**Clostridium difficile** in patients with renal failure — management of an outbreak using biotherapy

Joyce Popoola, Andrew Swann and Graham Warwick

Department of Nephrology, Leicester General Hospital, and Clinical Microbiology and Public Health Laboratory, Leicester, UK

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**Introduction**

*Clostridium difficile* is a Gram-positive, spore-forming, toxin-producing, obligate anaerobe that is ubiquitous in nature. Over the past decade, it has become a very prominent nosocomial infection worldwide. It is notable that *C. difficile* infection caused ward closures in 5% of UK hospitals in 1993, and by 1996 this figure had risen to 16% [1]. However, the available epidemiological data may not be accurate. Diagnosis depends on stool culture and testing for toxin, but wide variation in practices for stool collection and in laboratory methods for diagnosis make it difficult to know the true incidence.

It was first recognized as a potential pathogen in 1935 when it was described as ‘*Bacillus difficile*’ [2]. However, its identification as a normal bowel commensal and subsequent association with pseudomembranous colitis in relation to broad spectrum antibiotics was only established in the late 1970s [3,4].

Renal, oncology, haematology, geriatric, intensive care and surgical patients are particularly prone to infection with this microbe, emphasizing its potential threat to patients with depressed immunity. Infection has been noted to be of a greater severity and to cause higher mortality among patients with chronic renal failure, more so than can be accounted for by age differences alone [5]. The increasing use of broad spectrum antibiotics and the expanding population of patients with depressed immunity has resulted in an increase in the frequency of outbreaks of infection which may be prolonged and difficult to control [6].

**Clinical presentation**

Patient presentation can range from asymptomatic colonization or self-limiting diarrhoea through to severe diarrhoea, pseudomembranous colitis, megacolon, colonic perforation and death [6]. Most patients, however, present with passage of large volumes of watery stool which experienced healthcare workers can often recognize from its characteristic smell [7,8]. A prospective case-controlled study found that patients also had paralytic ileus (21%), abdominal pain (22%), fever (28%) and a raised white cell count (50%) [9]. Dehydration and electrolyte imbalance are often found and, when disease is prolonged, significant malnutrition can develop [8].

The incubation period for disease after exposure or acquisition is probably <1 week. Infection with *C. difficile* can be diagnosed up to 4 weeks after discontinuing an implicated agent. Particularly implicated antibiotics are clindamycin, lincomycin and thecephalosporins, although any antibiotic can cause it, including those used to treat the infection (i.e. vancomycin and metronidazole). Other medications such as cytotoxic medications, antacids and antibiotics are also implicated [10].

**Table 1. Therapies for *C. difficile* infection**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Pulsed oral vancomycin</td>
<td>12</td>
</tr>
<tr>
<td>Rectal vancomycin</td>
<td>12</td>
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<tr>
<td>Intravenous metronidazole</td>
<td>15</td>
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<tr>
<td>Fusidic acid</td>
<td>13</td>
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<td>Bacitracin</td>
<td>12, 13, 15</td>
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<td>Teicoplanin</td>
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<tr>
<td>Rifampin</td>
<td>15</td>
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<tr>
<td>Cholestyramine</td>
<td>12, 15</td>
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<tr>
<td><em>Saccharomyces boulardii</em></td>
<td>12-15</td>
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<tr>
<td>Lactobacillus</td>
<td>12, 13</td>
</tr>
<tr>
<td>Administration of non-toxicogenic <em>C. difficile</em></td>
<td>15</td>
</tr>
<tr>
<td>Faecal enemas</td>
<td>12, 13, 15</td>
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</tbody>
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Correspondence and offprint requests to: Joyce Popoola, The Nephrology Department, Leicester General Hospital, Gwendolen Road, Leicester LE5 4PW, UK.
drugs, antacids, stool softeners and laxatives may trigger *C. difficile*-associated diarrhoea [8]. Certain procedures such as nasogastric intubation, enemas and other intensive care procedures may also predispose to it [5].

**Diagnosis**

The most important diagnostic tool is a high clinical suspicion. However, further tests are required for confirmation. Endoscopy carried out with a rigid or preferably flexible endoscope reveals findings dependent on severity of disease, and can range from normal colonic mucosa, mild erythema and some oedema; granular, friable or haemorrhagic mucosa; through to pseudomembrane formation. Examination of stool samples is performed by different methods depending on laboratory preferences. They consist of culture methods for detection of *C. difficile* in faeces or, more usually, detection of cytotoxins. The detection of cytotoxins by tissue culture is regarded as the ‘gold

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**Fig. 1.** (A) Pre-inoculation tissue culture. (B) Post-inoculation tissue culture showing the cytopathogenic effect produced by organisms with cellular destruction.
standard’ by many [8], although immunoassay techniques are also available. (Figure 1).

Current recommendations for treatment

There are two broad lines of attack against C. difficile infection: control of bacterium and control of the precipitating antimicrobial therapy. Both are required if all truly preventable cases of C. difficile infection are to be avoided. The terms ‘high risk’ and ‘low risk’ antibiotics should be placed in the context of the local patient population and the endemicity of C. difficile. Limiting patient exposure to virulent C. difficile may also be crucial. Strain differences clearly play some role. For example, an epidemic clone (ribotype 1), identified by Brazier and colleagues, accounts for ~60% of associated isolates [7] associated with outbreaks in the UK.

In the UK, the Department of Health and Public Health Laboratory Service Joint Working Group (Clostridium difficile infection prevention and management) has established guidelines on the treatment of initial infections, and first and second relapses with C. difficile. This involves a first and possibly second course of metronidazole followed by vancomycin if required, but there are no clear guidelines for persistent infections [11].

A variety of other therapies have been proposed, with varying protocols and results (Table 1). These include pulsed oral and rectal vancomycin, intravenous metronidazole, other oral antibiotics (e.g. fusidic acid, bacitracin, teicoplanin and rifampin), cholestyramine as an adjuvant, and the introduction of competing, non-pathogenic organisms into the intestinal tract, such as Saccharomyces boulardii (as tablets, capsules or powders), Lactobacillus acidophilus and bulgaricus given in the form of bio-yoghurts, administration of non-toxicogenic C. difficile, and pooled faeces given as enemas have all been advocated. Most of the non-antibiotic agents (biotherapy) are thought to act by re-colonizing the bowel with bacterial flora, thus displacing the C. difficile.

The role of yeast (S. boulardii)

The Saccharomyces belong to the Ascomycetes fungi class, the most well known of which is S. cerevisiae colloquially known as brewer’s yeast. The form used in the treatment of diarrhoea however is S. boulardii, and the types are differentiated based on fermentation of various sugars. Saccharomyces boulardii has been used extensively for many years in Europe for the treatment of antibiotic-associated diarrhoea. Large numbers of the organism can be taken safely via the oral route and do not colonize the gut permanently [10]. The mechanism of the presumed beneficial effect is not fully understood, but several studies [14,16] have shown that S. boulardii suppresses C. difficile in the gut.

Management of a cohort of patients

Between January and May 1998, an outbreak of C. difficile colitis affected 25 patients in the nephrology wards at Leicester General Hospital. The presence of infection was confirmed in all cases by cytotoxin detection using tissue culture. Most patients responded to a first or second course of oral metronidazole (10–14 days) or an additional course of oral vancomycin for the same duration. Other systemic antibiotics were discontinued as far as possible, and infection control policies were implemented. Symptomatic patients were isolated or nursed in cohorts.

Seven patients, however, had persistent infection despite sequential treatment. These patients were treated with yeast (S. boulardii), supplied by Phillips yeast products limited, 640 mg (i.e. two tablets) three times a day before meals. The diarrhoea resolved in five patients within 5–10 days as monitored by stool charts. Prior to therapy, all patients had an average of three or more episodes of loose stools per day, and a reduction to once or less daily with passage of formed stools was considered as a positive response. Of the two cases that did not respond, one had multiple co-morbid factors, had difficulty complying with the treatment and eventually died from cardiac causes. The other had severe continuous ambulatory peritoneal dialysis (CAPD)-related fungal peritonitis requiring abdominal surgery and also eventually died.

Although this was not a controlled study, five out of our worst affected patients responded promptly to this therapy. Previous studies [14,16] have demonstrated that S. boulardii has been beneficial in the treatment of C. difficile infection, although none have recruited patients with renal failure. A study carried out in Bristol [10] found no effect of S. boulardii in prevention of antibiotic-related diarrhoea. However, all the patients in the Bristol study were elderly, some were on laxatives, all were on concurrent antibiotics and the doses of S. boulardii used were lower than those used to treat the patients reported here.

Conclusion

Infection with C. difficile is becoming a major cause of significant morbidity and mortality in nephrology patients in the western world as broad spectrum antibiotics are often required to treat infections, especially in those on renal replacement therapy. In addition, renal patients often have multiple co-morbid factors which may be additional risk factors and result in greater disease severity and higher mortality.

The ultimate aim should be prevention of spread of infection by prompt isolation and treatment of symptomatic patients and strict antibiotic policies. Cross-infection can be avoided by thorough hand washing by all attending staff after contact with patients and their environments. Daily cleaning helps to reduce the environmental load of spores [11]. Passive immunization, currently being developed, may be of some help. Vancomycin
should be used with caution in view of possible risk of development of vancomycin-resistant enterococci.

Where *C. difficile* infection persists despite conventional treatment, there are limited data to identify the best treatment. *Saccharomyces boulardii* (yeast) is a relatively cheap, easily administered, readily available therapy with no defined side-effects. The potential of this therapy in this serious and sometimes life-threatening condition should be more widely publicized, and further studies are required to compare its effectiveness with conventional therapies.

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References

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