PRIMEVIEW

CLOSTRIDIUM DIFFICILE INFECTION

nature REVIEWS DISEASE PRIMERS

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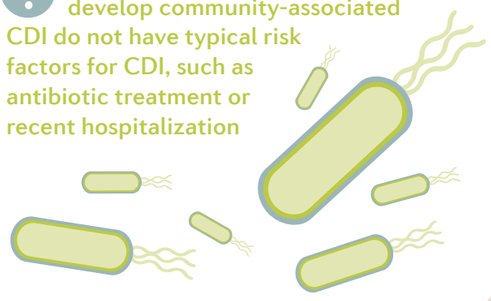
Clostridium difficile **is an obligate anaerobic Gram-positive bacterium that is the leading cause of health-care-associated infective diarrhoea. Antibiotic exposure during hospitalization and older age (>60 years) are major risk factors for developing *C. difficile* infection (CDI).**

EPIDEMIOLOGY

Epidemiological studies depend on standardized typing methods; PCR ribotyping is the most commonly applied typing system. PCR ribotype 027 strains have caused outbreaks globally, but other PCR ribotypes (such as PCR ribotype 010) are usually non-pathogenic because they lack the toxin genes.

More than 30% of patients who develop community-associated CDI do not have typical risk factors for CDI, such as antibiotic treatment or recent hospitalization



MECHANISMS

C. difficile is transmitted via the oral–faecal route, with spores being the main infectious agent. Spores are ubiquitous in the environment and can enter the food supply

Antibiotic-induced dysbiosis of the protective intestinal microbiota often underlies *C. difficile* outgrowth and toxin production

In the gut, the metabolically active bacteria produce high molecular weight clostridial toxins toxin A and toxin B

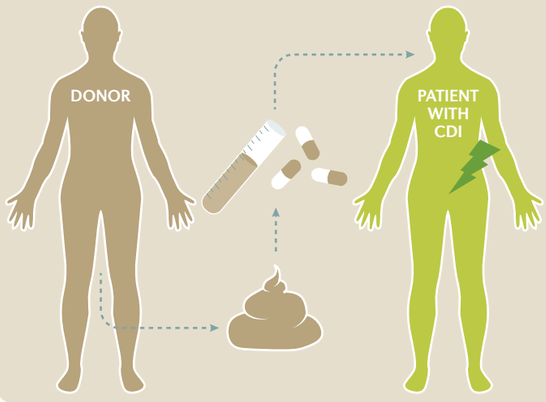
Toxins A and B are implicated in a complex cascade of events that eventually leads to the consequences of CDI

Some strains of *C. difficile* also produce the *C. difficile* transferase (binary toxin), which destroys the actin cytoskeleton, leading to cell death and possibly contributing to (or enhancing) symptoms

One result of this cascade is the inactivation of RHO family proteins, causing apoptosis and cytopathic 'rounding' effects of colon epithelial cells

MANAGEMENT

Infections are commonly treated with specific antimicrobial agents that target the *C. difficile* metabolically active vegetative cells (but not the virtually inactive spores). In patients who have recurrent episodes of CDI, faecal microbiota transplantation can be an effective rescue treatment. However, this procedure — in which faeces from healthy donors are processed and transplanted into patients — is still being defined and long-term results are unknown. Fulminant CDI is a highly lethal disease (mortality rates of up to 80%) that often requires total abdominal colectomy. Given that the faeces of patients with CDI are rife with spores, treatment should always be combined with patient isolation to prevent the spread of *C. difficile* or other enteropathogenic microorganisms.



DIAGNOSIS

Given that individuals can be asymptomatically colonized by *C. difficile*, diagnosis requires a test for the presence of the bacteria and another for the presence of bacterial toxins in the faeces. For those with symptoms, these can include mild self-limiting diarrhoea, fulminant colitis, pseudomembranous colitis, toxic megacolon, bowel perforation, sepsis and/or multiple organ dysfunction.

QUALITY OF LIFE

The high mortality rates of CDI underline the serious consequences of the disease. As patients are typically older and have comorbidities, the additional burden of CDI can greatly affect quality of life. Furthermore, in Europe, the median length of hospital stay for patients with CDI is 8–27 days, which imposes economic and personal burdens on patients, families and health-care systems.

OUTLOOK

Future therapies for CDI will probably involve defined combinations of key gut microbiota to restore the bacterial environment of the gut. Treatments currently being explored also include drugs to neutralize the *C. difficile* toxins (including monoclonal antibodies), to inhibit *C. difficile* proliferation and to prevent off-target effects of antibiotic treatment on the intestinal microbiota.

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