REVIEW

Clostridium difficile-associated disease: update and focus on non-antibiotic strategies

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Abstract

Clostridium difficile-associated disease (CDAD) is a problem of especially the frail elderly. Changes in virulence of prevalent strains in the early years of the new century saw mortality and morbidity increase from historical levels. This article explores non-antibiotic strategies including the use of probiotics. A number of avenues of ongoing research appear to have potential future clinical application. Evidence exists linking acid-inhibiting drugs to an increased risk of CDAD, and the adjunctive use of Saccharomyces boulardii and infection control measures in the treatment of CDAD.

Keywords: Clostridium difficile, probiotics, elderly, Saccharomyces boulardii

Introduction

Clostridium difficile-associated disease (CDAD) is a common problem in secondary healthcare causing significant morbidity and associated with mortality, especially in the older person [1]. Clostridium difficile (CD) is a Gram positive, spore-forming obligate anaerobe that causes a spectrum of presentations from asymptomatic carriage through unexplained leucocytosis [2], toxin-mediated self-limiting diarrhoeal illness to pseudomembranous colitis and toxic megacolon.

In the hospital setting, CDAD is associated with the use of most antibiotics (especially clindamycin, broadspectrum penicillins, cephalosporins, quinolones and fluoroquinolones but also even those antibiotics used to treat the condition—metronidazole, and vancomycin) [3, 4, 5]. Its incidence is proportional to the length of hospital stay —8% per week incidence in one study [6]. The use of proton pump inhibitors and H2 receptor antagonists have been shown to be significantly associated with the development of CDAD [7]. Studies are, however, not entirely in agreement on this point [8].

Its effect on discharge is to delay by 3–4 days or more incurring an attributable cost of around US$ 3,700 at 2002 prices [9] or £4,000 at 1998 prices [10] although Spencer records the many difficulties in calculating attributable cost. Incidence is going up—the UK Health Protection Agency recorded 51,690 cases in the over-65 population of the United Kingdom in 2005 [11], probably due to a number of factors including increased surveillance for nosocomial infection in hospitals as well as changes in the virulence of the organism. Recently reported outbreaks in Europe and Canada have been due to the toxin-hypersecreting NAP1 (North American pulsed-field gel electrophoresis, PFGE, type 1) also variously called ribotype 027 or simply NAP1/027 [4, 12, 13]. Asymptomatic carriage varies from 2% in the community to 20–30% or more in hospitalised adults [14, 15, 16]. These figures include carriage of both toxin-secreting (both toxin A+/B+ and A−/B+ being potentially disease-causing) and non-toxin-secreting strains (invariably benign). In CDAD associated with antibiotic use, diarrhoea will cease in 2–3 weeks in 23% on cessation of the offending antimicrobial [17]. Up to 2/3 of cases of community-acquired CDAD in a recent study, however, had not had antibiotics in the 90 days prior to the development of symptoms suggesting a different pattern of disease between community-acquired and nosocomial cases [7].

Antimicrobial therapy is with oral metronidazole or vancomycin. The mean time to resolution of diarrhoea with metronidazole ranges from 2 to 4 days and courses of 10 days oral therapy are recommended [18]. Metronidazole is associated with a failure rate (diarrhoea not settled in under 6 days) of 2%, and a relapse rate of 7% owing to a combination of recrudescence from retained spores and reinfection [16, 19]. Changes in organism virulence may mean that historical studies of disease natural history become obsolete and data obtained from them should be interpreted
with the caution that sequelae may be underestimated. Thirty day mortality, for example, has been reported as historically 4.7% rising to 13.8% in an outbreak of NAP1/027 [20].

There is an ongoing debate about the first-line antibiotic of choice [21]. There is no clear answer; however, the use of metronidazole first-line is supported by cost and avoidance of selection for vancomycin-resistant enterococci. Kelly and Cloud suggest that a low threshold for vancomycin use in severe or refractory cases should exist. Indications for favouring vancomycin might include intensive care unit (ICU) admission, high leucocytosis, renal impairment due to sepsis, septic shock, toxic megacolon and a failure to improve on metronidazole in 48–72 h. Current local prevalence of the NAP1/027 strain has also been cited as an indication for first-line use of vancomycin [20]. Local guidelines should be developed and kept under review with relevant stakeholder input from, for example, colleagues in microbiology, infection control and pharmacy. Owing to the high prevalence and mortality of CDAD in the elderly, geriatricians should also be stakeholders in the author’s opinion.

Other antibiotics that may be considered in the unusual event of allergy to both first-line agents include bacitracin, teicoplanin, fusidic acid and nitazoxamide [22], rifaximin and rifampin [23].

The old adage that prevention is better than cure could not be more relevant than in the context of preventing nosocomial infection [16, 24]: measures such as antibiotic prescribing policies [25], isolation of suspicious index cases, increased vigilance, barrier nursing, environmental decontamination [26], hospital design [27] and staff handwashing with soap and water [28] all play an important role in prevention.

**Non-antibiotic strategies in CDAD**

**Cessation of antibiotics**

Cessation of offending antibiotics (where implicated and appropriate) and avoidance of antimotility agents should accompany adequate fluid and electrolyte replacement. Although not proven in the aetiology or treatment of CDAD, consideration of cessation of antacid medications seems appropriate in the author’s opinion.

**Passive and active immunisation**

Pooled human immunoglobulin is a costly and finite resource available for provision of passive immunity to CD toxins that has been shown in limited case reports to be effective in severe pseudomembranous colitis not responding to metronidazole and vancomycin [29]. Immunoglobulin was given in parallel with antibiotics and one of two cases reported had a recrudescence of CDAD 4 weeks after infusion, compatible with the natural attrition of infused immunoglobulin. The experience of colleagues in Leeds with five patients over 2 years suggests that this adjunct is useful in recalcitrant CDAD [30].

Active immunisation against one or both CD toxins is another possible strategy but those most likely to benefit—the frail, hospitalised elderly—are also those least likely to adequately respond [29, 30]. A preventative vaccination strategy may in the future prove most useful in the context of elective surgery in the elderly in the opinion of the author. Vaccination may, in the future, assist in treating younger, healthier persons with recurrent CDAD.

**Specific monoclonal antibodies**

CD toxin monoclonal antibodies are in phase II clinical trials as adjunctive therapy to be used with antibiotics [22].

**Toxin-binding agents**

Cholestyramine binds CD toxins A and B and has been employed as an adjunct to conventional antibiotic therapy with limited case reports supporting its use. Its clinical effectiveness is limited however [31], possibly explained by its affinity for vancomycin and less than avid binding of toxin [32]. Cholestyramine is still recommended by some authors, however [33]. A novel toxin-binding resin tolevamer may prove to be more clinically useful but is not yet clinically available [34].

**Faecal therapy**

Homologous faecal enemas have been used in recalcitrant cases of CDAD with stool donated usually by the partner of the patient. The widespread application of such a strategy has its problems, not least in terms of acceptability and the possible of transmission of communicable disease. The mechanism of action of faecal bacteriotherapy apart from ‘reconstitution of a normal flora’ cannot be measured as stool contains hundreds of bacterial species [35–37]. It is, however, an adjunct in sporadic clinical use and administration of donor stool via nasogastric tube in 18 cases of recurrent CDAD with benefit in 15 has recently been reported [38].

**Use of non-toxigenic strains**

Administration of a non-toxigenic strain of CD has been attempted in two patients with relapsing CDAD [39] after repeated, failed courses of antibiotics. This strategy is hampered by a lack of knowledge of its effects in any animal model although priming with a non-toxigenic strain protects against later acquisition [40].

**Amino acid restriction or supplementation**

*In vitro*, CD is dependent on a minimum amino acid requirement of cysteine, isoleucine, leucine, proline, tryptophan and valine [41]. Toxin production *in vitro* is increased by, for example, addition of arginine [42] or butyrate [43] and decreased by the addition of cysteine and its derivatives acetylcysteine, glutathione and cysteine [43]. Methionine is metabolised to alpha-ketobutyrate by CD methionine gamma-lyase [44] and human methionine...
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Restriction has been shown in the field of oncology not to have any short-term detrimental effects. As a methionine-depleted diet already exists for the treatment of homocystinuria, a potential agent exists that could be supplemented with, for example cysteine, if mammal models suggest that this might be beneficial. This is the author’s own conjecture.

Related to bacterial metabolism, quorum sensing is a term that describes the ability of some bacterial species to sense their environment and ‘switch on’ complex behaviours such as toxin formation, conjugation, biofilm formation, invasiveness or bioluminescence once a certain ‘quorum’ of bacteria—and therefore concentration of metabolite(s)—is reached. This behaviour, which is well described in other bacterial species such as V. harveyi, might function to conserve resources to make best use of the ‘switch’ from one population behaviour to another. For example, one invasive bacterium might be overwhelmed by host defences whilst a larger number ‘switched on’ at the same time might be at an advantage. An excellent review occurs in [45]. CD appears to share a quorum-sensing metabolic pathway with V. harveyi but it is not entirely clear what the clinical relevance of this finding might be. A proposed sensing/signalling molecule is a furanone produced in mid- to late-stage exponential growth of CD in culture before toxin production reaches a maximum in stationary-phase growth. This molecule, when produced by a recombinant E. coli strain, ‘switches on’ CD toxin production in vitro [46]. This is a potential clinically useful area of ongoing research for novel drug targets.

The role of surgery

The role of surgery in the management of severe, fulminant or life-threatening CDAD is not to be underestimated. Severe CDAD may be defined as CDAD with any evidence of systemic inflammatory response syndrome (SIRS) [47]—one or more of temperature greater than 38°C or less than 36°C, tachycardia of 90/min or greater, tachypnoea of 20/min or greater, pCO2 of less than 4.26 kPa (32 mm Hg), leucocytosis or leukaemoid reaction, and therefore concentration of metabolite(s)—is reached. This behaviour, which is well described in other bacterial species such as V. harveyi, might function to conserve resources to make best use of the ‘switch’ from one population behaviour to another. For example, one invasive bacterium might be overwhelmed by host defences whilst a larger number ‘switched on’ at the same time might be at an advantage. An excellent review occurs in [45]. CD appears to share a quorum-sensing metabolic pathway with V. harveyi but it is not entirely clear what the clinical relevance of this finding might be. A proposed sensing/signalling molecule is a furanone produced in mid- to late-stage exponential growth of CD in culture before toxin production reaches a maximum in stationary-phase growth. This molecule, when produced by a recombinant E. coli strain, ‘switches on’ CD toxin production in vitro [46]. This is a potential clinically useful area of ongoing research for novel drug targets.

The incidence of severe-fulminant symptoms is reported as in the range 1.6–3.2% and increased as hypervirulent strains became more prevalent worldwide although no reference to the strain type is made by the authors.

The proportion of patients with colitis having colectomy was 0.48–2.6%. The median time from recorded onset of symptoms to colectomy was 9 days (range 0–30 days). The outcome after colectomy was death in 57% reflecting a critically ill patient population and/or a significant contribution to mortality from CDAD. Dallal and coauthors reported that no patient over the age of 80 years survived colectomy. Careful selection of patients for consideration of surgery is suggested by this finding. The authors did not find significant predictors of survival in APACHE scores, pH or lactate levels, neutrophil counts or percentage immature neutrophils. Vasopressor requirement was, as noted above, a poor prognostic marker for survival post colectomy.

A Canadian group, reporting on surgical experience during an ongoing outbreak of NAP1/027, reported their experience of colectomy in severe CDAD necessitating ICU admission [50]. A survival benefit (judged by 30 day mortality) was noted in those over 75 years of age, without immunosuppression (haematological malignancy, organ transplantation, neutropaenia or greater than 1 month treatment with systemic corticosteroids), with a peak white cell count of >20 × 10⁹/l, and with a serum lactate level between 2.2 and 4.9 mmol/l. Mortality was severe (94% without colectomy, 86% with colectomy, the difference not statistically significant) in all age groups once the serum lactate level exceeded 5 mmol/l. It should be borne in mind that the elderly patients included in this group had been selected as being robust enough for ICU care.

The author would suggest that daily surgical review and serial abdominal radiographs be considered in any patient who is fit for surgery whatever the age with any of the signs of SIRS above but especially if accompanied by an acute abdomen. This follows the British Gastroenterology Society guidance for the management of the colitis of inflammatory bowel disease [51].

Probiotics in CDAD

A probiotic may be defined as an organism or substance that contributes beneficially to healthy intestinal microbial flora [52].

A 2003 Cochrane review [53] of randomised controlled trials (RCTs) of probiotic use in presumed infectious diarrhoea (unspecified enteritis or rotavirus enteritis), across all age groups concluded that ‘a variety of probiotics reduced infectious diarrhoea in various settings’. The authors concluded that further work on specific agents in specific infections is warranted. Safety issues, for example of use in the immunocompromised, were not resolved in the studies under scrutiny. RCTs of antibiotic-associated diarrhoea (AAD) were excluded, therefore unlikely
to have included CDAD. Only one trial reported a subset of bacterial diarrhoea. Most commonly used agents were Lactobacilli species, then *Saccharomyces boulardii*, and *Streptococcus faecium*.

A meta-analysis of probiotics in AAD and CDAD [54] included 6 RCTs of probiotics in CDAD, two using *S. boulardii*, the rest using named Lactobacilli species/strains showed a clear benefit only for *S. boulardii* in treating CDAD. Studies were generally underpowered and an exhortation for complete agent identification (species, strain) in future RCTs was made.

A study published recently by an English group found a significant benefit, in preventing CDAD in hospitalised patients on antibiotics, of using a cheap, commercially available live yoghurt drink [55]. This study can be criticised for excluding 92% of eligible persons, including those on ‘high-risk’ antibiotics. The authors also did not completely and comprehensively classify the strains of organisms being used.

Probiotics are considered safe although endocarditis has been reported [56]. Most cases of systemic infection are due to *Lactobacillus rhamnosus* and *Lactobacillus casei* [57]. Use of *L. rhamnosus* GG in treated HIV is considered safe [58]. The use of probiotics in the immunocompromised including the frail elderly, individuals with HIV or neutropenia carries possible risks which should be balanced with the (substantial) risk of ongoing, recalcitrant CDAD [59].

The issue of the use of probiotics in the elderly is one with its own special considerations. An elderly inpatient with CDAD could be regarded by definition as relatively immunocompromised by dint of the lack of protective response to infection. The elderly are also more likely to have multiple comorbidities—especially cardiac valvular abnormalities—that make the administration of live organisms potentially risky.

**Summary**

In clinical practice infection control measures and *S. boulardii* remain the only clearly beneficial evidence-based adjuncts to antibiotic therapy of CDAD.

Outside clinical trials, it is the author’s opinion that only oral *S. boulardii* should be used as an adjunct to the treatment of CDAD, although many institutions informally employ a variety of commercially available live yoghurt preparations as widely-acceptable, but as yet unproven, adjunct to medical therapies.

The recent UK report quoted [55] shows a significant effect of one specific commercially available live yoghurt product in preventing CDAD in a small subgroup of hospitalised patients. This measure could reasonably be combined with infection control measures and, possibly, consideration in deciding whether to prescribe acid-inhibiting drugs in preventing CDAD.

What remains unknown is how nutritional status as well as medical comorbidity affects outcome in CDAD and further research on these issues as well as probiotic use and ideal antibiotic treatment is warranted [60].

**Author statement**

The author has no conflict of interest to report.

**Supplementary data**

Supplementary data for this article are available online at http://ageing.oxfordjournals.org.

**References**

The long list of references supporting this review has meant that only the most important are listed here and are represented by bold type throughout the text. The full list of references is available on the journal website http://www.ageing.oupjournals.org as Appendix 3.

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