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Nightmare in the ward: difficult *Clostridioides* infection

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Clostridioides difficile is a Gram-positive, anaerobic, spore-forming bacillus. It is isolated in 80% of the stools of children and infants and in 3% of healthy adults. It causes gastrointestinal tract infections and affects patients who make prolonged use of antibiotics. It causes *C. difficile* colitis with symptoms ranging from diarrhoea to pseudomembranous colitis to toxic megacolon. The main virulence factors of *C. difficile* are toxin A, toxin B, and binary toxin. It is one of the most common nosocomial infections but in recent years, however, many infections have also been found at the community level. They are associated not only with a high risk of mortality but also with a prolongation of hospital stay. One of the critical aspects of *C. difficile* infections is also represented by the high frequency of relapses. Consequently, the economic impact is significant. Specific situations constitute risk factors for infection, such as exposure to antibiotic therapy in the previous months, in particular fluoroquinolones, third-generation cephalosporins, clindamycin, repeated hospitalizations in healthcare facilities, including long-term care, as well as the patient's clinical conditions such as comorbidities, age >65, chemotherapy and immunosuppressive treatments, recent surgery of any type, and pump inhibitor therapy. Treatment protocols will be described in the paper.

General consideration

Clostridioides difficile (*C. difficile*) is an anaerobic, Gram-positive, spore-forming and toxigenic bacillus, with faecal–oral transmission, widely distributed in the environment and able to colonise the intestinal tract of humans and other mammals.[1] Many antibiotics upset the balance between the types and numbers of bacteria that live in the gut. Thus, some pathogenic bacteria, such as *C. difficile*, can overgrow and displace the harmless bacteria that normally live in the intestine. When *C. difficile* bacteria overgrow, they release toxins that cause diarrhoea, colitis, and the formation of abnormal membranes (pseudomembranes) in the large intestine. Most of the diarrhoeas associated with antibiotic treatment are due to this pathogen and are more often of moderate intensity and resolve spontaneously with drug suspension. The patient generally complains of 5–15 loose stools per day associated with cramping abdominal pain. But more than half of hospitalized patients with *Clostridioides difficile* infection (CDI) have more severe disease defined by WBC counts above 15 000 cells/mL or blood creatinine above 1.5 g/dL. The disease can be fulminanted in up to 10% of affected patients. In this case, the patients are febrile, haemodynamically unstable with distention and abdominal pain. Diarrhoeic discharges can reach up to 30 per day and in any case the diarrhoea can stop or seem to improve in patients with ileus or with fulminant disease.[1,2] Laboratory findings suggestive of severe disease are white blood cells above 30 000/mL, albumin levels below 2.5 g/dL (due to protein loss and enteropathy), elevated serum lactate values, and elevations in serum creatinine. The symptomatology is due to the release of two exotoxins by the bacterium, toxin A and toxin B encoded by the genes tcdA and tcdB. Toxin A is an enterotoxin that damages actin in target cells and leads to neutrophil infiltration, inflammation and necrosis of intestinal epithelial cells resulting in increased permeability, fluid secretion, and neutrophil recruitment which leads to the formation of pseudomembranes. Cytotoxin B triggers apoptosis and

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damages the tight junctions of epithelial cells, increasing vascular permeability and causing haemorrhage.[1,2] A more virulent strain of *C. difficile* (NAP1/B1/027) contains a mutation of an inhibitor gene leading to overproduction of the toxins. This hypervirulent strain is more prevalent among healthcare-associated infections (HAIs) (31%) than community-acquired infections (19%) and is associated with higher mortality (7%).[3]

Some epidemiological data

A population-based study from Olmsted County, Minnesota, demonstrated that 41% of *C. difficile* infection cases were community-acquired and that the incidence of both community- and hospital-acquired CDI increased significantly from 1991 to 2005.[4]

Situation in the hospitals

About 20% of hospitalized patients are colonized with *C. difficile* and more than 30% of these develop diarrhoea making this disease one of the most common HAIs.[5,6] In Europe, in the early 2000s the incidence was about 4-5.5/10 000 days of hospitalization/patient. In the USA, rates of CDI have increased steadily over the past few decades and it is the most commonly identified cause of acute bacterial diarrhoea in the USA. In 2008, there were ~1 million cases of CDI in the USA.[7] In 2010, a study showed that, for the first time, hospital CDI cases exceeded methicillin-resistant Staphylococcus *aureus* (MRSA) cases; rates of CDI were 25% higher than those of MRSA in 28 community hospitals located in several states.[4] CDI also exceeds the incidence of many other hospital-acquired infections, such as catheter-associated intravascular infections, vancomycin-resistant enterococcal infections, and ventilator-associated pneumonia.[4] However, a recent CDC report showed a promising 20% reduction in CDI rates in <2 years in 71 hospitals that followed infection control recommendations. In many countries (USA, Canada, UK, and the Netherlands), the CDI outbreaks and the global increase in incidence have been attributed to a hypervirulent strain called 027/NAP1/BI.[2,8] To date, CDI is not a mandatory notification disease in the USA and many other countries. Registration is mandatory in some provinces of Canada and some European countries. At the European level, the European Centre for Disease Prevention and Control survey of incidence in 34 European countries in 2008 showed that the incidence of CDI was generally higher than documented in 2005, but varied widely between different hospitals and countries. In Great Britain where recording of all CDI cases has been mandatory since 2004, the incidence of CDI has increased significantly from <1000 cases/year in the early 1990s to around 60 000 cases in 2007/2008. However, since 2007, the incidence of CDI in the UK has decreased by as much as 61% in some cases in parallel with successful control of the prevalence of ribotype 027.[8] In Australia, after a high incidence of CDI in the early 1980s, a significant reduction was observed in the late 1990s and early 2000s, which was attributed to a decrease in the use of broad-spectrum cephalosporins.[9] The first case of ribotype 027 identified in Australia was reported in 2009.[10] In Asia, ribotypes 027 and 078, which have caused significant outbreaks in other parts of the world, do not appear to be very common, while ribotypes 017 and 018 have caused outbreaks in many countries. In other regions (Latin America and Africa), little or no data is available.[7] In countries, the incidence of CDI has recently begun to decline. This decrease has been attributed to several factors: (i) introduction of advanced surveillance plans (in the UK, mandatory screening of all hospitalized patients aged >65 years with *C. difficile* diarrhoea), (ii) awareness and increased accountability of hospital administrators on CDI rates, and (iii) enhanced implementation of infection prevention and control measures. The study 'Global burden of *C. difficile* infections: a systematic review and meta-analysis' published in 2019 in the *Journal of Global Health* indicates that globally the incidence of CDI is 2.2 per 1000 hospitalizations per year and 3.5 for 10 000 patient days per year.[1]

In Italy, the incidence of CDI is not known as a national surveillance system is not yet active, even if a pilot project for the surveillance of this infection was launched in 2019.

Situation in the general population

The incidence of infection is increasing in communities and in populations we used to consider low risk such as children and pregnant women with no history of hospital admissions or who are on recent or ongoing treatment with antibiotic drugs. The emergence of more virulent strains of *C. difficile*, such as the 027 strain, could be a more frequent and more severe cause of disease in these populations as well. But it has long been that increased awareness has led to an increase in the number of community CDI assessments. Infection is even more frequent among elderly people and old age can favour susceptibility to colonization and disease.[1] A study by Nylund *et al.*[11] suggested an increase in CDI among hospitalized children, especially in those with medical conditions such as inflammatory bowel disease (IBD) and immunosuppression.

Diagnosis

The practical elements for the diagnosis are shown in *Table 1*.

The diagnosis of CDI should be suspected in any patient with diarrhoea who has received antibiotics in the previous 3 months, has recently been hospitalized, and/or has an onset of diarrhoea within 48 h or more after admission. Additionally, *C. difficile* can be a cause of diarrhoea in community dwellers without prior hospitalization or exposure to antibiotics.[2,3]

To make the diagnosis we make use of analyses to be performed on the faeces, sigmoidoscopy, radiographic images.[2,12]

Stool analysis

Stool testing for *C. difficile* is recommended in hospitalized patients with dysentery or more than three loose stools in 24 h, or in outpatients with persistent diarrhoea for more than 1 week. There are three types of diagnostic tests:

(1) 'immunoassay' for glutamate dehydrogenase (GDH) which has sensitivity and negative predictive value (95%) for the detection of *C. difficile*, but is unable

Table 1 Essentials of clinical practice in *Clostridioides difficile* infection[2]

Signs and symptoms	Physical examination may reveal the following in patients	Diagnosis	
Mild-to-moderate watery diarrhoea, rarely bloody	Fever: especially in the most severe cases	Laboratory tests	Stool tests from most to least sensitive:
Crampy abdominal pain	Dehydration	Complete blood count: leucocytosis may be present (levels can be very high in severe infections)	Body culture (sensitivity, 90–100%; specificity, 84–100%), but results are slow and may lead to a delay in diagnosis when used alone
Anorexia	Pain on palpation of the abdominal quadrants	Electrolytes, creatinine: (dehydration, anasarca, and electrolyte imbalance may accompany severe illness)	Glutamate dehydrogenase (EIA): (sensitivity, 85–100%; specificity, 87–98%); detects the presence of glutamate dehydrogenase produced by *C. difficile*
Malaise	'rebound pain' on abdominal palpation. Indication of possible colonic perforation and peritonitis	Albuminaemia: (hypoalbuminaemia may accompany severe disease)	PCR: alternative gold standard to stool culture (sensitivity, 86%; specificity, 97%); used to detect the *C. difficile* toxin gene
		Lactate. [usually elevated (≥5 mmol/L) in severe disease]	Stool cytotoxin test (sensitivity, 70-100%; specificity, 90–100%)
		Stool exam: stools may test positive for blood in severe colitis (coarse bloody stools are unusual) faecal leucocytes are present in about half of the cases	EIA for the detection of toxins A and B: used in most laboratories (moderate sensitivity, 79–80%; excellent specificity, 98%)

EIA, enzyme immunoassay; PCR, polymerase chain reaction.

to distinguish between active infection with secretion of toxins and simple colonization;

(2) Polymerase chain reaction (PCR) which amplifies the toxin-producing gene (generally TcdB) with very high sensitivity (97–99%) and capable of identifying the hypervirulent NAP1 strain but this test is not able to distinguish between active infection and colonization;

(3) Rapid enzyme immunoassay which detect the presence of toxins A and B with 75–95% and confirm the presence of infection. In our hospital setting, the initial diagnostic test is GDH and/or PCR. Glutamate dehydrogenase negativity rules out infection.[2,12]

Flexible sigmoidoscopy

This procedure is not necessary in patients who have typical symptoms and positive stool analysis. But it can be decisive in those subjects with a positive stool test with atypical symptoms or have persistent diarrhoea despite appropriate therapy.[2,12] In patients with moderate symptoms, fluoroscopy may show no abnormalities or nonspecific colitis, while in patients with severe disease, pseudomembranous colitis will be described.[2,12]

Radiographic images

Abdominal CT without contrast in a patient with severe disease shows colonic dilatation with thickening of the walls. Furthermore, in hospitalized patients with abdominal pain and ileus without significant diarrhoea, thickening of the colonic walls suggests unsuspected CDI. CT is helpful in detecting a possible perforation.

Risk factors

Exposure to antibiotics

The main risk factor for CDI is previous exposure to antibiotics; agents most commonly implicated include cephalosporins (especially second generation and third generation), fluoroquinolones, ampicillin/amoxicillin, and clindamycin. Less commonly implicated antibiotics are macrolides (i.e. erythromycin, clarithromycin, azithromycin) and other penicillins. Agents occasionally reported to cause disease include aminoglycosides, trimethoprim-sulfamethoxazole, metronidazole, chloramphenicol, tetracycline, imipenem, and meropenem.[2,3,12]

Even a brief exposure to a single antibiotic can cause CDI. A prolonged course of antibiotics or the use of two or more antibiotics increases the risk of disease. In addition, the antibiotics traditionally used to treat *C. difficile*, vancomycin and metronidazole, have also been shown to cause disease.[6] Hospitalized patients occupying a bed whose previous occupant received antibiotics appear to have an increased risk of CDI.[13]

Proton pump inhibitors

On 8 February 2012, US Food and Drug Administration (FDA) safety communication described a possible

Table 2 Recommendations for the treatment of *Clostridioides difficile* infection

Treatment of *Clostridioides difficile* infection	
Asymptomatic carriers	No treatment
Mild or moderate disease	Vancomycin 125 mg orally 4 times a day for 10 days or Fidaxomicin 200 mg 1cp 2 times a day for 10 days Alternative for non-serious disease in case of unavailability of the above: metronidazole per os 500 mg 3 times a day for 10–14 days
First recurrence of CDI	Fidaxomicin 200 mg × 2 for 10 days or 2 times a day for 5 days + 1 a day for another 20 days Alternatives: (1) Oral vancomycin in a reduced and pulsed regimen (2) Vancomycin 125 mg 4 times a day for 10 days
Recurrence prophylaxis	Bezlotoxumab 10 mg/kg intravenously during administration of one of the above therapies
Second recurrence	See first recurrence
Third recurrence	Faecal microbiota transplantation
Fulminant CDI	Vancomycin 500 mg 4 times a day by nasogastric tube. If ileus add enema with vancomycin. In the presence of ileus add metronidazole (500 mg i.v. every 8 h)

Recommendations from IDSA and SHEA guidelines.[12]

association between the use of proton pump inhibitors (PPIs) and the development of CDI. The FDA also reviewed a total of 28 observational studies described in 26 publications. Of these studies, 23 showed a higher risk of CDI, associated with PPI exposure, than with no PPI exposure.[14]

Other risk factors

Antidepressants such as mirtazapine and fluoxetine increase the risk of CDI.[15] Older age (>60 years) and hospitalization (particularly sharing a hospital room with an infected patient, admissions to intensive care units, and prolonged hospital stays) are known risk factors for *C. difficile* infection. Severe illnesses, immune suppression are also well-established risk factors. Furthermore, in recent years, IBD has been implicated as a strong risk factor for CDI infection. Early emergency general surgery has also been associated with a high incidence of CDI, particularly in patients receiving three or more post-operative antibiotics and in those undergoing bowel resections.

Treatment

At the time of the therapeutic choice, some considerations must be made: (i) if possible, the antibiotic therapy in progress is suspended; (ii) ~20–25% of patients experience a recurrence, less frequent with fidaxomicin; (iii) antiperistaltic drugs must be avoided in the acute phase; (iv) generally 10 days of therapy are sufficient which can be extended to 14 if the diarrhoea improves but does not disappear.

In case of mild or moderate disease, vancomycin 125 mg orally 4 times a day for 10 days or fidaxomicin 200 mg orally every 12 h for 10 days is used. Fewer relapses occur with fidaxomicin but only in the case of non-NAP1 strains and in patients who require concomitant antibiotic therapy. The cost of a treatment with fidaxomicin is much higher than that with oral vancomycin.

In the event of severe or fulminant disease, vancomycin 500 mg is used every 6 h orally or with a nasogastric tube and metronidazole 500 mg i.v. every 8 h. In patients with ileus, enemas with vancomycin 500 mg in 100 mL of physiological solution are used. In severe disease with toxic megacolon the last option remains colectomy.[2,12]

Treatment of recurrences

A separate issue is the treatment of relapses (*Table 2*). Approximately 20% of patients have a recurrence of CDI within 20 days of finishing initial treatment. This usually occurs due to reinfection and failure to eradicate the organism. International guidelines tell us that the drug of choice is fidaxomicin 200 mg every 12 h for 10 days especially if the first episode was treated with vancomycin. Alternatively, prolonged treatment with 200 mg fidaxomicin every 12 h for 5 days followed by one tablet a day for another 20 days, or vancomycin 125 mg orally 4 times a day for 10 days is indicated. Finally, there is the possibility of a tapering scheme with vancomycin (*Table 2*).[2,12] In case of three or more relapses, the guidelines recommend faecal microbiota transplantation, where a suspension of faecal bacteria from a healthy donor is administered to the patient with CDI. The faecal microbiota can be instilled in three ways: (i) infused by colonoscope in the terminal ileum and in the colon; (ii) administered through a nasogastric tube into the duodenum; and (iii) by taking capsules containing freeze-dried microbiota. This practice leads to a chance of eradication in over 90% of patients with multiple relapses. However, in this practice, there is the possibility of transmitting fatal infections especially if the recipients of the transplant are immunocompromised. But with accurate donor stool screening precautions the risk is currently very low.

Finally, recurrence prophylaxis is possible using bezlotoxamab, a monoclonal antibody that binds toxin B to be

used in combination with one of the aforementioned therapies.[12] This association reduces recurrences by 11–14%.

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Data availability

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