulent strain number. In IBD patients, CDI can occur at a younger age and not necessarily in association with antibiotic use, but due to bowel inflammation and steroid therapies. It has been proven that CDC may present a great risk to ileoanal pouch anastomosis (Berg et al., 2013).

IBD and CDC have a common risk factor – bowel inflammation – that can generate relapses and CDI. In other words, either of them can potentiate or support the other’s occurrence although studies say that the association of CDI with IBD is weaker than that with ulcerative colitis or Crohn’s disease (Berg et al., 2013). This variable association rate can be explained by the CDI bowel localization and metronidazole use in CDI therapy (Nguyen et al., 2008).

IBD surgical interventions can lead to CDC-specific clinical features such as Crohn’s enterocolitis. In this case, CDC affects the small bowel following

proctocolectomy and can be treated with metronidazole and vancomycin. Failure to diagnose CDC in this case leads to 60-83% mortality (Shivashankan et al., 2013). Proctocolectomy may be also be applied more frequently in men in severe ulcerative colitis, followed by ileoanal pouch anastomosis due to CDI (Issa et al., 2008).

Studies show that during cold seasons CDI increase by 20% due to longer indoor activities, facilitating contamination, and incautious antibiotic use in respiratory tract infections (Kariv et al., 2011).

Another CDI risk factor is immunosuppressant therapy use. Steroid therapy particularly causes a three-fold increase of CDC risk (Ananthakrishnan et al., 2009). Ongoing steroid therapy following CDC diagnosis increases mortality rates in patients with IBD. It has been shown that other IBD immunosuppressant therapies (thyopurine, methotrexate and others) do not promote CDI (Schneeweiss et al., 2009).

Age can also be considered a CDI risk factor. Due to a physiological decrease in immunity, older IBD patients can develop a high risk for CDI. Recently it has been shown that younger IBD patients can also be affected by CDI due also to immunity deficiencies particular to the growth period (Banaskiewicz et al., 2012) and aggressive immunosuppressant therapies (Coates et al., 2013).

Broad-spectrum antibiotic therapy can be associated with CDC in non-IBD patients. Their association with CDC in IBD patients is questionable. Some studies show that ciprofloxacin therapy one or two months prior, during or after a CDC episode may worsen an acute IBD relapse (Issa et al., 2007). On the other hand, other studies suggest that antibiotic therapy does not affect IBD evolution in CDC and IBD patients (Singh et al., 2009).

Proton pump inhibitors' (PPI) mechanism of action is not yet well established. It is thought that long term gastric acid secretion suppression creates an alkaline environment unable to inactivate the veg-

etative form of CD. In other words, long-term PPI usage can lead to initial or recurrent CDI. This effect decreases as the PPI therapy aggressiveness decreases (Honda et al., 2014). On the other hand, other studies do not support the risk factor feature of PPI therapy (Shivashankan et al., 2013).

Specific features of the CDC diagnosis in IBD

Acute CDC clinical features occur approximately 24-72 hours after contact with an infectious source (Issa et al., 2007). It is generally characterized by bacterial infection-specific fever, abdominal pain, tenesmus and loose feces. Differential diagnosis can exclude other causes through investigating the intestinal peristalsis and peritoneal presence or absence. It has been shown that diarrhea is not a differential symptom due to its absence in severe forms such as toxic megacolon or perforation (Greenstein et al., 2009) excluded by X-ray investigation.

Computer tomography (CT) provides information regarding IBD status and complications, but not about an eventual CDI (Cheng et al., 2011).

During colonoscopy, more than 50% non-IBD patients show characteristic 2-10 mm yellow pseudomembranes. Studies show that these occur in only 13% of IBD patients (Ben Horin et al., 2010). Ananthakrishnan et al. (2012) demonstrated that during colonoscopy or sigmoidoscopy, a physician must evaluate some features besides pseudomembrane presence including an assessment of severity of IBD endoscopic features, local biopsy in order to exclude *Cytomegalovirus* infection and fecal sampling for laboratory investigation.

Laboratory investigations allow the assessment of disease severity and further guidance in disease management. CDI severity can be predicted by several markers such as fever higher than 38°C and increased leukocytosis (higher than 15 000/mm³) associated with leukemoid reactions (Ananthakrishnan, 2012). In addition, hypoalbuminemia, acidosis, and high serum creatinine concentrations (higher than 1.5 mg/dL) show CDI complications. Electrolyte

imbalance and physiological pH disturbance due to severe diarrhea (Shivashankan et al., 2013), as well as anemia and malnourishment can cause severe evolution of CDI to inpatients (Ananthakrishnan, 2012).

In CDI, differential diagnosis relies on highlighting toxin or microorganism presence in the feces of patients' diarrhea (Surawicz et al., 2013). In IBD patients, CDI testing is recommended in patients known to be suffering from IBD relapse or remission IBD patients that have loose feces and that have been exposed to CDI risk factors (hospital admission, recent antibiotic therapy).

Various laboratory methods for acute CDC have been developed. More than 90% of hospitals use A or B toxin enzyme immunoassay (EIA). This test is a fast and effective detection method that is 63-94% sensitive and 75-100% specific (Surawicz et al., 2013). Another testing method is the fecal glutamate dehydrogenase (GDH) presence test presently used as a screening method (Cheng et al., 2011). This enzyme can be associated with CD presence but this method lacks in specificity. A positive GDH test requires a confirmation test, usually an EIA test.

Drug therapies used in CDC treatment

CDC passes mainly horizontally, from one human to another, due to poor hand hygiene and healthcare practices (rectal thermometers, nasogastric tubes and other inpatient resources). The infection risk proportionally increases with the duration of hospital stay. *Clostridium difficile* can be found in soil, cats, dogs, horses, pigs and in foods such as meat or readymade salads. Incubation time is approximately 2-3 days (Cohen et al., 2010).

Preventive measures for horizontal infection propagation include proper hand hygiene, use of disposable gloves, patient isolation, good cleansing of hospital spaces and instruments. In addition, it is very important to focus on the rational use of antibiotics, anticholinergics, non-steroidal anti-inflammatory drugs and the close monitoring of patients on cortisone therapy (Issa et al., 2007).

Initial CDI in IBD

Initial infection treatment mainly involves discontinuation of antibiotic use and decreasing immunosuppressant therapy. Due to its infection effects, cortisone doses should be reduced or even stopped. Biological immunosuppressant therapy is preferable. Cortisone therapy brings a three-fold increase of CDI risk compared to anti-TNF agents, the most low-risk therapy. Furthermore, in order to prevent venous thromboembolism, corrections in fluid and electrolyte imbalance must be applied. Complications development can be screened by imaging.

Mild stage disease treatment

Standard mild disease treatment consists of 10 days of metronidazole or vancomycin oral administration. Studies prove that a prolonged 14-day therapy has many advantages (Surawicz et al., 2013). Due to the adverse effects of vancomycin that can occur (vancomycin-resistant *Enterococcus* sp., nausea, vomiting due neurotoxic effects), it is widely considered that metronidazole treatment is more suitable and more effective. Nevertheless, metronidazole can be replaced by vancomycin only if no clinical response was observed, or biochemical markers improvement or if allergic reactions or intolerance occurred (Surawicz et al., 2013).

In IBD patients, the most effective therapy is vancomycin oral administration disregarding costs and adverse reactions. It has been proven that vancomycin therapy prevents complications, IBD relapses and colectomy imminence (Khanna et al., 2013).

Severe stage disease treatment

Often colonic dilatation, toxic megacolon or ileus require oral vancomycin therapy suspension. Further therapy relies on enteral vancomycin administration generally through enemas. In several cases, this therapy may be associated with intravenous metronidazole administration and electrolyte level monitoring (Berg et al., 2013).

If resistant to therapy, the only way the infection may be stopped is by surgical means. Taking into consideration infection severity, surgery may be performed in total or subtotal colectomy and even subsequent ileoanal reconstruction. Unfortunately, segmental resections lead to poor prognosis (Cohen et al., 2010).

Treatment of recurring infections

Recurrent infections may be possible due to immune response changes and/or GIF changes (Chang et al., 2008). The most effective treatment for recurrent infections is fecal transplantation (Zain et al., 2013).

The first recurrent episode can be cured the same way an initial infection can, by using metronidazole or vancomycin administered according to infection severity. Second or third recurrent episodes may occur (40-65% of cases), possibly due to insufficient therapy doses for previous episodes and can be cured using severe infection treatment (Cohen et al., 2010). As there are no universally approved therapy protocols, CDI treatment relies on dose probing and decreasing dose plan. Since 2011, fidaxomicin can be used as an alternative treatment both in initial and recurrent forms of CDI in both IBD and non-IBD patients.

Fecal transplantation – a new approach to treating CDI

Fecal transplantation was used for the first time over 2000 years ago in China in order to treat severe diarrhea and food poisoning. In more than three recurrent CDI non-IBD patients, fecal transplantation can be performed as a lifesaving procedure (Surawicz et al., 2013). The American College of Gastroenterology and the Fecal Microbiota Transplantation Working Group both recommend fecal matter transplantation in patients with recurrent infections.

Fecal transplantation can be performed through nasogastric or nasojejunal tube, during colonoscopy or via enemas. Fecal donors must be healthy and previously screened for any modifications in GIF. It is

generally believed that fecal transplantation can be used as a therapeutic measure in 84-94% of CDI cases (Zain et al., 2013).

In IBD patients, the relative proportions and concentrations of GIF species become altered due to bowel inflammation, mesalamine, antibiotic and immunodepressant therapies (Angelberger et al., 2013). Thus, this imbalance is a consequence of inflammation and not an ethiopathogenic factor, so fecal transplantation in IBD is still controversial. Some studies even suggested that fecal transplantation might lead to IBD relapse after a long period of remission (De Leon et al., 2013).

Other therapies

Saccharomyces boulardii is the most used probiotic in IBD and non-IBD CDC. Used with antibiotics, probiotics can reduce relapse rates from 50% to 17% (Pillai et al., 2008). However, probiotic therapy should not be used in the elderly or critically ill due to their characteristic immune response.

The therapeutic potential of intravenous administrations of immunoglobulins in IBD CDC patients remains to be confirmed on larger cohort studies. Monoclonal toxin A and B antibodies are currently in Phase II clinical trials on IBD relapses (Lowy et al., 2010). Vaccines against CD are being tested with great prognosis (Sougioultzis et al., 2005).

Early surgical consultation and surgical interventions might be essential in mortality reduction, as well as prevention of complication events (Khanna et al., 2013).

CONCLUSIONS

CDC diagnosis should be considered in all IBD patients that present acute diarrhea episodes. The most accurate diagnostic method is the EIA tests for A or B toxin presence in patient feces. IBD baseline treatment should be preserved even if CDI occurs, but immunosuppressive therapy must be reduced. CDI therapy must be built according to infection severity,

using proper metronidazole and/or vancomycin doses. The therapeutical potential of fecal transplantation is still controversial, especially in IBD CDI patients.

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