Atti della Accademia Lancisiana
Anno Accademico 2017-2018
Vol. LXII, N. 2 Aprile-Giugno 2018
II: 136-138

Lettura Magistrale: Treatment of Clostridium difficile infection: focus on faecal microbiota transplantation

G. Cammarota, G. Ianiro

Among different clinical pictures of *Clostridium difficile* infection (CDI), severe disease represents a therapeutic conundrum in clinical practice, for several reasons. First, classical treatment options appear to be still unsatisfactory. As pointed out in a recent Cochrane review, the efficacy of antibiotics in severe CDI has not yet been established, because most available studies excluded this subgroup of patients. Surgery, usually considered when antibiotic therapy is failing, is known to reduce the risk of death in the short-term period, but it is jeopardised by high rates of morbidity and mortality in the long run.

The incidence of multiply recurrent CDI episodes following an initial infection is increasing, because of the lack of currently available therapeutic options to recover the microbiota and prevent a new episode. After treatment of an initial episode of CDI, the chance of a recurrence within 8 weeks is 15–25%; for a patient with 1–2 previous recurrences, the risk of further recurrences is 40–65%. A recent analysis showed that relative to CDI, the multiple recurrent CDI incidence has disproportionately increased, indicating a rising demand for prevention of recurrent CDI. Interestingly, the increase in recurrent CDI incidence was independent of known risk factors for CDI.

Faecal Microbiota Transplantation (FMT) appears to be a powerful treatment option against recurrent CDI[1]. After publication of the first randomized trial showing the efficacy of FMT in patients with recurrent CDI, it has been legitimised as a standard therapy for this condition, after failure of antibiotic therapy alone to prevent recurrent CDI, both in European and in American guidelines for the management of CDI. Less evidence exists on the role of FMT as a direct therapy for severe CDI refractory to antibiotic treatment. In this scenario, FMT is not applied to prevent recurrent disease, but in the actual management of severe disease refractory to antibiotic therapy, by combatting toxin producing *C. difficile* directly. To date, FMT was shown to be effective not only in studies mixing patients with different levels of disease severity, but also in several cohorts including only patients with severe CDI.

THE BURDEN OF CLOSTRIDIUM DIFFICILE INFECTION

Clostridium difficile (recently re-classified as *Clostridioides difficile* based on phenotypic, chemotaxonomic and phylogenetic analyses[2] - for simplicity and consistency with previous literature *C. difficile* will be used in this paper - is an anaerobic, spore-producing bacterium responsible for CDI. *C. difficile* spores are ubiquitous in the environment. *C. difficile* is a human pathogen but can also infect and cause disease in

animals that can enter the food chain; however, the relevance of foodborne transmission in human disease is unclear.

Diagnosis of infection

The diagnosis of CDI is based on a combination of signs and symptoms, confirmed by microbiological evidence of *C. difficile* toxin and toxin-producing *C. difficile* in stools, in the absence of another cause. Although colonoscopic or histopathological findings of pseudomembranous colitis are also considered as specific for CDI, there are reports that other microorganisms can cause similar findings. No single commercial test can be used as a stand-alone test for diagnosing CDI because of inadequate positive predictive values at low CDI prevalence. Therefore, the use of a two-step algorithm is recommended. This algorithm should start with either a nucleic acid amplification test (NAAT) to the presence of toxin genes or an enzyme-immunoassay to the glutamate dehydrogenase of *C. difficile* (GDH EIA). Samples with a positive first test result should be tested further with an assay to detect free toxins in faeces. An alternative algorithm is to screen samples with both a GDH and toxin A/B EIA[3].

Epidemiology

C. difficile is the main causative agent of antibiotic-associated and healthcare acquired diarrhoea in humans, but there is also an increasing realisation that CDI can occur in subjects not recently exposed to healthcare interventions or antibiotics. Since the early 2000s, the epidemiology of CDI has changed dramatically, reflected by an increasing incidence, increasing number of recurrences after antibiotic therapy, and an increased mortality. These changes have been driven to a major degree by the emergence and epidemic spread of two novel strains, known as PCR ribotype 027 and PCR ribotype 078. Currently, the epidemiology of CDI is complex and varies considerably across countries in Europe. Some countries (UK) have had major epidemics of CDI due to type 027 and successful control programs, whereas others (e.g. Germany, Eastern Europe) are currently confronted with epidemics associated with hypervirulent strains. The European Centre for Disease Prevention and Control (ECDC) has recognised the urgency of the CDI threat by recommending that all EU countries institute surveillance.

Costs and burden

CDI is associated with high healthcare costs due primarily to prolonged hospitalisation of CDI patients. In the USA in 2013, the Centers for Disease Control (CDC) identified *C. difficile* as one of the top three antibiotic resistant threat pathogens. Estimated 30-day mortality rates for CDI range from 6 to 16%. The US (CDC) estimated that almost 500,000 patients had CDI, with 29,000 attributable deaths in the United States in 2011[4]. With an ageing population across Europe, CDI is likely to remain a significant threat to public health, which requires a major coordinated and sustained effort to reduce patient morbidity, mortality, and healthcare and societal costs. The first ECDC point-prevalence survey in 2011 and 2012 estimated that ~124,000 patients developed health-care-associated CDI within the European Union each year[5]. The total direct cost of CDI to the European Union in 2006 was estimated at €3 billion per year. Assuming a 3% annual inflation rate, this approximates to >4 billion € in 2015. The cost will further significantly

increase, since the European Union has predicted that the demographic old-age dependency ratio (the ratio of those aged >65 years old to those aged 15–64 years) will increase from 27.8 to 50.1% between 2013 and 2060.

Conclusions

FMT has been implemented as a highly effective treatment against recurrent CDI, providing a significant advantage over treatment with classical antibiotics alone. FMT has also been shown to be a potential salvation therapy for a severe presentation of CDI with a reduction of the need for emergency surgery (and related complications). FMT is only occasionally applied in the setting of severe CDI refractory to antibiotic treatment, and only few centers have sufficient experience. Both the dissemination of FMT centres and the design of face-to-face trials of FMT with surgery are advocated to assess the efficacy of FMT in the setting of severe CDI.

REFERENCES

1. Cammarota G, Ianiro G, Tilg H, et al. European FMT Working Group. European consensus conference on faecal microbiota transplantation in clinical practice. GUT 2017; 66: 569-80.
2. Lawson PA, Citron DM, Tyrrell KL, Finegold SM. Reclassification of Clostridium difficile as Clostridioides difficile (Hall and O'Toole 1935) Prévot 1938. Anaerobe 2016; 40: 95-9.
3. Crobach MJ, Planche T, Eckert C, et al. European Society of Clinical Microbiology and Infectious Diseases: update of the diagnostic guidance document for Clostridium difficile infection. Clin Microbiol Infect 2016; 22 Suppl 4: S63-81.
4. Smits WK, Lyras D, Lacy DB, Wilcox MH, Kuijper EJ. Clostridium difficile infection. Nat Rev Dis Primers 2016; 2: 16020.
5. European Centre for Disease Prevention and Control. Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals 2011–2012. ECDU. 2013; http://www.ecdc.europa.eu/en/publications/Publications/healthcare-associated-infections-antimicrobial-use-PPS.pdf. Last access on 18 September 2017.

Prof. Giovanni Cammarota, Dott. Gianluca Ianiro**,** Internal Medicine, Gastroenterology and Liver Unit, Gastroenterology Area, Fondazione Policlinico Universitario Gemelli, Università Cattolica del Sacro Cuore, Rome, Italy

Correspondence: giovanni.cammarota@unicatt.it