
**Clostridium difficile and antibiotic-associated diarrhoea—importance of *C. difficile* for the nephrologist**

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*Clostridium difficile*-associated diarrhoea (CDAD) is particularly likely to occur, and to be more severe, in elderly and/or immunosuppressed patients [1,2]. It is also a common problem in hospital units in which there is a high level of antibiotic use [3]. These factors are likely to pertain to most nephrology and/or renal transplant units. Indeed, chronic renal failure has been identified as an independent risk factor for severe CDAD [4].

**Epidemiology and pathogenesis**

CDAD is intimately linked to antibiotic use, though it can occur following the use of some antineoplastic drugs that have inherent antibiotic activity [5] and can occur up to 8 weeks after even a single dose of any antibiotic [6]. The risk is greatest with broad spectrum beta-lactam agents. Second and third generation cephalosporins, broad spectrum penicillin derivatives and clindamycin are the most frequently implicated drugs [7].

CDAD is caused by an overgrowth of toxin-producing *C. difficile* within the large bowel. Nontoxigenic strains are not considered pathogenic. The proportion of *C. difficile* strains that are toxigenic range from 75% to 90%, with higher rates among hospital strains, compared to those in the community [7]. Both toxigenic and non-toxigenic strains may be carried in the large bowel asymptomatically. Up to 5% of the general adult population may carry the organism, with carriage rates of 10–30% among hospitalized patients. A recent report suggests that asymptomatic carriage, of either toxigenic or non-toxigenic strains, protects against subsequent symptomatic CDAD [8].

Heat-resistant spores produced by *C. difficile* allow the organism to survive in the hospital environment. The immediate environment around a patient with CDAD can be heavily contaminated with these spores [9]. This allows for ready transmission to other patients, usually on the hands of health care workers [10]. Although most commonly associated with hospitals, CDAD can be community acquired in up to one quarter of cases [11]. The increasing incidence of such cases is probably linked to the escalating use of broad spectrum oral antibiotics in the community.

**Clinical features of CDAD**

Most patients (75–85%) with antibiotic-associated diarrhoea are not infected with *C. difficile*. Such patients develop a mild, self-limiting diarrhoea that is rarely associated with abdominal pain or constitutional symptoms. Of the remaining 15–25%, who are infected with *C. difficile*, many will still have a relatively mild illness. Typically, however, *C. difficile* causes crampy abdominal pain with profuse, foul-smelling, greenish, watery stools. This is often accompanied by a low grade fever and leukocytosis. Up to 5% of patients may present as an ‘acute abdomen’, without diarrhoea, particularly if the inflammation is confined to the right side of the colon [6].

In 3–10% of cases a severe colitis can develop with marked constitutional symptoms, abdominal pain, ileus and fever [3]. This may progress to toxic mega-colon and severe prostration. Reported rates for the severe form of the disease vary but a number of factors appear to increase the likelihood of its occurrence. These include chronic renal failure, underlying malignancy, chronic pulmonary disease, hypoalbuminaemia, three or more recent antibiotics, advanced age and infection with specific serotypes of *C. difficile* [2,4].

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Diagnosis

Because *C. difficile* may be carried asymptomatically, isolation of the organism from stools does not automatically imply that the patient has CDAD. Direct detection of *C. difficile* toxin in stool has become the standard method of diagnosis. The tests used are rapid (typically requiring 2–4 h) and specific. They have reported sensitivities of 63–94% and specificities of 75–100% [6,9]. Two negative stool toxin assays virtually rule out a diagnosis of CDAD.

Sigmoidoscopy is useful for diagnosing severe CDAD, where characteristic pseudomembranes may be seen in 51–55% of cases [9]. However, macroscopic changes seen in milder forms are non-specific and are difficult to distinguish from other causes of colitis.

There is no role for screening of asymptomatic patients for the presence of *C. difficile* or for further testing of stools in patients who have responded to therapy for CDAD.

Therapy

Most patients with antibiotic-associated diarrhoea do not have CDAD and therefore do not require specific antibiotic therapy. Even in those infected with *C. difficile*, 20–25% will respond to withdrawal of the causative antibiotics alone. With the availability of rapid, sensitive toxin assays from stool, empiric therapy for CDAD without diagnostic testing is inappropriate.

There are advantages to avoiding therapy in mild cases of CDAD. It has been shown that patients who receive specific therapy for CDAD have a higher rate of relapse than those who respond to discontinuation of antibiotics alone. In addition the drugs used to treat *C. difficile* (metronidazole and vancomycin) are both associated with the emergence of vancomycin-resistant enterococci [12].

Who should be treated? Unfortunately there are no evidence-based clinical guidelines to aid the clinician in this decision. The first step in treatment is to discontinue any current antibiotic therapy, if possible. Patients who have abdominal pain, tenderness, fever, constitutional symptoms or profuse diarrhoea should receive specific therapy directed against *C. difficile*. For haemodynamically stable patients with mild to moderate diarrhoea, without the above signs or symptoms of severe CDAD, it is reasonable to monitor them for 48–72 h. Therapy should only be started if there is no improvement in clinical status over this time.

Initial therapy

Oral metronidazole and oral vancomycin are the two most frequently used agents for CDAD. In comparative trials they have been found to be equally effective. However, vancomycin may be associated with higher rates of relapse of CDAD and emergence of vancomycin-resistant enterococci, as well as being considerably more expensive. Metronidazole may not be tolerated by every patient and it should be avoided in pregnancy. In either case the drugs must be given orally (to achieve sufficient concentrations within the bowel lumen). A 10-day course of either agent is usually sufficient, though it may take 2–4 days for a clinical response to be seen. Shorter courses may be associated with a higher relapse rate.

Severe cases of CDAD, which may be associated with ileus, pose greater therapeutic problems. Some success has been reported with intravenous metronidazole, which can enter the bowel via biliary excretion. Either agent can be given directly into the bowel via a retention enema, colostomy or small bowel feeding tube. There is no role for intravenous vancomycin, which does not enter the bowel lumen.

Patients with severe disease should have an early surgical opinion. In one study 5% of patients with CDAD required surgical intervention [13]. This figure is likely to be higher in nephrology patients with CDAD. Reported attributable mortality in this subgroup ranges from 14 to 38% [14].

Recurrent episodes

Relapse of CDAD occurs in up to 20% of patients who have received treatment for CDAD. Most patients will respond to a second 10-day course of metronidazole or vancomycin. A number of novel biotherapies have been reported for treating and preventing further relapses. To date the only therapy shown to reduce the rate of further relapses in a randomized control trial is the yeast *Saccharomyces boulardii*. A dose of 500 mg twice daily orally, starting 4 days before the end of a 10-day course of specific antibiotic therapy and continued for 1 month, has been shown to reduce the rate of further relapses by 50% [15]. There are anecdotal reports of the use of other biotherapies, such as live yoghurt, *Lactobacillus* and brewer’s yeast.

Prevention of CDAD

*Antibiotic control*

Avoiding unnecessary antibiotics, and excessive duration of antibiotic therapy, are the most important measures for preventing CDAD. In particular, overuse of second and third generation cephalosporins and broad spectrum penicillin derivatives should be avoided. Antibiotics should be used with caution in any patient who has had CDAD in the previous 2–3 months as they are likely to still be colonized with *C. difficile* and therefore prone to relapse.

There is no role for prophylactic antibiotic therapy for CDAD. Treatment of asymptomatic carriers may increase the risk of symptomatic CDAD.
Anaemia in the patient with renal insufficiency: documenting the impact and reviewing treatment strategies

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Introduction
The care of patients in the early phases of progressive renal insufficiency has received increasing attention over the past decade, as there is an increased recognition that much of the comorbidity seen in dialysis patients exists prior to the initiation of dialysis. Anaemia has been identified as an important predictor of morbidity and mortality in the dialysis population [1–3]; however, there are only a few studies addressing anaemia therapy specifically in the population with progressive renal insufficiency.

In an attempt to clarify some of the issues, this editorial will address the definition of anaemia in the context of early renal insufficiency, and the impact of anaemia in patients with renal insufficiency not yet on dialysis, and will review the evidence to date about the treatment of anaemia in this patient group.

Defining anaemia in the patient with renal insufficiency
The definition of anaemia in patients with renal insufficiency is problematic. While in all other realms...