The bacterium *Clostridium difficile* was first described in 1935, but its role as a human pathogen was not discovered until 1978, when it was identified as being responsible for cases of pseudomembranous colitis. Since then, *C difficile* has become, along with meticillin-resistant *Staphylococcus aureus*, one of the most common causes of healthcare-associated infection (HCAI) in the UK (see Box 1, p251).

**Microbiology**

*C difficile* is a Gram-positive, anaerobic, sporing bacillus that colonises the gastrointestinal tract asymptomatically in 2–3% of the adult population. Although *C difficile* infection (CDI) can be asymptomatic, clinical manifestations range from mild diarrhoea through to pseudomembranous colitis and toxic megacolon.

Two microbiological aspects of *C difficile* contribute to its role in human disease. The first is the ability of the organism to sporulate, and the propensity for these spores to remain viable on biotic and abiotic surfaces for prolonged periods. This, coupled with the innate resistance of the spore to many cleaning products, encourages fast and widespread dissemination to people in closed environments, such as healthcare facilities.

Secondly, the pathology of *C difficile* is closely linked with two bacterial exotoxins — toxin A (*TcdA*) and toxin B (*TcdB*). Patients with symptomatic *C difficile*-associated diarrhoea are invariably infected with *C difficile* that produces both toxins, or *TcdB* alone. Debate remains about the relative importance of the two toxins but, because they are similar in structure and function, both are likely to be involved.

**Diagnosis**

Testing for *C difficile* is based upon biological aspects of the bacteria. Three main stool specimen tests exist:

- Glutamate dehydrogenase (GDH) immunoassay — GDH is a *C difficile* antigen, which is detected using an enzyme immunoassay. This test is often used to screen for *C difficile*, but it lacks sensitivity; moreover, a positive result does not necessarily mean that the organism is producing the toxins that cause symptomatic disease.
- *TcdA* and *TcdB* gene detection by polymerase chain reaction (PCR) — although testing for the genes that are responsible for producing these toxins is

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**SUMMARY**

*Clostridium difficile* is a Gram-positive anaerobic bacterium that produces spores. It is a common cause of healthcare-associated infection. Although *C difficile* infection (CDI) can be asymptomatic, clinical manifestations range from mild diarrhoea through to pseudomembranous colitis and toxic megacolon.

Risk factors for the development of CDI include antimicrobial exposure, current or recent hospital admission, age (it is more common in people over 65 years of age) and proton pump inhibitor use. Healthcare organisations must have strategies in place to manage patients with CDI.
**Box 1: The cost of *Clostridium difficile* infection**

*C. difficile* is the most common cause of antibiotic-associated diarrhoea in the UK; the risk is highest among patients in hospital because antimicrobial use and cross-contamination occur frequently in this setting.

As healthcare provision has changed over the past 20 years, particularly with regard to antimicrobial selection and frequency of use, the prevalence of *C. difficile*-associated diarrhoea has increased in many high-resource countries. In the US the number of reported cases tripled between 1996 and 2005 — from 31 to 84 per 100,000 people. This trend is reflected across Europe where a recent study looking at 97 hospitals across 34 countries found incidence rates of *C. difficile* infection (CDI) of up to 36.3 per 10,000 bed days. Of greater concern is the rise in deaths caused by CDI. In the UK there was an eightfold rise in deaths caused by CDI between 1999 and 2007; the rate peaked at over 4,000 deaths per year.

Despite having these statistics, capturing the true impact of CDI is challenging and these figures are likely to be underestimates in many countries, due to an absence of global mandatory reporting and differing reporting parameters. Since 2004, in the UK it has been mandatory to report all cases of CDI that occur in NHS acute trusts in patients aged over 65 years of age; from 2007 the reporting criteria were extended to include all patients aged two years and over.

In addition to the climbing rates of hospital-acquired CDI there has also been a small rise in community-associated *C. difficile* disease. Initially it was thought that these cases were a result of increased hospital prevalence radiating into the community as patients were discharged. However, evidence around this is conflicting. Ribotyping has provided evidence that animals, particularly farm animals, might have a role in the development of community-associated CDI. Also implicated are non-farmed food sources and the increasing prescription of antibiotics and gastric-acid suppressants in the community. CDI has substantial financial implications for healthcare providers — a recent systematic review found that, per case, CDI costs a healthcare provider around £2,917 in Finland, £4,577 in Ireland, £6,986 in the UK and £8,843 in Germany (2010 costs). Interventions aiming to reduce rates of CDI, through infection control or antimicrobial stewardship, are crucial for healthcare providers given the restrictive economic environment.

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**Antimicrobial use**

Antibiotic exposure is the most widely recognised modifiable risk factor for development of CDI. Antibiotics disrupt bowel flora, which allows *C. difficile* to gain a foothold and cause disease.

Use of antibiotics precedes up to 90% of cases of CDI. Although almost all antibiotics have been implicated in CDI, certain classes have a stronger association with development of the condition, namely cephalosporins, clindamycin, broad-spectrum penicillins (eg, co-amoxiclav) and quinolones (which have been linked with the hypervirulent BI/NAPO1/O27 strain).

Studies have also identified that longer duration of antibiotic therapy and greater total consumption (ie, multiple courses) of antibiotics is associated with a higher risk of CDI. Patients treated for less than four days experience fewer episodes of CDI than those who are treated for longer (*P*<0.009). However, it should be noted that even single-dose surgical prophylaxis has been associated with development of CDI. The risk appears to be greatest for up to two weeks after starting antibiotic therapy, but can last for many weeks after an antibiotic is stopped.

**Age**

Another well documented independent risk factor for developing CDI is age; increasing age raises the risk of CDI and the severity of the disease. The risk for patients 65 years of age and older is as much as 10-fold higher than that for younger patients. A recent study showed that, for every additional year of age over 18 years, the risk of healthcare-associated CDI increases by around 2%. However, this trend does not appear to hold true for community-associated CDI — one study showed that a substantial proportion of diagnoses in the community was...
in the group aged 45–65 years who had not been exposed to antibiotics or the healthcare environment.\(^6\)

**Hospital admission** Although data suggest that the prevalence of CDI within the community is increasing, hospital admission and length of stay remain considerable risk factors for developing the disease. There is a linear correlation between length of stay and rates of CDI, with risk climbing after seven days in hospital (however, this could be confounded by the fact that patients who are older and sicker are more likely to have prolonged stays in hospital).\(^7\) Recent hospital admission (within the past two months) has been identified as a risk factor for CDI.\(^8\)

**Proton pump inhibitor use** There is a growing body of evidence linking acid-suppressive therapies, in particular proton pump inhibitors (PPIs), with development of CDI. A recent meta-analysis suggested that use of PPIs increased the incidence of CDI by 65%.\(^9\) Adding to this evidence is the fact that, despite a reduction in antibiotic prescriptions, the number of cases of CDI is increasing; one possible explanation for this is the increase in the number of PPIs prescribed.\(^9\)

Data demonstrate that this effect is dose-related, with increasing doses of acid suppressive medicines raising the risk of acquiring the condition. Use of an H₂-receptor antagonist increases the risk of CDI by 53%; with daily PPI therapy the risk is increased by 74% and for PPI therapy prescribed more frequently than daily, the risk is increased by up to 236%.\(^9\)

With the acknowledged high rates of inappropriate PPI prescribing,\(^10,11\) it would seem judicious to review all patients prescribed PPIs with a view to stopping these medicines if they are not required.

In February 2012 the US Food and Drug Administration issued a drug safety communication alerting healthcare professionals to the risk of CDI with erythromycin; \(^12\) with daily PPI prescribing, the number of cases of CDI is increasing; it would seem judicious to review all acid-suppressive therapies, in particular proton pump inhibitors (PPIs), with development of CDI.\(^13\)

There is mounting evidence linking acid-suppressive therapies, in particular proton pump inhibitors, with development of Clostridium difficile infection.\(^13\) A nested case-control study.\(^14\)

**Other factors** Exposure to anticancer chemotherapy is thought to increase a person’s risk of CDI, perhaps because such treatments are both antibacterial and immunosuppressive. Similarly, other immunosuppressed patients (eg, those with HIV or who have received an organ transplant) are believed to be at greater risk of CDI. A possible explanation for this is a combination of diminished immune response to C difficile, regular antibiotic use and frequent visits or admissions to hospital.

Other recognised risk factors include the use of feeding tubes, comorbidities (chronic renal failure, multiple previous episodes of CDI), admission to intensive care units, use of laxatives, surgery and non-surgical gastrointestinal procedures (eg, endoscopy).

References