

# **New Recommendations Issued for Clostridium difficile-Associated Disease CME**

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February 12, 2008 — Diagnosis and treatment of *Clostridium difficile*-associated disease, including use of existing and new antibiotic and nonantibiotic agents, are reviewed in the February 5 Online First issue of *Gut*.

"*C. difficile* is a Gram-positive, anaerobic spore-forming bacillus that was identified as an aetiological agent of antibiotic-associated pseudomembranous colitis in the late 1970s," write Tanya Monaghan, from the University of Nottingham and Nottingham University Hospitals National Health Service Trust, Nottingham, United Kingdom, and colleagues. "It is believed to be responsible for 15-20% of antibiotic-related cases of diarrhoea and nearly all cases of pseudomembranous colitis. Over the last decade, the incidence of *C. difficile*-associated disease has progressively increased and is now a significant clinical problem in North America and Europe."

The review covers recent developments in the management of acute and recurrent *C difficile*-associated disease (CDAD), highlighting use of currently available and newly developed antibiotic and nonantibiotic agents for treatment. Other topics include details regarding the current developmental stage of new agents in the pipeline, and the role of surgery for management of patients with severe disease is discussed.

A multipronged approach to infection control includes prudent use of antimicrobial agents, prevention of cross-infection, and ongoing surveillance.

The review also discusses an epidemic, hypervirulent strain of *C difficile* that has emerged recently; pathogenesis and clinical presentation of *C difficile* colitis; and approaches to facilitate rapid diagnosis and evaluation of colonic manifestations.

CDAD is an important nosocomial infection associated with healthcare, and it may recur in 15% to 30% of patients. Recent outbreaks have been attributed to a virulent strain of *C difficile*. Judicious use of antimicrobial agents, prevention of cross-infection, and active surveillance of cases may facilitate control of CDAD.

Rapid diagnosis of CDAD further allows implementation of infection control measures and timely treatment. Although stool assays for *C difficile* toxin have significant false-negative rates, flexible sigmoidoscopy allows rapid identification of *C difficile*-associated pseudomembranous colitis.

For patients with mild CDAD, discontinuation of the causative antibiotics may suffice, without the need for further treatment.

Currently available antibiotics in widespread use for treatment of recurrent CDAD are vancomycin, which is a glycopeptide, and metronidazole, an imidazole derivative. Controlled clinical trials have shown efficacy for CDAD treatment with vancomycin, metronidazole,

bacitracin, and fusidic acid, and a retrospective study suggested that mean duration of symptoms was significantly shorter with vancomycin vs metronidazole.

Although many guidelines recommend the use of metronidazole in patients thought to need antibiotic treatment, recent studies have reported high failure rates of metronidazole, and resistance to metronidazole has been reported. However, resistance may not necessarily be the cause of treatment failure.

Evidence from a randomized controlled trial (RCT) supports the use of vancomycin with the probiotic *Saccharomyces boulardii*, whereas the evidence base underlying pulsed, tapered use of vancomycin is an uncontrolled trial and clinical experience.

Therapeutic options may increase as a number of new antimicrobial and nonantimicrobial agents are currently being evaluated to treat acute and recurrent CDAD. There was a small, uncontrolled trial of rifaximin, a rifamycin derivative.

Nonantimicrobial agents include fecal bacteriotherapy administered by fecal enema, supported by case reports and retrospective review. An RCT has been conducted with the prebiotic oligofructose. In addition to *S. boulardii*, evaluated in an RCT, another probiotic agent is *Lactobacillus plantarum*, which has been tested in a small RCT.

There have been case reports of use of human gamma globulin, a form of pooled immunoglobulin, in CDAD. Another form of immunotherapy is anti-*C. difficile* whey protein concentrate, which has been tested in an open-label pilot study. Finally, there have been phase 1 studies of *C. difficile* vaccine, a form of toxoid vaccine.

For patients with severe CDAD, intensive care unit (ICU) admission may be needed. A combined medical and surgical approach is recommended, with surgical resection of the inflamed colon as a therapeutic option.

Findings from recently completed, and from still ongoing, clinical trials should further improve the evidence base supporting future recommendations for the management of patients with *C. difficile* infection.

"Recent changes in the epidemiology of *C. difficile* infection and the emergence of an epidemic hypervirulent strain serve to emphasise the need for greater attention to infection control, early diagnosis of CDAD, and more effective treatments for those with severe and recurrent disease," the reviewers write. "A significant proportion of patients with mild disease may not require any further treatment, if the offending antibiotics can be discontinued. Currently, a number of therapeutic avenues are being pursued for treatment of acute and recurrent CDAD."

The review authors have disclosed no relevant financial relationships.

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## **Clinical Context**

In the late 1970s, *C. difficile* was first recognized as a causative organism in antibiotic-related pseudomembranous colitis. Approximately 15% to 20% of antibiotic-associated cases of diarrhea and nearly all cases of pseudomembranous colitis have been attributed to this gram-positive, anaerobic spore-forming bacillus. The incidence of CDAD has steadily climbed in the past decade, and it is an important cause of morbidity both in North America and in Europe.

The present review offers suggestions, based on recent evidence and experience, for diagnosis and management of acute and recurrent CDAD, including use of currently available antibiotic and nonantibiotic agents. Agents in the developmental pipeline, diagnostic suggestions, and the role of surgery in patients with severe CDAD are also covered. Therapeutic options may increase as new antimicrobial and nonantimicrobial agents are being evaluated to treat acute and recurrent CDAD.

## Study Highlights

- A recently emerged epidemic, hypervirulent strain of *C difficile* has caused recent outbreaks.
- Rapid diagnosis of CDAD allows implementation of infection control measures and timely treatment.
- Stool assays for *C difficile* toxin have significant false-negative rates.
- Flexible sigmoidoscopy allows rapid diagnosis of *C difficile*-associated pseudomembranous colitis.
- Control of *C difficile* infection requires prudent use of antimicrobial agents, prevention of cross-infection, and ongoing surveillance.
- For patients with mild CDAD, discontinuation of the causative antibiotics, without further treatment, may be sufficient.
- For treatment of recurrent CDAD, currently available, widely used antibiotics are vancomycin and metronidazole.
- Vancomycin, metronidazole, bacitracin, and fusidic acid have been shown to be effective for CDAD in controlled clinical trials.
- In a retrospective study, mean duration of symptoms was significantly shorter with vancomycin vs metronidazole.
- Metronidazole is secreted only by the inflamed colonic mucosa.
- Many guidelines recommend metronidazole for patients with CDAD thought to require antibiotics, but there is recent evidence for high failure rates of, as well as resistance to, metronidazole. Resistance may not necessarily be the cause of treatment failure.
- An RCT supports the use of vancomycin with the probiotic *S boulardii*.
- Pulsed, tapered use of vancomycin is supported by 1 uncontrolled trial and clinical experience.
- Intracolonic vancomycin may be an effective adjunctive treatment in patients with severe *C difficile*-associated colitis, based on a small, retrospective case series.
- A small, uncontrolled trial of rifaximin, a rifamycin derivative, suggests good tolerability and early resolution of symptoms as effective as vancomycin.
- Teicoplanin, which may not currently be available in all countries, may be as effective as or slightly more effective than vancomycin, according to a Cochrane review.
- Other antimicrobials in development include nitazoxanide (a nitrothiazole benzamide; RCT); PAR-101 (a macrocyclic antibiotic; phase 3), and ramoplanin (a lipoglycopeptide; phase 2).
- An RCT has been conducted with the prebiotic oligofructose.
- Probiotics include *S boulardii*, tested in an RCT, and *L plantarum*, tested in a small RCT.
- Immunotherapy includes human gamma globulin (case reports), anti-*C difficile* whey protein concentrate (open-label pilot study), and *C difficile* vaccine (phase 1).
- Human monoclonal antibodies include CDA1 (MDX-066) against toxin A (phase 2) and MDX-1388 against toxin B (phase 2).
- Nonantimicrobial agents include fecal bacteriotherapy given by fecal enema, supported by case reports and retrospective review; and tolevamer (an anionic polymer; phase 3).
- A combined medical and surgical approach (resection of the inflamed colon), with ICU admission, may be needed for patients with severe CDAD.

## Pearls for Practice

- For treatment of recurrent CDAD, currently available, widely used antibiotics are vancomycin and metronidazole; bacitracin and fusidic acid also have been shown to be effective. Although many guidelines recommend metronidazole for patients with CDAD thought to require antibiotics, there is recent evidence for high failure rates of, as well as resistance to, metronidazole.
- Control of *C difficile* infection requires prudent use of antimicrobial agents, prevention of cross-infection, and ongoing surveillance. For patients with mild CDAD, discontinuation of the causative antibiotics, without further treatment, may be sufficient. A combined medical

and surgical approach (resection of the inflamed colon), with ICU admission, may be needed for patients with severe CDAD.