steps to improve coordination in global health, such a mechanism would help to meet several challenges faced by the current fragmentation in global heath; in particular it would increase transparency and accountability.

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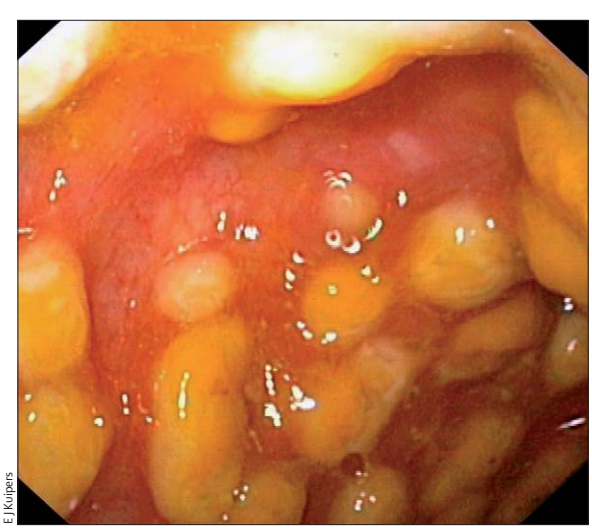
Clostridium difficile infection

In 1935, a new species of bacteria was named *Bacillus difficilis*, the species name given because of its difficult anaerobic isolation from human faeces. 40 years later, it was renamed *Clostridium difficile* and identified as the cause of pseudomembranous colitis. This organism is the most common cause of nosocomial diarrhoea, and incidence has increased since the appearance of a hypervirulent strain in 2000. Diagnosis and management of *C difficile* infection are challenging because of varied clinical presentation, limited treatment options, common concomitant illness, and disease recurrences.



E J Kuijpers

Figure: **Typical endoscopic appearance of *C difficile*-induced pseudomembranous colitis**
Pseudomembranes are yellow-white adherent plaques on an inflamed but intact colonic mucosa without ulceration.

C difficile is an anaerobic gram-positive, spore-forming bacterium. The spores persist in the environment and are difficult to eradicate. Asymptomatic carriage occurs in 1–3% of healthy adults and 40–60% of neonates, particularly those born in hospital.[1] Prior antibiotic use is the most common risk factor. Prolonged stay in hospital or in extended care facilities adds additional risk. Factors that lead to *C difficile* associated disease (CDAD) include altered faecal flora allowing the organism to proliferate, and impaired host immune response.[2] Transmission occurs among people by bacteria and spores passing from stools; people may also become infected by spores in the environment. There are many strains with differing pathogenic potentials related to the production of toxins A and B—toxin-negative strains do not cause disease. Most pathogenic strains produce both toxins, but 2–5% produce only toxin B. Both toxins are encoded by a cluster of genes, including the regulatory gene *tcdC*. A hypervirulent strain, characterised by different microbiological methods as North American pulsed-field type 1, PCR ribotype 027, and restriction endonuclease analysis group BI, and referred to as NAP1/027,[3] has caused epidemics in the USA, Canada, Europe, and Japan.[3-5] This isolate has a mutation in *tcdC* that is associated with high concentrations of both toxins.[6]

CDAD ranges from mild diarrhoea to fulminant, pseudomembranous colitis, sepsis, multiorgan failure, and death. Mild cases may present with slight fever, loose stools, and abdominal cramps. Diagnosis is commonly delayed: in one study over half of 60 inpatients with

unexplained leucocytosis had CDAD, and the leucocytosis often preceded signs of colitis.[7] *C difficile* colitis can start with non-specific signs of oedema and erythema on endoscopy. Inflammation usually predominates in the left colon. The disease can progress to severe colitis with typical adherent pseudomembranes (figure). These pseudomembranes can coalesce to obscure the mucosa. Severe CDAD is associated with fever, leucocytosis, hypoalbuminaemia, and high serum concentrations of C-reactive protein. Such patients need aggressive therapy because severe colitis can result in toxic megacolon, colon perforation, and progressive multiorgan failure. Mortality in patients with CDAD ranges from 3–30%, with most series showing 5–10%,[3,8] which is, in part, attributable to comorbidity in elderly patients. The direct CDAD-attributable mortality is 1·5% in isolated cases and 7% during outbreaks with the hypervirulent strain.[8]

Diagnosis of *C difficile* requires bacterial culture or demonstration of toxins in faeces. Culture does not differentiate carriers from those with disease nor does it identify presence of toxins. Toxin-B tissue culture assay was the gold standard but enzyme immuno-assays are faster and cheaper. Sensitivity and specificity range from 60–85% compared with 95% for tissue culture, and some enzyme immuno-assays detect only toxin A and miss strains that produce only toxin B. However, they also test for a common clostridial antigen; a toxin-A-negative, common antigen-positive result requires additional testing for toxin B, for example with PCR. Endoscopy can be done to assess severely ill patients as the presence of pseudomembranes is almost pathognomonic. However, the absence of pseudomembranes does not exclude CDAD, because they are commonly absent in mild cases or patients with concomitant inflammatory bowel disease. Most importantly, there are no perfect diagnostic tests, so clinical suspicion should prevail with empiric therapy if diagnostic test results are inconclusive.

Asymptomatic carriers need no treatment. If possible the precipitating antibiotic drug should be discontinued. Symptomatic patients, however, require oral antimicrobials of which vancomycin and metronidazole are the most widely used (table).[9–11] Resistance to these two drugs is either absent or rare.[3,12] A recent meta-analysis included 1157 patients from 12 randomised trials, assessing eight antibiotics for the treatment of CDAD.[13] None of the antibiotics was superior for various outcomes including symptomatic cure and prevention of complications.[13] This finding favours metronidazole as initial treatment because of similar efficacy, lower cost, and the risk of selecting for vancomycin-resistant enterococci. In patients with severe disease, this approach is under reconsideration because three recent studies reported 22–38% failure rates with metronidazole,[12,14,15] especially in patients with more severe disease.[15] A comparison of vancomycin 125 mg four times daily with metronidazole 250 mg four times daily showed similar cure rates (98% *vs* 90%) in patients with mild disease, but higher cure rates (97% *vs* 76%) with vancomycin in those with severe disease.[10] These data support vancomycin as first-line treatment in patients with severe CDAD. In addition, switching to vancomycin is recommended when patients on metronidazole do not improve within 72 h.[16] Whether treatment can decrease the incidence of severe complications is unclear. A retrospective analysis of 1616 patients between 1991 and 2006 showed that vancomycin was initially associated with a lower incidence of severe or complicated CDAD than metronidazole, but this difference disappeared in recent years, possibly due to the limited efficacy of both drugs to alter the natural course of CDAD caused by the hypervirulent NAP1/027 strain.[17] Severe CDAD needs aggressive treatment. Higher

	Treatment*	Other measures
Asymptomatic carrier	No treatment required	Preventive measures†
Initial CDAD	Metronidazole 250 mg four times daily or 500 mg three times daily	Close monitoring for development of complications
Severe CDAD‡	Vancomycin 125 mg four times daily§; vancomycin enema	Close monitoring for development of complications
Complicated CDAD	Vancomycin 500 mg four times daily; Ileus: intravenous metronidazole or vancomycin enema; toxic megacolon: consider early colectomy	
1st recurrence CDAD	Metronidazole 500 mg three times daily¶; vancomycin 250–250 mg four times daily¶	
2nd recurrence CDAD	Vancomycin 500 mg four times daily¶ for 10–14 days, then pulse at lower doses	*S boulardii* 1 g per day||; use of chaser**
>3rd recurrence CDAD	Vancomycin 500 mg four times daily††	Consider stool repopulation via enema, colonoscopy, nasogastric tube

*Treatment usually lasts 10–14 days. †Measures for the prevention of spread of bacteria and spores are relevant for all cases. ‡Criteria for severe CDAD include white-blood-cell count >15×10⁹ or >50% rise in serum concentration of creatinine;[9] others include severe diarrhoea, temperature >38·3°C, albumin <25· mg/dL;[10] these criteria have not been prospectively validated. §Vancomycin may in patients with severe CDAD be associated with higher response and lower recurrence rates. ¶Followed by 2–3 weeks pulsed treatment with vancomycin 125–250 mg twice daily. ||To be considered during and 2 weeks after antibiotics, but not in immunocompromised patients. **Additional course with second antibiotic immediately after vancomycin. Rifaximin, a poorly absorbed rifamycin derivative, has been used, but is not licensed in the European Union. ††Followed by additional prolonged pulsed treatment with vancomycin 125–250 mg twice daily, increasing days off antibiotics by one day each week.[11]

Table: **Treatment of *C difficile* infection in different categories of patients**

doses of vancomycin, up to 2 g/day, are recommended by recent guidelines from the Infectious Diseases Society of America as primary treatment for complicated CDAD.[9] In addition to oral vancomycin, small uncontrolled series have shown benefit with intravenous metronidazole or vancomycin enemas. Patients with severe CDAD require close monitoring and urgent colectomy if they do not improve, they show clinical deterioration, or they develop toxic megacolon or rising concentrations of serum lactate.

Recurrent disease is a challenge with no standard, uniformly effective therapy. Diarrhoea usually recurs within a week, but may be delayed up to 30 days. Demonstration of *C difficile* toxin in stools justifies a second 10–14-day course of metronidazole or vancomycin. Long tapering courses of vancomycin or pulsed treatment on alternating days help prevent recurrence.[11] Prolonged metronidazole therapy is not recommended because of the risk of irreversible neuropathy. The probiotic *Saccharomyces boulardii* 500 mg twice daily given as an adjunct to antibiotics reduced recurrences in two controlled trials, though in the second trial only in a subset in conjunction with high-dose vancomycin.[18] *S boulardii* should, however, not be used in immunosuppressed patients or those with central intravenous lines, because fungaemia may occur. Administration of stools from healthy subjects by colonoscopy, enema, or nasogastric tube reconstituted faecal flora in patients with therapy-resistant disease in small series.[9] Other treatments under study include active and passive immunisation by intravenous administration of immunoglobulins, parenteral vaccination to inactivated toxins A and B, or oral administration of antitoxin antibodies isolated from colostrums of toxin-immunised cows.[19]

Prevention of CDAD requires both control of environmental exposure to *C difficile* bacteria and spores, and wise use of antibiotics. Preventive measures include use of gloves, hand washing, avoiding the use of rectal thermometers, and staff education. In epidemic settings, restriction of specific antibiotics, in particular clindamycin, has led to decreased rates of CDAD. Although some probiotics decrease antibiotic-associated diarrhoea, there are no strong data that they prevent CDAD.

The incidence of CDAD is increasing worldwide in association with a hypervirulent strain, with more severe disease and mortality, and more common failure of therapy. Current diagnostic tests are imperfect and may delay diagnosis and treatment if their limitations are not understood. For sick patients, empiric therapy should be started as soon as CDAD is suspected. Decreased responses to antibiotics are particularly ominous and highlight the need for further studies of alternative immunomodulating therapies, such as vaccination and oral administration of antitoxin antibodies.

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