J R Coll Physicians Edinb 2006; **36**:216–219

Clostridium difficile-associated disease – an increasing burden

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ABSTRACT Although *Clostridium difficile* has been recognised as the cause of antibiotic-associated PMC and diarrhoea for almost 30 years, especially in elderly patients undergoing antibiotic treatment, it is only recently that it has been acknowledged as a major hospital pathogen. It is usually acquired exogenously – in the form of resistant spores – from the contaminated hospital environment, after the normal colonisation resistance afforded by the normal colonic microflora has been disturbed. Production of at least one of two toxins causes damage to the colon wall and subsequent symptoms. Recent recognition of a hyper-virulent type that produces enhanced levels of toxins and is resistant to fluoroquinolone antibiotics is causing outbreaks of serious disease in North America and several European countries – but not yet in Scotland. Current treatment is with metronidazole or vancomycin but relapse is common. Removal of the spores – which are resistant to alcohol and most disinfectants – is crucial to controlling infection.

KEYWORDS Antibiotic-associated diarrhoea, *Clostridium difficile*, high relapse rate, hospital-acquired infection, hyper-virulent 027 strain, pseudomembranous colitis.

LIST OF ABBREVIATIONS *C. difficile*-associate disease (CDAD), methicillin-resistant *staphylococcus aureus* (MRSA), pseudomembranous colitis (PMC)

DECLARATION OF INTERESTS No conflict of interests declared.

Published online ***May 2006***

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THE BACTERIUM AND THE DISEASE

Clostridium difficile, a Gram-positive, strictly anaerobic, spore-forming bacterium was recognised as the cause of antibiotic-associated diarrhoea and colitis almost 30 years ago. The spectrum of CDAD ranges from mild, self-limiting diarrhoea, to serious diarrhoea, to life-threatening PMC. *C. difficile*-associate disease was uncommon until the early 1990s when it began to increase almost exponentially, and the number of cases in many of our hospitals have now reached levels that are generally higher than those caused by the better-known MRSA. Figures for Scotland, based on submissions to Health Protection Scotland, are summarised in Figure 1. It is the most common cause of healthcare-associated (nosocomial) diarrhoea and results in much morbidity in elderly hospital patients. Mortality has been associated with the disease, mainly as a contributory factor. Although not commonly considered a problem in the community, CDAD is certainly acquired there and it is not uncommon for patients to be carrying it on admission to hospital.

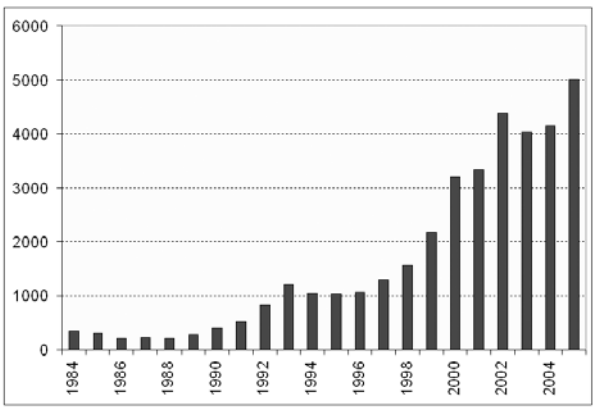

FIGURE 1 Voluntary reports of *Clostridium difficile* 1984–2005 for Scotland. Figures taken from Health Protection Scotland (formerly Scottish Centre for Infection and Environmental Health) Weekly Reports.

CURRENT STATUS

The disease has certainly increased over the past decade or so, with a consequent increasing burden on health service providers. Anecdotal evidence also suggests the disease may be increasing in severity. A press release by the Health Protection Agency in December 2005 highlighted the current status of the organism and disease.[1] In this web reference, there is a link to the Healthcare Commission's full report, *Management, prevention and surveillance of* Clostridium difficile – *Interim findings from a national survey of NHS Acute Trusts in England*. The need for isolating infected patients or barrier-nursing them in outbreaks, together with their increased lengths of stay in hospital, especially for those who experience

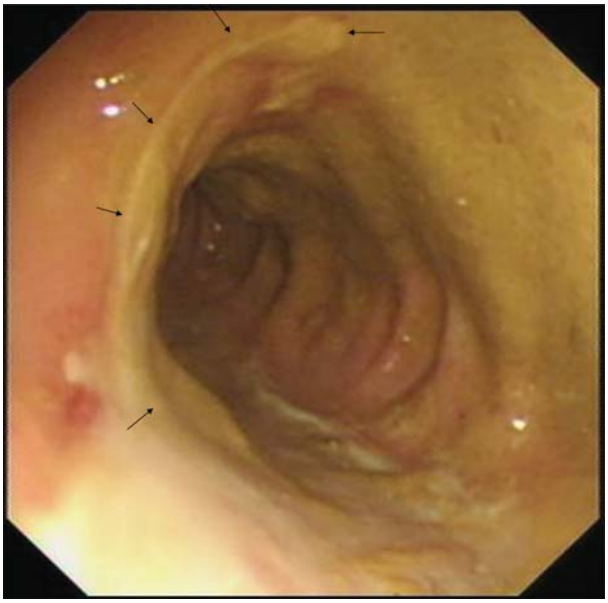

FIGURE 2A *Clostridium difficile*-associated pseudomembranous colitis. Endoscopic appearances of pseudomembranous colitis. The characteristic plaque-like pseudomembranes are present (arrows).

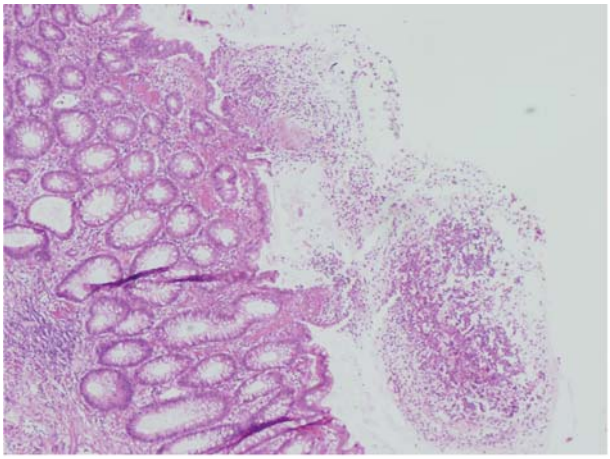

FIGURE 2B *Clostridium difficile*-associated pseudomembranous colitis. Histopathology of section through mucosal layer; massive numbers of neutrophils are 'exploding' between damaged colonocytes. Images courtesy of Paul Fineron.

recurring disease, has resulted in considerable extra costs. In 1996, additional costs were reported to be in the region of £4,000 per patient,[2] and recent unpublished estimates from the USA are in the region of US$6,000.

TRANSMISSION OF *C. DIFFICILE*

Our early understanding of the disease assumed that the bacterium was of endogenous origin: small numbers of *C. difficile* that were present in the colon were allowed to flourish after the normal microbiota was severely affected by antibiotic exposure. However, this does not explain the occurrence of outbreaks. When carefully looked for in the healthy adult population the organism is rarely encountered. It is now accepted that *C. difficile* is an infectious agent and is spread by faecal–oral transmission

FIGURE 2C *Clostridium difficile*-associated pseudomembranous colitis. Part of resected colon revealing large areas of pseudomembrane formation (raised plaques).

of spores from patient to patient, or from contaminated environment to patient.

THE DISEASE: PATHOGENESIS AND EPIDEMIOLOGY

The stages in the disease process are usually:

- The normal protective properties of the gut – especially the colonisation resistance promoted by the normal resident bacteria (microflora) of the healthy gut – are compromised by antibiotics or less frequently other therapeutic agents.
- If *C. difficile* spores are in the local environment of the patient the colon becomes colonised via the oral route.
- The bacterium evades the immune response and multiplies, producing toxins A and B.

If a patient is susceptible – i.e. is unable to withstand the insult of the toxins, probably as a result of lowered immunity – pathology results. Symptoms ranging from diarrhoea of varying severity to PMC are caused by the destruction of colonocytes, a loss of absorptive capacity, leakage of electrolyte and an influx of inflammatory cells – predominantly neutrophils which produce in the more severe cases the pseudomembrane typical of PMC (see Figure 2).

THE HYPER-VIRULENT STRAIN

The recent recognition of a hyper-virulent strain, firstly in Canada and the USA,[3] and more recently in England, the Netherlands and Belgium, has brought the organism to the attention of the general public as the latest 'superbug'. Clinicians familiar with the disease suggested early in the North American outbreak that a strain of increased virulence was probably responsible for the problem. This strain is now known in North America as BI/NAP1 and in Europe as ribotype 027. In the UK, it

was first recognised as causing a problem at Stoke Mandeville Hospital in Buckinghamshire, where at least 12 deaths were reported from 150 cases in the period February–June 2004 (personal communication, Jon Brazier). Since then, other centres have experienced problems with this 027 strain – notably in Exeter and Romford, Essex. The Secretary of State for Health was questioned in the House of Commons, and in his written answer, 12 other hospitals throughout England were reported to have the strain – from Truro in the South West, to Newcastle and Sunderland in the North East.[5] At the time of writing this article (August 2006) none have been identified in Scotland.

It appears that the new hyper-virulent strain (BI/NAP1 or ribotype 027) has the following characteristics:

- It produces higher than normal levels of toxins A and B *in vitro,* and almost certainly *in vivo*.
- There is a deletion in the gene (tcdC) which normally negatively regulates toxin production – resulting in constant maximum level of trancription of toxin genes.
- It belongs to ribotype 027 and toxinotype III.
- It is resistant to fluoroquinolone antibiotics such as ciprofloxacin and moxifloxicin.
- It produces an additional toxin – the binary toxin.
- The North American and European strains are probably identical.
- The disease that it causes is more severe with more colectomies required and more deaths attributable to it.

It is becoming apparent that the deletion in the toxin-regulating gene is not restricted to the 027 ribotype so a family of super strains may soon become apparent.

For an update on the hyper-virulent strain see 'News and Activities' at the European Study Group for *Clostridium difficile* website.[6]

TREATMENT OPTIONS FOR CDAD

Many patients, especially in wards for the elderly, carry the organism asymptomatically, and detection of the organism in the stool is not an indication to treat. If the disease is mild, no treatment may be necessary as the symptoms may resolve naturally. For more severe disease, stopping the administration of the precipitating antibiotic is the first option. If this is not possible or it is ineffective, administration of metronidazole or oral vancomycin is recommended. Although both work equally well, the former is usually used initially with the latter reserved for more severe or unresponsive disease.

As many as 25% of patients suffer a relapse after initial resolution of symptoms.[7] This could be a real relapse or a re-infection with the same or a different strain of *C. difficile*. This common problem of recurrent CDAD – together with the anathema of treating a disease caused by antibiotics with another antibiotic – has necessitated a thorough review of treatment schedules.

Alternative treatment options fall into four main areas: a) prebiotics and probiotics; b) absorbents for toxins – to eliminate them from the gut; c) 'faecal transplants/enemas' – where stools donated from a healthy donor are placed in the bowel in an attempt to restore the normal microbiota; and d) immunotherapy – either active or (probably more usefully) passive immunisation. Lynn McFarlane has recently reviewed 'alternative treatments' for CDAD.[8] Currently none of these alternatives has become routine, but efforts are progressing in earnest. Anti-peristaltic drugs are strongly contra-indicated as they may precipitate toxic megacolon and perforation.

INFECTION CONTROL AND THE FUTURE

Many of our hospitals and institutions caring for the elderly are now highly contaminated with spores of *C. difficile* and increasing numbers of susceptible, antibiotic-treated patients are propagating the organism. Infection control is difficult, but its importance cannot be overestimated. Control measures include regular surveillance, isolation or barrier nursing, personal hygiene, and intensive cleaning of affected wards to remove the bacterial spore load. Spores of *C. difficile* are resistant to alcohol-based antiseptics (alcohol hand-washing gels are ineffective), and chlorine-based disinfectants are only partially effective. Adherence to strict antibiotic policies: restricting the use of those antibiotics such as oral cephalosporins and clindamycin, which are known to precipitate the disease, is well recognised but crucially important. Fluoroquinolones – once not thought to precipitate the disease – now seem to select for the new fluoroquinolone-resistant 027 strains.

Future research must concentrate on: a) developing improved diagnostic methods; b) increasing our knowledge of what makes a strain virulent; c) increasing our knowledge of the mechanisms by which the host becomes resistant/susceptible to infection; d) developing new therapies; and e) perhaps most crucially, developing disinfecting/cleaning methods that remove the spores from the patient environment. Additionally antibiotic-prescribing policies should be tailored to decrease the precipitation of disease, and improved surveillance must be instituted with mandatory reporting by specialist laboratories.

- *Clostridium difficile*-associated disease ranges from mild to moderate diarrhoea, to life-threatening pseudomembranous colitis. It is increasing and causes massive morbidity, is more often a cause of death and places a huge financial burden on the Health Service.
- The disease occurs primarily in elderly patients following disturbance of the gut microflora by antibiotics. Pathology is a result of the effect of toxins A and B killing colonocytes and inducing immunopathology.

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- A hyper-virulent ribotype 027 strain (known as BI/NAP1 in the USA) has recently been recognised. It produces higher levels of toxin, causes more severe disease and is resistant to fluoroquinolone antibiotics.
- The source of the disease is the resistant spores of the bacterium that contaminate the environment of infected patients. They are embedded in many of our hospitals and long-stay institutions for the elderly.
- The spores are extremely difficult to eradicate. They are resistant to alcohol-based antiseptics and most disinfectants.

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