

**Clostridium difficile** diarrhoea in the immunosuppressed patient—
update on prevention and management

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**Introduction**

In recent years, infections with *Clostridium difficile* have become more frequent in immunocompromised renal and transplanted patients [1,2]. There is widespread uncertainty as to the optimal management and prevention of this problem, particularly in the above patient group. It is for this reason that these issues are reviewed here.

*Clostridium difficile* is a spore-forming Gram-positive anaerobic bacterium. It was identified as the cause of antibiotic-associated diarrhoea (AAD) and
colitis in the late 1970s [3] and currently accounts for ~15–25% of all episodes of AAD and for virtually all cases of antibiotic-associated pseudomembranous colitis (PMC) [4,5]. Worldwide, the incidence of infections with this organism among hospitalized patients is increasing continuously [6,7]. The average incidence of C. difficile-associated diarrhoea (CDAD) among hospitalized patients in eight European countries was 1.1 per 1000 patient admissions [8]. Clostridium difficile infection increases the length of the stay in the hospital by 8 days and in geriatric patients by 36 days [9]. It recently has been estimated that this type of infection accounts for >US$1.1 billion per annum of health care costs in the USA [10].

Pathogenic strains of C. difficile produce an enterotoxin (toxin A) and a cytotoxin (toxin B) which cause mucosal damage and inflammation of the colon. It previously was thought that toxigenic strains of C. difficile always produce both toxin A and toxin B, but recent studies have demonstrated the presence of toxin A(−) B(+) strains among clinical isolates. Nevertheless, the most pathogenic strains produce both toxins. However, no statistically significant difference was found between patients with CDAD caused by A(−) B(+) strains and those with A(+) B(+) strains with respect to body temperature, serum concentration of C-reactive protein, leukocyte count, frequency of diarrhoea or type of underlying disease [11]. Non-pathogenic strains also exist which fail to produce any toxins.

The gastrointestinal infections range in severity from asymptomatic colonization to severe diarrhoea, PMC, toxic colon, colonic perforation and death [12].

**Risks factors**

Patients who are at highest risk for CDAD are those who are currently taking or have recently been on antimicrobial agents. Antibiotics are the most important risk factor for CDAD. They reduce resistance against colonization of the bowel, facilitating colonization and infection with C. difficile [13]. To prevent C. difficile infection, it is necessary to use antibiotics in a responsible fashion. Widespread overuse and misuse of antibiotics is illustrated by the data of the US medical system. In US hospitals, >75% of patients are treated with antimicrobial agents although more than half of the patients receiving antimicrobial therapy have no evidence of infection or clear indication for antibiotics [14]. Antibiotic agents that are active against anaerobic bacteria present the greatest risk because they alter the intestinal microecology [15]. Clindamycin, cephalosporins (in particular third generation cephalosporins such as cefotaxime and ceftriaxone) and broad spectrum penicillins are notorious for provoking CDAD. According to Aronsson et al., cephalosporins are implicated 40 times more often in CDAD than narrow spectrum penicillins [16]. The incidence of CDAD is less with levofloxacin compared with β-lactams [17]. Clostridium difficile-related complications are uncommon with linezolid [18] and the same is true for aminoglycosides, metronidazole, rifampicin and vancomycin. An important risk factor is the duration of antimicrobial therapy. In a large prospective study, Wistrom et al. documented that patients treated for <3 days had a significantly lower incidence of C. difficile infection than those receiving longer courses of antimicrobial therapy [19]. In principle, each antibiotic has the potential to cause CDAD—paradoxically also those antibiotics used to treat CDAD.

Apart from the duration of treatment with antibiotics, further risk factors include advanced age, gastrointestinal surgery, long duration of stay in health care settings, serious underlying disease and use of proton pump inhibitors [20]. CDAD is rare in patients who have not been exposed to antibiotics [21].

Infections with C. difficile associated with chemotherapy may have been under-reported. Their true incidence presumably is masked because antibiotics and chemotherapeutic agents are often used concomitantly, especially in neutropenic patients [22]. Chemotherapeutic agents such as adriamycin, cyclophosphamide, methotrexate and 5-fluorouracil have the capacity to precipitate CDAD, as demonstrated by Cudmore et al. [23] and Blot et al. [24]. According to Svenungsson et al., the rate of CDAD is higher in nephrology, haematology and organ transplantation wards [1] and is particularly high in paediatric kidney and kidney–pancreas graft recipients [2]. Fulminant CDAD has also been described in lung transplant recipients exposed to high dose immunosuppression and repeated courses of antimicrobials because of frequent pulmonary infections [6]. Several reports pointed to the risk of CDAD associated with the use of tacrolimus [25]. The powerful immunosuppressive action of tacrolimus presumably is the reason for this association. Immunocompromised patients are more susceptible to develop infections with C. difficile, and in those patients CDAD tends to have also a poorer outcome [26,27].

Nosocomial outbreaks of C. difficile-associated colitis have been reported frequently in hospitals, nursing homes and other extended-care facilities. Often such nosocomial outbreaks are extremely difficult to control [28]. Admission to a hospital with a high frequency of endemic CDAD or admission during an outbreak of CDAD is a risk factor in and of itself.

**Route of transmission**

Colonization by C. difficile occurs via the oral–faecal route, once antibiotic therapy has rendered the bowel susceptible to colonization. Diarrhoea may occur within less than a week after colonization by C. difficile. It is primarily transmitted by contaminated hands of health care workers, but also via environmental contamination, including contamination of health care equipment. Only occasionally is direct spread
from patient to patient involved. An infected patient excretes up to $10^5$ *C. difficile* organisms per g of faeces. Asymptomatic hospitalized patients colonized by *C. difficile* are an important bacterial reservoir and are able to trigger and perpetrate epidemics of CDAD. Vegetative forms of *C. difficile* are killed when exposed to air, but *C. difficile* spores are resistant to oxygen, desiccation and most commonly used disinfectants [29]. Such spores resistant to cleaning and disinfection measures persist in the hospital environment for long periods of time [30].

### Standards of hygiene

Once CDAD is suspected or identified, full enteric precautions should be implemented and maintained for at least 48 h after the diarrhoea has stopped (Table 1). Each hospital should implement standards of hygiene for patients, staff and visitors. This requires educating the medical, nursing and other appropriate staff members, and informing patients and visitors about the disease, its epidemiology and its prevention as well as its treatment.

Staff and visitors should use disposable gloves and gowns whenever they are in contact with an infected patient or his body fluids. Gloves and gowns must be removed after caring for the patient. The hands must be disinfected and washed with liquid soap. Gloves alone do not guarantee that transmission of *C. difficile* is prevented. Isolation of patients with CDAD in separate rooms, if available, is recommended, especially if patients are incontinent or cannot practise adequate hand hygiene. Patients with CDAD should have separate toilets or share toilets only with other CDAD patients. Items such as blood pressure cuffs, stethoscopes, tourniquets and thermometers should be dedicated to the infected patient only and not shared with other patients. Single-use equipment should be provided whenever possible. It is important to ensure that the rooms are cleaned regularly to reduce the potential of reinfection which is the most common cause of recrudescence of symptoms [31]. Mechanical cleaning is generally more effective than chemical disinfection because most disinfectants are not able to eradicate spores. In the hospital environment, acidified nitrite and peracetyl ions are best suited for the disinfection of *C. difficile* spores [30]. If patients with *C. difficile* colonization or disease must be transferred to another ward or hospital, it is obligatory to notify the facility that the patient will excrete or has excreted *C. difficile*. Precautions should be continued until diarrhoea has ceased and, in the case of endemic outbreaks, until stool tests have become negative.

### Diagnosis

Non-specific, but suggestive hints pointing to *C. difficile* infection include leukocytosis, hypalbuminaemia and faecal leukocytes. In hospitalized patients, a prompt search for *C. difficile* infection has been recommended in cases of unexplained leukocytosis [32]. Delay in establishing the diagnosis is known to increase the risk of death in *C. difficile* colitis [33]. Testing the stool of asymptomatic patients is not clinically useful and is not recommended.

In symptomatic patients, however, the most sensitive test to establish the diagnosis of infection with *C. difficile* is the stool culture. In contrast, the toxin B cytotoxicity test is the most specific examination [15]. It is recommended to perform both tests for maximal diagnostic sensitivity and specificity [34]. The ESCMID study group on *C. difficile* underlined the need for guidelines in view of the ongoing controversy between different European laboratories regarding the diagnosis of CDAD [8].

A novel method for rapidly establishing the causes of diarrhoea, including infection with *C. difficile*, is based on the analysis of gaseous stool compounds using gas chromatography and mass spectrometry [35]. However, whether this method will become a standard diagnostic method has not been decided.

### Treatment

In 20–25% of patients with symptomatic CDAD, simply stopping administration of the offending antibiotic will stop the diarrhoea without any additional treatment [35]. Metronidazole (250 mg four times a day) or vancomycin (125 mg per os four times a day) for 10 days are recommended as effective treatments. Metronidazole may be preferable to avoid induction of vancomycin resistance in other nosocomial bacterial species. Another advantage of metronidazole is lower cost. Vancomycin should be reserved for patients who do not tolerate metronidazole or have not responded to its administration.

Recurrence of CDAD is seen in at least 20–25% of the cases. Patients with a first relapse of diarrhoea, following treatment of CDAD, should receive the same treatment as during the initial episode. Several

<table>
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<th>Table 1. Standards of hygiene</th>
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<td><strong>Isolation precautions for staff and visitors</strong></td>
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<tr>
<td>- Use disposable gloves and gowns</td>
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<tr>
<td>- Wash hands frequently with liquid soap and disinfect them frequently</td>
</tr>
<tr>
<td>- Do not share blood pressure cuffs, stethoscopes, tourniquets, thermometers, etc. with non-infected patients</td>
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<tr>
<td><strong>Room</strong></td>
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<tr>
<td>- Provide private room or cohort isolation</td>
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<tr>
<td>- Have patients with CDAD share toilets only with other CDAD residents</td>
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<td>- Clean rooms and environment regularly</td>
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<td><strong>Transfer of CDAD patients:</strong></td>
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<td>- Notify the recipient institution</td>
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treatment protocols have been proposed for patients with multiple relapses of CDAD. One approach is to use a 4–6 week regime of tapering, followed by pulsed doses of vancomycin (125 mg every 6 h for 7 days, followed by 125 mg every 12 h for 7 days, 125 mg/day for 7 days, 125 mg every other day for 7 days and 125 mg every 3 days for 7 days) [36].

Administration of probiotics to normalize faecal flora is an appealing preventive measure or adjunct to the treatment of recurrent CDAD. Normalization of the faecal flora is important to prevent a continued overgrowth with *C. difficile*. *Saccharomyces boulardii* is a non-pathogenic yeast that reduces the incidence of AAD [37]. McFarland et al. demonstrated that administration of *S. boulardii* in combination with metronidazole or vancomycin significantly reduced the rate of recurrences [38]. The procedure may not be absolutely safe in immunocompromised patients, since some cases of fungemia have been reported following its administration [39].

**Conclusion**

*Clostridium difficile* is the most common enteric pathogen in hospitalized patients. Standardized procedures to implement hygienic measures and restricted use of antibiotics are necessary to control the widespread occurrence of CDAD in immunocompromised renal patients.

**References**


