



comment

Clostridium difficile

Bacillus difficilis was first reported in 1935 as a component of the faecal flora of new babies. Renamed *Clostridium difficile*, this Gram-positive, strictly anaerobic spore-former received little coverage in the literature. Until 1976 it was regarded as harmless, but by 1977 it was recognized to be a dangerous pathogen, the major cause of pseudo-membranous colitis (PMC). *C. difficile* was subsequently identified as the main cause of hospital-acquired antibiotic-associated diarrhoea, a lesser form of the rarer PMC. Over the next decade, several outbreaks of *C. difficile*-associated disease (CDAD) occurred throughout the developed world.

The pathogenic mechanisms are now reasonably well understood. The major virulence factors, two large exotoxins, A and B, act on rho and other small GTP-binding proteins, resulting in the breakdown of the cytoskeleton of gut epithelial cells. Immunopathological mechanisms are also triggered and the resulting cellular damage and infiltration of neutrophils give rise to the pathology. Symptoms range from mild to serious diarrhoea and life-threatening PMC, megacolon and possible perforation. It was thought that the two major toxins worked in concert, but recently cases caused by Toxin A-negative strains have been found. Genetic approaches for studying pathogenesis have proved extremely difficult – the organism living up to its specific name!

During the 1990s, CDAD increased almost exponentially. It is now endemic in many hospitals, where it survives as resistant spores after dissemination by often explosive diarrhoea. It is

▲ Coloured SEM of *C. difficile*. D. Phillips/
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especially common in wards for the elderly and in other areas where antibiotics are widely used. About 30% or so of patients in geriatric wards carry it, and up to half of these can be symptomatic. It imposes a huge financial burden on the health services because of the increased length of stay of patients and the more intensive patient management required.

Most hospital staff are well aware of CDAD and recently it has overtaken MRSA in incidence and prevalence in some hospitals. Public awareness of the disease is only recent. During 2004 in parts of North America there was a noticeable increase in incidence and severity, with more deaths attributable to the disease. The causative strain was more virulent than those previously seen, now identified as a hypervirulent clone – ribotype 027. It has a deletion in the gene which encodes the negative regulator of the toxins; therefore, toxins are produced at higher levels than normal. It is also resistant to the commonly used quinolone antibiotics. In June 2005 this strain hit the UK headlines by causing problems in several hospitals, including Stoke Mandeville. There are also several current outbreaks in The Netherlands.

Most patients become colonized with the bacterium because the normally protective colonic microbiota has been disrupted by antibiotics. Subsequent susceptibility to disease is probably due to an inability of the host to mount a protective immune response to the organism and its toxin(s).

Although treatable with antibiotics (usually metronidazole or vancomycin), relapses or re-infections occur in up to 30% of patients. The unpleasantness

of the disease has meant that improved therapies are desperately required. Re-establishing the gut microbiota is a sensible approach to prevention or treatment, and the use of certain probiotics has been advocated. The euphemistically known 'faecal transplants' are more unusual. They involve repopulating the gut with healthy faeces usually donated by a close relative. Other treatments include the use of agents that bind the toxins in the gut and prevent their uptake, and passive immunotherapy to supplement antibody deficiencies.

MRSA is often in the news, but now a different hospital-acquired infection is hitting the headlines. As increasingly virulent strains of *Clostridium difficile* are discovered, **Ian Poxton** wonders what can be done to beat this pathogen.

What is certain about *C. difficile* is that it is now endemic in most of our hospitals and will remain so while the sick are being treated with antibiotics. Despite Herculean attempts to get rid of the spores by cleaning, it seems efforts are failing. The best short-term hope is that the disease is kept in check by a combination of 'infection control' procedures, judicious use of antibiotics and the development of more successful treatments. But now a 'super strain' has arrived...

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Further reading

- Special issue on *C. difficile* (2005). *J Med Microbiol* **54**, part 2 (Feb).
- Riley, T.V. (2004). Nosocomial diarrhoea due to *C. difficile*. *Curr Opin Infect Dis* **17**, 323.
- Voth, D.E. & Ballard, J.D. (2005). *C. difficile* toxins: mechanism of action and role in disease. *Clin Microbiol Rev* **18**, 247.

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