Clostridium difficile

Expert Statement: Royal Irish Academy Life and Medical Sciences Committee

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The Gram positive bacterium *Clostridium difficile* (*C. difficile*) is the most common cause of antibiotic associated diarrhoea in healthcare settings worldwide, and is also the primary cause of pseudomembranous colitis. Over the past 30 years, *C. difficile* has evolved into a highly effective human pathogen, associated with 25–30% of all cases of antibiotic associated diarrhoea. Significant media coverage over the last decade has identified it as the newest 'superbug' to threaten patients, and it is now mandatory for hospitals to report cases of *C. difficile* infection.

Clostridia are spore-forming bacteria that are found naturally in soils, as well as in the intestines of animals. *C. difficile* only grows in the absence of oxygen and can, under adverse conditions, form hardy, resistant spores that persist in the environment. These spores are recognised as the transmissible agent of *C. difficile* infection. *C. difficile* has a further advantage—it is resistant to many common antibiotics, whereas the normal, harmless gut microbes are not. Recent genomic evidence also suggests that *C. difficile* is evolving to become more pathogenic in response to healthcare practices such as antibiotic use.

The human gastrointestinal tract (gut) contains about ten times as many bacteria (the gut microflora) as there are cells in the human body. These play roles in both nutrition and disease, and the gut ecosystem is relatively robust: gut microflora help to prevent pathogenic bacteria gaining a foothold. However, disruption of this microbial ecosystem, for example by use of broad spectrum antibiotics, leaves an environment in which pathogenic bacteria can grow without competition. Under such conditions, *C. difficile*, which is carried by 3–10% of the population, can initiate an infection. *C. difficile's* flagellum allows it to swim towards and adhere to the gut epithelial cells, where it produces its two main virulence factors, toxin A and toxin B. The combined action of the toxins causes profound inflammation of the gut lining. The gut epithelial cells finally burst, with the gut lining becoming leaky. Fluid is then secreted into the colon, along with fragments of epithelial cells, giving rise to pseudomembranous colitis. Whilst the precise individual role of each toxin in disease is still under debate, the fact is that they cause the majority of the symptoms of *C. difficile* infection. The disruption of the normal colonic bacterial microflora, with resulting growth of toxigenic *C. difficile* and the physiological effects of toxins on the colonic epithelium, means the frequency with which stools are passed increases, while their consistency becomes more liquid. This is the '*C. difficile*-associated diarrhoea', which is usually the first sign of infection.

The main risk factors for *C. difficile* infection are (a) an extended duration of stay in hospital, (b) advanced age, that is being over 65 years, and (c) long-term treatment with broad spectrum antibiotics. It might be expected that *C. difficile* infection would only arise in hospitals, yet there is evidence that community acquired *C. difficile* infection is on the increase, due perhaps to increased use of antibiotics outside healthcare environments. *C. difficile* infection is estimated to cost in the order of €1.6 billion in Europe and more than $3 billion in the USA annually, and, worryingly, *C. difficile*has been attributed to five times more deaths than Methicillin-resistant *Staphylococcus aureus* (MRSA), the other 'superbug' of newspaper notoriety.

From a hospital Infection Control Team's point of view, rapid reliable tests are essential so that patients can be treated as quickly as possible. The UK's Health Protection Agency, for example, recommends a two-stage testing regime, which is deployed in most hospitals, in which samples are initially tested for glutamate dehydrogenase (GDh), a metabolic enzyme present at high levels in *C. difficile*. GDh+ samples are then tested biochemically for the physical presence of the toxins, or analysed by Polymerase Chain Reaction (PCR) for presence of the toxin genes in those samples with low toxin titre. This two-step algorithm gives almost 100% accuracy in testing, allowing diagnosis to be made within a day. In addition, pure cultures of *C. difficile* can be isolated from samples to allow molecular biological analysis of their genomes in a process known as ribotyping. The vast majority of infections are caused by only a few ribotypes—for example ribotypes 027, 106, 078 or 014—but ribotyping provides the clinician with further epidemiological information about disease-causing *C. difficile*strains, as well greater insight into the prevalence and spread of the pathogen.

So, when a patient is diagnosed with *C. difficile* infection, how does the clinician set about effecting a cure? As a primary measure, stopping the antibiotics that caused the problem in the first place may be sufficient to allow the patient's gut microflora to re-establish, although this strategy may not be possible in all cases. Therefore isolation of the patient, implementation of stringent hand-washing and hygiene procedures for staff and visitors, coupled with a rapid diagnosis of *C. difficile* is necessary. The primary treatment is administration of the antibiotic metronidazole, for example a dosage of 500mg given orally 3 times daily for 10 to 14 days, where it is very effective. In cases where metronidazole side-effects are not well tolerated by the patient, vancomycin is used. *C. difficile* is a rapidly evolving microorganism, however, and the emergence of new hypervirulent strains with increased pathogenicity requires the development of new therapeutic approaches. One such new drug, fidaxomycin, is the first bacteriocidal antimicrobial agent to be approved by the US Food and Drug Administration for the treatment of *C. difficile* infection in adults in the last 25 years. Fidaxomycin significantly reduces recurrence rates for *C. difficile* infection and is thus an improvement on existing treatments.

While development of new antibiotics is one approach, continued basic research into the organism's biology is also vital to a full understanding of the essential components that underlie *C. difficile* hypervirulence. Modern systems biology research techniques, measuring the responses of thousands of individual cellular components—such as proteins—to environmental perturbations gives researchers greater insight into how *C. difficile* functions under infection-relevant conditions. This approach should lead to further improvements in testing, diagnosis and treatment, and it is hoped that this scientific effort will ultimately improve patient outcomes, thereby reducing the burden of *C. difficile* on society.

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