**Introduction**

*Clostridium difficile* is a rod-shaped, Gram-positive spore-forming anaerobic bacillus. The organism most commonly exists in a vegetative form, which is highly sensitive to oxygen, or in spore form, which is heat stable and able to survive a variety of harsh conditions. Transmission occurs by the fecal-oral route from person to person and instrument to patient. *C. difficile* was first isolated in 1935, but it was not until 1978 that it was identified as the causative pathogen of antibiotic-associated diarrhea and colitis (Bartlett, 1994).

*Clostridium difficile* is commonly present in the stools of 5% of healthy adults and in about 30–70% of infants (Fekety and Shah, 1993, Falsen et al., 1980, Delmee et al., 1988). The majority of hospitalized patients infected by *C. difficile* are asymptomatic carriers, who serve as silent reservoirs for continued *C. difficile* contamination of the hospital environment. Over the past decade, severe *C. difficile* infection (CDI) outbreaks due to hypervirulent strains resistant to conventional therapy have emerged (Noren, 2010). This article summarizes the recent changes that have occurred in the epidemiology of *C. difficile* associated disease and focuses on the diagnosis, management, and prevention of this infection.

**Virulence Factors– Pathogenesis**

*C. difficile* is spread via the fecal-oral route. The organism is ingested either as the vegetative form or as spores, which can survive for long periods in the environment and can traverse the acidic stomach. In the small intestine, spores germinate into the vegetative form. In the large intestine, *C. difficile* associated disease can arise if the normal flora has been disrupted by antibiotic therapy (Bartlett, 2006).

The very first condition to induce pathology is a disturbance of the normal intestinal flora. The gut flora act as a colonization barrier that protects against *C. difficile*. This barrier is compromised when the normal gut flora have been altered by antibiotic therapy (Bartlett, 2006). After endogenous or exogenous contamination by *C. difficile* spores, spores germinate into the vegetative form. In the large intestine, *C. difficile* associated disease can arise if the normal flora has been disrupted by antibiotic therapy (Bartlett, 2006). After colonization, the organism produces and releases the main virulence factors, the two large clostridial toxins A (TcdA) and B (TcdB). TcdA and TcdB are exotoxins that bind to human intestinal epithelial cells and are responsible for inflammation, fluid, and mucous secretion, as well as damage to the intestinal mucosa (Voth and Ballard, 2005). TcdA is responsible for the activation and recruitment of inflammatory mediators such as...
as IL-6, IL-8 by human intestinal epithelial cells, and IL-1, IL-6, IL-8, TNF-α by human monocytes (Sun et al., 2009). However, only TcdB, which demonstrates cytoxic effects, appears essential for virulence (Lyras et al., 2009). These toxins are encoded by the *tcdA* and *tcdB* genes, respectively, that are located within a 19.6 kb pathogenicity locus, the PaLoc. This locus is composed of five genes: *tcdA* and *tcdB* encoding the two toxins, *tcdE* encoding a putative holin, and *tdcR* and *tdcC* (Dupuy et al., 2008, Tan et al., 2001).

*TcdA* and *TcdB* are encoded together with *tdcR*, which encodes an alternative sigma factor that is involved in positive transcriptional regulation (Mani and Dupuy, 2001), and *tdcC*, which encodes a negative regulator (Matamouros et al., 2007). The PaLoc is present at the same chromosomal integration site in all toxigenic *C. difficile* strains. In non toxigenic (*TcdA*− and *TcdB*−) strains, the PaLoc is replaced by a short 115 bp sequence.

The binary toxin called binary ADP-ribosyltransferase toxin Clostridium difficile transferase (CDT) was described from the *C. difficile* strain CD 196 by Popoff et al. (1988). Binary toxin consists of a binding component (CDTb) and an enzymatic component (CDTa). The genes encoding these two components, *cdtA* and *cdtB*, are co-located on the chromosome outside the PaLoc (Figure 1) on a locus called CdtLoc (Carter et al., 2007). This toxin might potentiate the toxicity of TcdA and TcdB and lead to more severe disease and could, thus, be considered an additional virulence factor (Barbut et al., 2005).

**Epidemiology**

The epidemiology of CDI has changed dramatically over the last decade; since 2000, there have been significant increases in the incidence and severity of CDI in the US, Canada, and Europe (Kuijper et al., 2006).

In the early 2000s, reports from Quebec, Canada noted an increased incidence of *C. difficile* associated disease from 35.6 cases per 100 000 persons in 1991 to 156.3 per 100 000 in 2003. In addition, the severity of infection increased from 7.1% in 1991–1992 to 18.2% in 2003 (Loo et al., 1988).

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**Figure 1.** Toxins produced by *Clostridium difficile*. (a) Two large toxins, toxin A and toxin B (*TcdA* and *TcdB*), are encoded on the pathogenicity locus (PaLoc), which comprises five genes. (b) A third toxin, the binary toxin or CDT, is encoded on a separate region of the chromosome (CdtLoc) and comprises three genes. The binary toxin is composed of two unlinked proteins, CdtB and CdtA. CdtB has a binding function, and CdtA is the enzymatic component.
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et al., 2005, Pepin et al., 2004, Pepin et al., 2005). Similarly, the incidence has increased in Europe in association with outbreaks, first in the UK from 2003 to 2004 and then in the Netherlands, Belgium, France, and other European countries (Loo et al., 2005).

In the UK, two large outbreaks have been reported. In the period between October 2003 and June 2004, the first known large UK outbreak caused by ribotype 027 occurred at the Stoke Mandeville Hospital (Buckinghamshire Hospitals NHS Trust), involving 174 cases and 19 (11%) deaths that were definitely or probably due to *C. difficile* (Smith, 2005). A second outbreak occurred between October 2004 and June 2005 in the same hospital, involving 160 new cases and 19 (12%) deaths.

In North America, there has been a five-fold increase in the incidence in the whole population and an eight-fold increase in the elderly (Pepin et al., 2004). In 2006, the CDI discharge diagnosis rates in US hospitals exceeded 300 000 cases per year, an increase from <150 000 cases in 2000. It is currently estimated that there are ~500 000 cases of CDI per year in US hospitals and long-term care facilities. An estimated 15 000 to 20 000 patients die from CDI in the US each year (Dallal et al., 2002, Klevens et al., 2007).

These changes in CDI epidemiology are, at least partially, due to a new hypervirulent and epidemic strain of *C. difficile*. This new epidemic strain has been characterized, by several typing methods, as group BI by restriction endonuclease analysis (REA), as North American pulse-field type 1 (NAP1) by pulse-field gel electrophoresis (PFGE), as ribotype 027 (BI/NAP1/027) by PCR ribotyping, as toxinotype III by restriction fragment length polymorphism (RFLP-PCR), and as ST-1 by multilocus sequence typing (MLST; McDonald et al., 2005, Griffiths et al., 2010). The epidemic strain 027 has been shown to produce higher levels of TcdA and TcdB than the toxinotype 0 (Warny et al., 2005). The NAP1/BI/027 strain encodes a tcdC mutation, which leads to a truncated, inactive TcdC protein. The severe truncation of TcdC seems responsible for the unsuppressed and unregulated toxin production. Consequently, levels of toxins A and B are 16 and 23 times higher, respectively, in patients with this strain of CDI (Warny et al., 2005). Another virulence factor is the production of binary toxin CDT (encoded by the *cdtA* and *cdtB* gene), which may potentiate the toxicity of TcdA and TcdB and lead to more severe disease. The contribution of binary toxin remains controversial, but it is thought to have an adjunctive role in severe disease (Loo et al., 2005). All 027 strains are binary toxin-positive and possess the entire Cdt locus of 6.2 kb, but there are also other non-027 strains that also produce this toxin (Carter et al., 2007). A further characteristic of the hypervirulent 027 strain is its antibiotic resistance profile. The epidemic hypervirulent 027 strains are resistant to fluoroquinolones with an MIC of >23 mg/L (Warny et al., 2005, MacCannell et al., 2006, Goorhuis et al., 2007).

Depending on the country, other strains, including PCR ribotypes 001, 018, 078, and 106, can be responsible for outbreaks and severe cases. In the Netherlands, the incidence of *C. difficile* ribotype 078 has increased from 3% in 2005 to 13% in 2008 (Goorhuis et al., 2008). This new strain can cause severe symptoms as well as produces less TcdA and TcdB than 027 (Jhung et al., 2008). It is usually isolated from livestock, but it seems to have increased incidence in human disease (Burns et al., 2007).

A large epidemiological study involving 38 hospitals from 14 European countries revealed that the incidence of CDI is highly variable between hospitals in Europe (Barbut et al., 2007). In this study, PCR-ribotypes 001 and 014 were the most prevalent, followed by 027 and 020. Most recently, Bauer and colleagues provided further evidence regarding the extent of *C. difficile* infection in Europe (Bauer et al., 2011). Theirs is the largest epidemiological study in Europe to date, which included a network of 106 laboratories in 34 European countries. The most frequent PCR-ribotypes of toxigenic isolates were 014/020 and 078, followed by 018 and 106 (Bauer et al., 2011). Epidemic PCR-ribotype 027 was less prevalent in this study compared to the study by Barbut and colleagues (Bauer et al., 2011, Barbut et al., 2007). The differences in the PCR ribotypes identified by these 2 studies are most likely due to geographical or methodological issues. However, both studies underscore the importance of local surveillance to detect and control endemic and epidemic CDI.

### Risk Factors

Prior exposure to antimicrobial agents is the most widely recognized and modifiable risk factor for CDI (Morris et al., 2002). In a recent study, 85% of patients with CDI had received antibacterial therapy within the 28 days prior to the onset of symptoms. Nearly all antibiotics have been associated with CDI, but those at highest risk are clindamycin (Bartlett, 1981), broad-spectrum cephalosporins (McFarland et al., 1990), and fluoroquinolones (McFarland et al., 1995, Bauwens et al., 1997). This is probably related to those antibiotics’ propensity for disrupting normal intestinal flora, therefore providing a niche for *C. difficile* to multiply and elaborate toxins (Bartlett, 2006). In addition, the fact that *C. difficile* is resistant to a wide range of antibiotics enables the bacterium to colonize and infect in the presence of antibiotics. Increased duration of antibiotic use and use of multiple antimicrobial agents are also associated with increased risk of CDI (Owens et al., 2008).

Other major risk factors for CDI are hospitalization and advanced age (>65 years). Elderly patients with severe underlying illnesses and prolonged hospitalization are particularly vulnerable; colonization rates can be as high as 73% for these patients (Ananthakrishnan, 2011). During the course of their hospital stay, 15–21% of inpatients are infected by the organism. The majority of them (almost...
two-thirds) remain asymptomatic carriers who serve as silent reservoirs for continued \textit{C. difficile} contamination of the hospital environment. Other risk factors associated with CDI include treatment with proton-pump inhibitors or H2 antagonists (Dial et al., 2005). It is not entirely clear why gastric acid suppression may increase the risk for the development of CDI. A potential explanation is that these gastric acid suppression agents may decrease the colonization barrier against \textit{C. difficile} by increasing gastric pH. However, \textit{C. difficile} spores are resistant to gastric acid, and it is likely that spores represent the main mode of acquisition (Dial et al., 2005). Immunosuppressive drugs such as methotrexate have also been associated with the development of CDI (Keven et al., 2004). Patients receiving immunosuppressive drugs are debilitated and, therefore, are unable to mount an effective IgG antibody response against \textit{C. difficile} toxin A, thereby increasing the risk for CDI (Kyne et al., 2001). Finally, the presence of gastrointestinal diseases such as inflammatory bowel diseases has been linked with CDI as well (Rodemann et al., 2007).

**Asymptomatic Carriage of \textit{C. difficile}**

Colonization of \textit{C. difficile} is the presence of the organism in a person with no clinical symptoms like diarrhea. Approximately 3-5% of adults and 50% of neonates are infected with \textit{C. difficile} and most remain without symptoms. Patients with \textit{C. difficile} colonization and a serum IgG response to \textit{C. difficile} enterotoxin usually become asymptomatic carriers (Kyne et al., 2001). Asymptomatic carriage of \textit{C. difficile} is quite common (about 25–30%) in hospitalized patients (Shim et al., 1998). As recently shown, asymptomatic carriers could play an important role in the transmission of CDI (Riggs et al., 2007). Compared with non-carriers, asymptomatic carriers had higher percentages of skin (61% vs. 19%; P=.001) and environmental contamination (59% vs. 24%; P=.004). Moreover, spores on the skin of asymptomatic patients were easily transferred to the hands of investigators (Riggs et al., 2007). These data suggest that CDI may have been transmitted from the environment or from the hands, clothes, or equipment of the health-care worker caring for another patient with CDI. Moreover, pets and livestock animals frequently carry \textit{C. difficile} in their gastrointestinal system and, thus, may be a potential reservoir for clinical relevant strains eventually causing CDI in humans (Arroyo et al., 2005). Moreover, as recently demonstrated, \textit{C. difficile} has been isolated from foods in the US, Canada, and Europe and from meat products intended for consumption by pets (Gould and Limbago, 2010). However, it is currently unclear whether ingestion of contaminated food can result in colonization or infection and therefore, at present, human CDI is not considered a zoonotic or foodborne disease.

**Clinical Manifestations**

\textit{C. difficile} causes a broad spectrum of clinical symptoms ranging from mild diarrhea to severe life-threatening colonic perforation and toxic megacolon (Bartlett, 2002). The most common clinical manifestations are:

**i. \textit{C. difficile} diarrhea**

One of the most common presentations of CDI is mild to moderate watery diarrhea, which is usually not bloody and sometimes accompanied by lower abdominal cramps. Symptoms begin during or shortly after antibiotic therapy, but occasionally these may be delayed for several weeks. The diarrhea typically resolves with the discontinuation of antibiotics (Farrell and LaMont, 2000). \textit{C. difficile} toxins can be detected from fecal specimens, even though endoscopy does not reveal significant abnormalities (Sunenshine and McDonald, 2006).

**ii. \textit{C. difficile} colitis**

The most common clinical manifestation of CDI is colitis without pseudomembrane formation. This is a more severe form of CDI characterized by fever, malaise, high-volume watery diarrhea in which stools can have some trace blood, nausea, anorexia, and abdominal pain. Leukocytosis is common and could serve as a diagnostic clue. On sigmoidoscopy, erythematous colitis is patchy without pseudomembranes (Farrell and LaMont, 2000).

**iii. Pseudomembranous colitis (PMC)**

PMC is a systemic illness; patients have abdominal pain and tenderness, fever, and severe diarrhea that can be bloody. White blood cell counts of 20 000 or greater and hypoalbuminemia of 3.0 g/dl or lower can be observed in severely ill patients (Gebhard et al., 1985). Hypoalbuminemia is the result of large protein losses attributable to leakage of albumin. Sigmoidoscopy shows the presence of classic pseudomembranes, which are raised yellow plaques ranging from 2-10 mm in diameter scattered over the colorectal mucosa (Johal et al., 2004). Most patients with PMC have involvement of the rectosigmoid area. A minority of patients have disease primarily in the right colon, presenting with marked leukocytosis and abdominal pain but little or no diarrhea. CDI affecting the small bowel (enteritis) after total colectomy has also been reported (Freiler et al., 2001). Colonic inflammation can also be shown on computed tomography as increased colonic-wall thickening (Ash et al., 2006).

**iv. Fulminant colitis (paralytic ileus - toxic megacolon - colonic perforation)**

CDI presents as fulminant colitis in approximately 3% of patients and accounts for most of the serious complications, including colonic perforation, prolonged ileus, toxic megacolon, and death (Rubin et al., 1995). It is a systemic inflammatory syndrome that may include severe lower quadrant or even diffuse abdominal pain with or without diarrhea, high fever, chills, hypotension, tachypnea, and marked leukocytosis (Dallal et al., 2002,
Byrn et al., 2008). It should be noted that diarrhea can be absent in patients with severe CDI when the infection causes paralytic ileus. Patients with toxic megacolon have a dilated colon with symptoms of severe toxicity such as fever, chills, dehydration, and marked leukocytosis (Rubin et al., 1995).

**Diagnosis**

The diagnosis of CDI is established by a combination of clinical suspicion (presence of symptoms and predisposing factors) and laboratory confirmation. Clearly, all patients with diarrhea and risk factors for CDI should be further investigated. The most commonly used laboratory tests are:

i. **Cytotoxin assay**

Cytotoxin assay is traditionally considered the gold standard for the diagnosis of CDI, with a sensitivity of 67–100% and specificity of 85–100% (Crobach et al., 2009, Shanholzter et al., 1992). This test is based on identifying *C. difficile* toxin B in cell culture. The stool is incubated with culture cells to look for the characteristic cytopathic effect as a consequence of disruption of the cell cytoskeleton. Almost all cell lines can be used to detect fecal cytotoxin, but Vero cell lines are considered to be the most sensitive. However, like other tissue culture tests, it is expensive and takes as long as 1–3 days to get the test results (Fekety, 1997).

ii. **Enzyme-linked immunosorbent assay (ELISA)**

The ELISA test can be used instead of the cytotoxin assay. Commercially available ELISA tests can detect TcdA alone or both TcdA and TcdB with a sensitivity of 75–85% and excellent specificity of 95–100% (Crobach et al., 2009). Enzyme immunoassays are inexpensive, easy to perform, and rapid (results within a few hours). The use of an ELISA test may reduce the time from the onset of symptoms to diagnosis and treatment (Frenz and McIntyre, 2003). The main disadvantage of the assay is its low sensitivity (75–85%) that can commonly produce false negative results (Turgeon et al., 2003, Bartlett and Perl, 2005, Alden et al., 2000). Although the commercial immunoassays are inadequate as stand-alone tests for laboratory confirmation of CDI, toxin detection together with culture and isolation of *C. difficile* strains is considered the most accurate method in CDI diagnostics, also enabling typing of the isolates that is needed for epidemiological studies (Barbut et al., 2003).

iii. **Anaerobic stool culture isolation of C. difficile**

Anaerobic stool culture is the most sensitive method to detect *C. difficile*, but it is not very specific due to the possibility of isolating non-toxigenic strains. Anaerobic stool culture also provides *C. difficile* isolates for molecular typing, which is essential for epidemiological investigation by reference laboratories. The selective agar that is used by most laboratories for *C. difficile* isolation from stool specimen is called cycloserine cefoxitin fructose agar (CCFA). The selective agents are cycloserine at a concentration of 250 mg/L, cefoxitin at a concentration of 8 mg/L, and also include egg-yolk, which can be replaced by blood (Levett, 1985). Stools are directly inoculated and incubated in an anaerobic atmosphere for 2–5 days (George et al., 1979, Peterson et al., 1996). Colonies of *C. difficile* are easily recognized on culture plates due to their typical morphology (ground glass appearance), the characteristic odor (horser manure), and fluorescence under UV illumination (yellow-green; Delmee, 2001). Recently, a new prototype chromogenic medium (ID *C. difficile* prototype [IDCd]) has been evaluated for *C. difficile* isolation within 24 hours and even higher colony counts on IDCd irrespective of alcohol pre-treatment or duration of incubation. So, IDCd might be an effective medium for isolation of *C. difficile* from stool samples within 24 hours (Perry et al., 2010).

iv. **Molecular methods**

Molecular techniques provide rapid and sensitive detection of *C. difficile* with simultaneous genotyping. These methods are advantageous compared to standard laboratory tests. They allow the identification of outbreaks in real time so that rapid, appropriate interventions, preventing further transmission, can be taken. This is important because it enables the early control of national outbreaks caused by more virulent strains. Indeed, real-time PCR was employed to rapidly detect CDI and identify the hypervirulent outbreak strain such as ribotype 027 (Peterson et al., 2007, Sloan et al., 2008). The main genotyping methods used for *C. difficile* are:

- **PCR ribotyping**
  - PCR ribotyping exploits differences in the spacer regions of 16S and 23S ribosomal RNA, using specific primers that encode these RNA regions (Bidet et al., 1999, Stubbs et al., 1999). The gel electrophoresis reveals a few DNA bands that are referred to as ribotypes. PCR-ribotyping results have very good inter-laboratory agreement (Killgore et al., 2008). This molecular typing technique is more commonly used throughout Europe.

- **Pulsed field gel electrophoresis (PFGE)**
  - PFGE uses a restriction enzyme (Smal) that cuts the bacterial genome infrequently, resulting in large DNA fragments, which are then slowly separated in a polyacrylamide gel (Janezic and Rupnik, 2010, Kato et al., 1994). These DNA fragments, according to their size, migrate varying distances through the gel and are visualized by DNA staining (with ethidium bromide). PFGE is widely used in the US.

- **Multilocus variable number tandem repeat analysis (MLVA)**
  - MLVA is a method of counting the numbers of repeat alleles in the genome for a series of loci that are amplified by PCR (Marsh et al., 2006). This method requires...
In most cases of CDI, the first therapeutic step is to discontinue the administration of the inciting antibiotic as soon as possible. This intervention together with fluid replacement to restore electrolyte balance may lead to symptom resolution in a minority of patients (Aslam et al., 2005).

The Infectious Diseases Society of America (IDSA) and the Society for Health Care Epidemiology of America (SHEA) have recently updated their guidelines regarding CDI treatment (Cohen et al., 2010). According to the guidelines, treatment recommendations are based on the clinical presentation of CDI (Cohen et al., 2010). (Table 1) Metronidazole is the first-line therapy for patients with mild or moderate CDI, based on equal efficacy with oral vancomycin, cheaper cost, and the theoretical risk of selecting vancomycin-resistant enterococci. The dosage is 500 mg orally 3 times per day for 10–14 days. Vancomycin is the drug of choice for patients with severe CDI. The dosage is 125 mg orally 4 times per day for 10–14 days. Intravenous vancomycin does not achieve high enough levels in the stool to treat CDI and should never be used for the treatment of CDI (Bartlett, 2002). For patients with the most severe and complicated CDI (leusus, toxic megacolon), a combination of oral vancomycin and intravenously metronidazole is recommended (Cohen et al., 2010). The dosage is 500 mg orally 4 times per day for vancomycin and 500 mg intravenously 3 times per day for metronidazole. The rationale for this drug combination is to get active drug to the colon as quickly as possible. In extreme cases, surgery with colectomy might be needed for the treatment of severe, complicated CDI (Lamontagne et al., 2007). Apart from metronidazole and vancomycin, several new therapeutic agents have been tested for the treatment of CDI. These include fidaxomicin, nitazoxanide, rifamixin, ramoplanin, tigecycline, rifalazil, probiotics, and passive immunotherapy (Koo et al., 2010). However, high costs and concerns over resistance may limit their use.

A small study showed that fidaxomicin, a novel macrolide, is as effective as vancomycin for treating CDI and possibly superior to vancomycin for preventing CDI recurrences (Miller, 2010). Nitazoxanide is similar in efficacy to metronidazole and possibly vancomycin as CDI therapy (Venuto et al., 2010). Clinical data supporting the use of other antimicrobial agents such as rifaximin, ramoplanin, tigecycline, and rifalazil, as well as the use of probiotics for CDI, are limited and warrant further study (Venuto et al., 2010). Protection against recurrent CDI with passive immunotherapy with human antibodies against toxins A and B is promising but costs may influence their indication for use (Koo et al., 2010).

### Recurrent CDI

Despite risk factor avoidance and CDI-targeted therapy, approximately 20% of patients with an initial episode of...
CDI will develop at least a second episode, and 60% of patients with at least two recurrences will develop additional recurrences.

Most relapses occur within 1-3 weeks of the initial episode, although rarely relapses can occur 2 months later. Relapses of CDI are caused by the same strain due to persistence of spores and should be distinguished from reinfections with another strain. Interestingly, studies using molecular methods have shown that up to half of recurrent episodes are reinfections rather than relapses of infection with the original strain (Pepin et al., 2006).

Treatment of the first recurrence of mild or moderate CDI should be with metronidazole, whereas severe cases of recurrent CDI should be treated with vancomycin (Cohen et al., 2010). Subsequent CDI relapses are usually treated with prolonged tapering or pulsed vancomycin regimens (Pepin et al., 2006). However, the most effective treatment for patients with multiple recurrences has been replenishment of the normal bacterial flora with a fecal transplant (from a healthy volunteer) delivered either by nasogastric tube or by enema (Aas et al., 2003).

Probiotics agents, although not appropriate for single treatment of CDI, may be useful as adjuncts for recurrent CDI (Pillai and Nelson, 2008). Probiotics are live microorganisms that are considered to affect host flora composition by their putative ability to colonize the colon in the hope these benign microbes can out-compete pathogens and prevent CDI. These include *Lactobacillus* species and *Saccharomyces* (Halsey, 2008). One approach to prevent the recurrence of CDI has been 2 weeks of rifaximin treatment after completion of standard therapy. Rifaximin is a non-absorbed rifamycin that may help prevent recurrences by allowing normal bowel flora to regenerate as the infection is being treated (Gerding et al., 2008b).

**Prevention**

Prevention has two aspects: prevention of the acquisition of *C. difficile* and prevention to stop transmission of *C. difficile* and its spores to other hospitalized patients. The primary prevention for CDI involves the improved antimicrobial prescribing practices (minimize the frequency and duration of antimicrobial therapy) and restriction of high-risk antibiotics, both are the most effective methods of reducing the incidence of CDI (McNulty et al., 1997). Moreover, controlling CDI in the hospital environment is a huge challenge. This is achieved through strict isolation (private rooms) of the hospital environment is a huge challenge. This is achieved through strict isolation (private rooms) of patients’ health-care workers, environmental decontamination by their putative ability to colonize the colon in the hope these benign microbes can out-compete pathogens and prevent CDI. These include *Lactobacillus* species and *Saccharomyces* (Halsey, 2008). One approach to prevent the recurrence of CDI has been 2 weeks of rifaximin treatment after completion of standard therapy. Rifaximin is a non-absorbed rifamycin that may help prevent recurrences by allowing normal bowel flora to regenerate as the infection is being treated (Gerding et al., 2008b).

**Conclusion**

Over the last few years, *Clostridium difficile* associated disease has been recognized as one of the most common nosocomial infections and a frequent cause of morbidity and mortality among hospitalized patients. Recent outbreaks of *C. difficile* due to new highly virulent strains and antibiotic resistance underline the changing nature of CDI. The need for more rapid and reliable diagnostic tools that will allow a better understanding of the molecular epidemiology of the disease is increasing. Finally, novel treatments with non-resistant antimicrobial agents together, better prevention strategies, and infection-control practices should be developed.

**Declaration of interest**

There are no conflicts of interest.

**References**


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