Clostridium difficile infection

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Clostridium difficile is a rod-shaped, Gram-positive anaerobic bacterium which produces spores that enable it to survive in the environment for prolonged periods (Fig 1). Although first isolated in 1935, it was identified as the causal agent of antibiotic associated diarrhoea and pseudomembranous colitis only in the 1970s. *C. difficile*-associated disease (CDAD) has become an increasingly important nosocomial infection in the UK and throughout the western world over recent years (Fig 2). In addition to morbidity and mortality, CDAD imposes a huge economic burden on the health services.

Epidemiology and pathogenesis

C. difficile is acquired by the faeco-oral route; it colonises the human intestinal tract and multiplies after the resident flora has been altered by antibiotic treatment. *C. difficile* releases two exotoxins (A and B) that bind to receptors on intestinal epithelial cells and cause secretory diarrhoea and acute inflammation. Ulcers form on the mucosal surface, and proteins, mucous and inflammatory cells leak out forming the characteristic 'pseudomembrane' appearance in severe disease (Fig 3).

About 2% of healthy adults in the community are colonised with *C. difficile* and act as a reservoir for infection.[1] Once colonised, about 60% will remain asymptomatic while the remainder develop diarrhoea.[1] It is likely that the host's antibody response plays a crucial part in controlling infection.[2]

Nosocomial outbreaks of CDAD are common and usually caused by a single strain. Hand-washing and personal protective equipment (PPE) programmes have been shown to reduce the spread of infection.[3] Recent hospital outbreaks in the USA and Europe have involved the highly virulent, quinolone-resistant strain, PCR ribotype 027 (BI), which produces up to 20 times the level of toxin A and B as other strains.[4,5]

Risk factors for Clostridium difficile

Antibiotic exposure is the principal risk factor for *C. difficile* acquisition and disease. All antibiotics have the potential to cause CDAD but some are associated with a higher risk (Table 1). Quinolones have been implicated in the emergence of the 027 strain. Other risk factors for colonisation and disease include nasogastric feeding and immunosuppressants. There is conflicting evidence on whether proton pump inhibitor (PPI) therapy increases the risk of *C. difficile* colonisation and CDAD,[6] although PPI use is associated with a higher relapse rate.

Clinical features

C. difficile causes a spectrum of disease from asymptomatic gut colonisation through to fulminant colitis. The usual presentation of mild *C. difficile* disease is with acute watery diarrhoea associated with low grade fever and leukocytosis. Patients usually develop diarrhoea within seven days of starting antibiotics, but symptoms may occur on the first day of antibiotic therapy and up to three months after completing a course. In mild cases symptoms often resolve with cessation of the offending antibiotics.

More severe cases of *C. difficile* colitis present with diarrhoea, up to 15–20 stools per day, although blood in the stool is unusual. Patients have systemic toxicity, with abdominal cramps, fevers, tachycardia and marked leukocytosis. Endoscopy may reveal a patchy non-specific colitis or the classic pseudomembranes which appear as raised yellow plaques up to one cm in diameter (Fig 3). Complications of severe colitis include small bowel ileus or toxic megacolon (Fig 4) which may be heralded by cessation of diarrhoea. *C. difficile* may complicate pre-existing

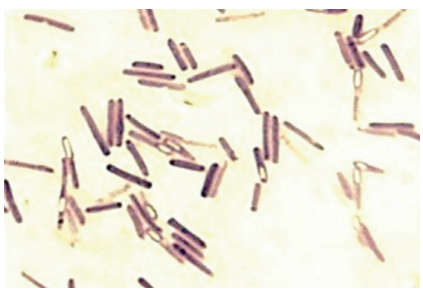

Fig 1. *Clostridium difficile*, showing spore formation.

Key Points

- ***Clostridium difficile* is an increasingly important nosocomial infection and the leading cause of hospital-acquired diarrhoea in the UK**
- ***C. difficile* causes disease through production of toxins. Diagnosis is usually based on detection of toxin in faeces specimens**
- **Factors associated with *C. difficile* infection include prior antibiotic therapy, prolonged hospital admission, immunosuppression, age and chronic medical conditions**
- **Large nosocomial outbreaks of infection have occurred in the UK over recent years coinciding with the emergence of the hypervirulent ribotype 027 strain**
- **Management includes withdrawal of the offending antibiotic(s) if possible, followed by oral metronidazole or vancomycin therapy**

KEY WORDS: *Clostridium difficile*, diarrhoea, epidemic strain, nosocomial infection

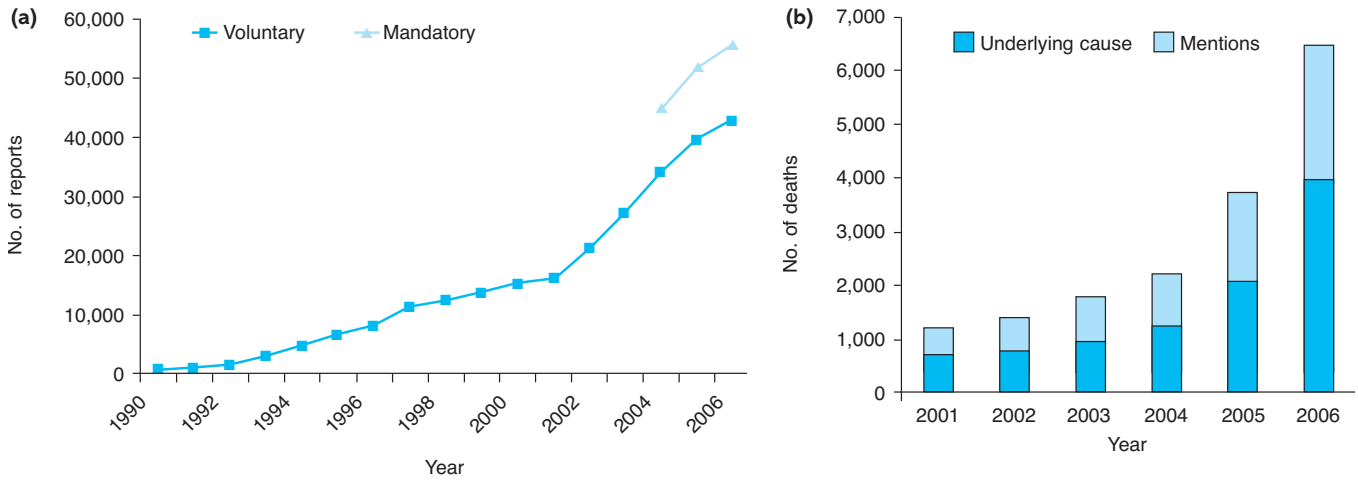

Fig 2. (a) *Clostridium difficile* reports in patients aged 65 years or above, England and Wales, 1990–2006; (b) *C. difficile*-associated deaths, England and Wales, 2001–2006. (a) Reproduced with permission from the Health Protection Agency, www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947378214 © Health Protection Agency; (b) Reproduced with permission from the Office for National Statistics, www.ons.gov.uk. Crown copyright material is reproduced with the permission of the Controller of OPSI. Mentions = *C. difficile* mentioned somewhere on the death certificate; underlying cause = *C. difficile* stated as a cause of death on death certificate.

inflammatory bowel disease (IBD). Treatment with steroids and immunosuppressants will worsen CDAD, so a high index of suspicion is required in assessing patients with apparent flares, particularly if they have received antibiotics or recently been hospitalised.

Diagnosis

Any patient developing diarrhoea in hospital should have their stool tested for *C. difficile*.

Cytotoxic bioassay

The gold standard for diagnosis is considered to be the cytotoxic bioassay. The stool is incubated with cultured cells to look for the characteristic cytopathic effect that is abolished by neutralising antibodies to *C. difficile* toxin. It is highly sensitive and specific, but its utility is limited by expense and the time needed to complete the assay (up to three days).

Rapid enzyme immunoassay

Because of the limitations of the cytotoxic bioassay, rapid enzyme immunoassay (EIA) tests are used more widely. Commercially available kits may detect toxin A or B or both. Results can potentially be obtained within one hour, with high throughput of samples. The main disadvantage of EIA is its low sensitivity (70–90%) so that false negative results are common.[7]

Anaerobic stool culture

Anaerobic stool culture is highly sensitive, but non-specific due to the existence of non-toxigenic strains of *C. difficile* that may colonise the bowel in hospitalised patients. Culture techniques are useful for epidemiological surveillance and resistance testing but usually performed only by reference laboratories.

Treatment

Offending antibiotics should be stopped wherever possible or changed to agents with a lower risk of inducing *C. difficile*. PPIs, steroids and other immunosuppressive agents should also be discontinued if possible. In symptomatic cases, empirical treatment with metronidazole or vancomycin is appropriate. It should be given if suspicion is high, even if the initial stool EIA is negative.

Metronidazole

Metronidazole is recommended for initial treatment of non-severe CDAD, based on

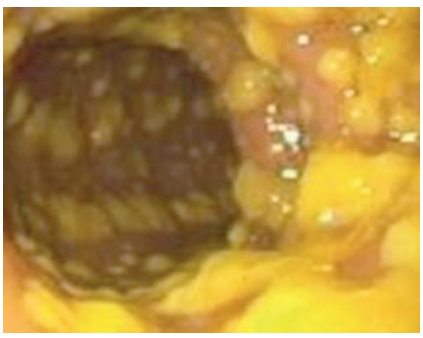

Fig 3. Sigmoidoscopic appearance of pseudomembranous colitis.

Table 1. Risk of *Clostridium difficile* infection associated with commonly used antibiotics.

High risk	Medium risk	Rare
Clindamycin	Macrolides	Metronidazole
Second/third generation cephalosporins	Tetracyclines	Vancomycin
Penicillins, particularly amoxicillin/clavulanate	Aminoglycosides	
Quinolones (027 strain)		

equal efficacy with oral vancomycin, cheaper cost and the theoretical risk of selecting vancomycin-resistant enterococci.[8] The standard duration of therapy is 10–14 days. Treatment should be continued for a week after cessation of other antibiotics. Repeat stool toxin testing is not warranted as the toxin test may remain positive for six weeks after resolution of symptoms.

Vancomycin

Severe disease should be treated with oral vancomycin, 125 mg four times daily.[8] Higher doses are often used, but supporting data are lacking. Intravenous (iv) metronidazole can be used in patients with intestinal ileus, but iv vancomycin has no effect on CDAD as it is not secreted into the lumen of the bowel. Intracolonic therapy with vancomycin has been used and good results reported in small case series.[9]

Surgery

Surgery with colectomy may be necessary in patients with severe disease refractory to therapy or in those with intestinal perforation.

Relapse of *Clostridium difficile*-associated disease

Relapse of CDAD is common, especially with the emerging ribotype 027 strain, occurring in 25–30% of cases with this strain.[10] Some data suggest that relapse is more common in those initially treated with metronidazole rather that vancomycin,[10] although resistance to metronidazole or vancomycin is not an important factor. Relapse usually occurs within two weeks of the initial episode but may arise up to three months later. Risk factors include old age, further antibiotic use, PPI therapy and residence in a nursing home.[11] Relapse may represent true relapse with the same strain due to persistence of spores or may be due to reinfection with another strain. Low antibody levels against toxin A appear to correlate with risk of relapse.[2]

Treatment of relapse

Treatment of the first relapse of CDAD should be with metronidazole or vancomycin.[12] Vancomycin is preferred if there are features of severe disease or if relapse occurs within one month of metronidazole therapy. Subsequent CDAD relapses are usually treated with tapering or pulsed vancomycin therapy.[13] If the patient remains symptomatic, it is important to exclude other aetiologies, including IBD, malignancy and ischaemic colitis.

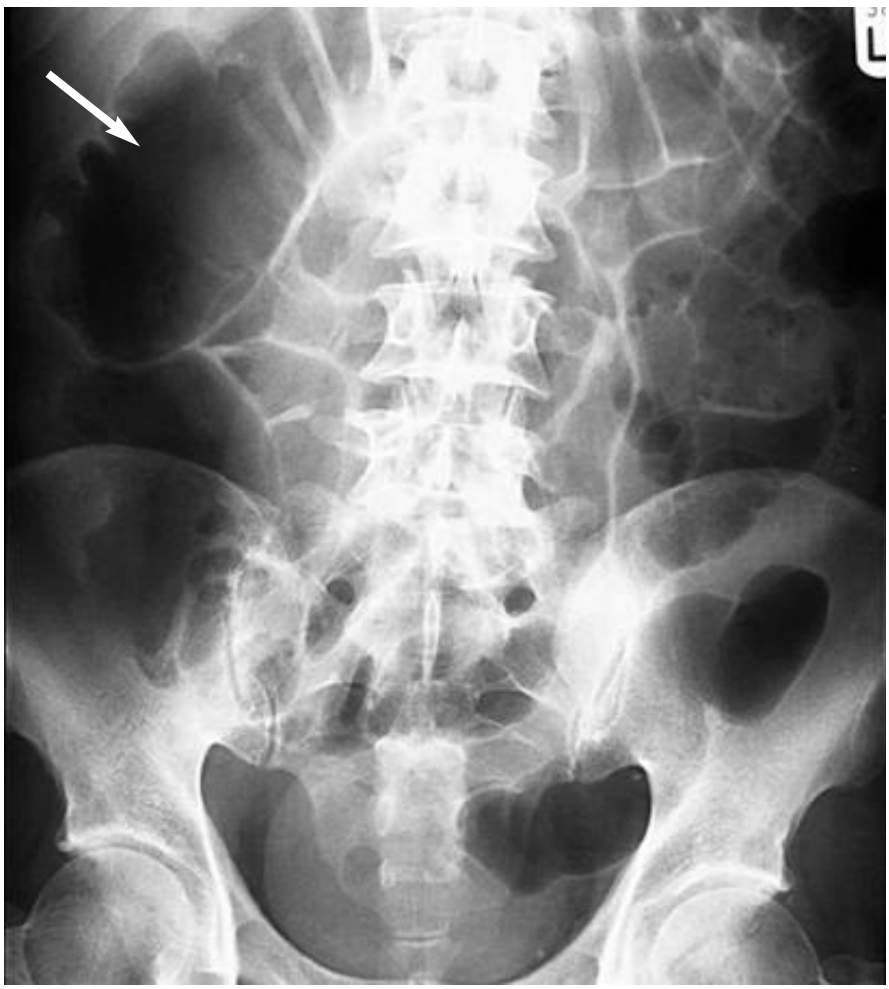

Fig 4. Toxic megacolon which may be associated with severe *C. difficile* infection. Plain abdominal radiograph showing dilated large bowel with mucosal oedema (arrow).

Experimental therapies

Other agents with efficacy against *C. difficile* include teicoplanin, fucidic acid, rifampicin, rifamixin and nitazoxanide, but none has been found superior to metronidazole or vancomycin. Probiotics have not been useful in initial disease but may have a role in relapsed disease.[14] Other agents used include iv immunoglobulin for severe CDAD cases, but its use is unsubstantiated.[15] Cholestyramine has been used as a possible toxin binding agent, but there is no good trial evidence to support this approach and it may reduce the intracolonic level of vancomycin.[16] The investigational agent tolevamer is a novel *C. difficile* toxin-binding resin that showed promise in initial studies but has recently been withdrawn. Research into a toxoid vaccine against *C. difficile* is currently underway. Faecal bacteriotherapy (the instilling of donor faeces into the bowel) seems to be successful in small case series but is not widely practised.[17]

Prevention and control

Primary prevention

Primary prevention for CDAD involves reduction of unnecessary antibiotic prescribing and the restriction of high-risk antibiotics. Both can be achieved through the use of clear hospital guidelines and antibiotic policies.[18] The administration of probiotics in hospitalised patients who require antibiotics has been associated with a reduction in the subsequent incidence of antibiotic-associated diarrhoea and CDAD.[19]

Secondary prevention

The aim of secondary prevention is to stop transmission of *C. difficile* and its spores from an index case to other hospitalised patients. This is achieved through strict isolation of patients, barrier nursing with appropriate PPE, good hand-washing procedures and environmental decontamination. Alcohol gel is ineffective against spores of *C. difficile* so hand-washing with soap and water is recommended for the care of CDAD patients. Environmental decontamination is vital as spores can survive on surfaces for several months. Solutions that reliably kill *C. difficile* spores contain sodium hypochlorite at strengths greater than 5,000 ppm.

There have recently been several high-profile outbreaks of *C. difficile* infection in UK hospitals and reporting of individual hospital infection rates was made mandatory in 2005. Many hospitals have been able to control outbreaks of infection using a comprehensive approach, combining good antibiotic stewardship, enhanced infection control measures and environmental decontamination.[20]

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