Medical treatment of *Clostridium difficile*-related gastrointestinal infection – whither vancomycin?

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One of the major advances in anaerobic microbiology in the past five decades has been clarifying the causal relationship between *Clostridium difficile* and pseudomembranous colitis, and its association with previous antimicrobial therapy. It is now clear that *C. difficile* is responsible for virtually all cases of pseudomembranous colitis and up to 20% of cases of antibiotic-associated diarrhoea. Clindamycin is widely recognised for its propensity to induce these diseases, but broad-spectrum penicillins and cephalosporins (reflecting their widespread usage) are much more common precipitating agents.

With two years of the discovery of *C. difficile* diarrhoea, vancomycin was shown to be an effective therapeutic agent. Increasing knowledge of the pathogenesis of this infection has confirmed oral vancomycin to be ideal in that it destroys *C. difficile* at low concentrations. It is also minimally absorbed, and therefore excreted in high levels in the faeces without significant metabolism. Numerous studies attest to its efficacy at doses of between 0.5 and 2.0 g per day for periods of seven to 14 days, leading to its widespread use in this condition.[1,2] However, the recent emergency of vancomycin-resistant enterococci (VREs), predominantly in the USA and with an apparent association with widespread use of parenteral and particularly oral vancomycin, has resulted in reconsideration of its place in treatment of *C. difficile*-associated diarrhoea. The US Hospital Infection Control Practices Advisory Committee for Prevention of the Spread of Vancomycin Resistance have discouraged the use of oral vancomycin in therapy for *C. difficile*-associated diarrhoea except for failure of metronidazole or severe potentially life threatening illness.[3]

Although VREs are not yet a problem in Australia, their appearance would herald a significant threat. Vancomycin usage in Australia would be difficult to curtail, given the endemic levels of methicillin-resistant *Staphylococcus aureus* in eastern state hospitals.

The following alternatives exist for the treatment of *C. difficile*-induced diarrhoea.

DISCONTINUATION OF THE OFFENDING DRUG

While this is a mandatory step in treatment, the initial question that must always be asked is whether 'specific therapy' is really needed. Most patients run a self-limiting course so that simply ceasing the initiating antibiotic may be sufficient.

ALTERNATIVE ANTIMICROBIAL AGENTS

Metronidazole

In controlled therapeutic trials metronidazole has been demonstrated effective with doses of 1.0-1.5 g per day in three or four divided doses.[4,5] It is available in Australia on PBS prescription and remains the most inexpensive treatment for *C. difficile*-associated diarrhoea, with over 95% efficacy and less than 10% relapse rate. However, metronidazole is, theoretically at least, highly absorbed from the upper gastrointestinal tract, unlike vanomycin. This leads to low faecal concentrations which may be even further diminished by the metabolic activity of faecal flora.

Bacitracin

Like vancomycin, bacitracin is active against *C. difficile* and is minimally absorbed from the gastrointestinal system. Clinical trials utilising 80-100,000 units per day in four divided doses have shown efficacy of greater than 80%, although with higher relapse rates than either vancomycin or metronidazole.[6,7] Although cheaper than oral vancomycin, it is not available on PBS prescription in Australia, only on formularies of a number of public hospitals. The disagreeable taste and propensity to induce nausea can be reduced by administering the agent in a capsule.

Other antimicrobials

A number of other antibiotics have useful activity against *C. difficile* in both primary and relapsing *C. difficile*-associated diarrhoea, including tetracycline,[8] teicoplanin,[9] fusidic acid [10] and rifampicin.[11] However, a role for these agents in routine practice cannot be recommended due to a number of considerations including the potential development of resistance, cost, availability and so on.

Parenteral therapy

It is preferable to treat with an oral agent where possible because of the lower cost, the pharmacokinetics and greater published experience. However, in certain patients unable to tolerate oral medication, parenteral therapy will be indicated. Metronidazole is drug of choice in this situation as excretion of drug from the inflammed colon results in bactericidal faecal concentration.[12] This is not the case with parental vancomycin where faecal levels have proved very poor.[13]

Anion-exchange resins

Cholestyramine and, to a lesser extent, colestipol are anion exchange resins which are entirely excreted in the stool, reversibly binding the toxins produced by *C. difficile*. Clinical studies have shown some efficacy when administered alone at 12-16 g in three or four divided doses.[14,15] As antibiotics and resin act by different mechanisms, it was hoped that the combination would be better than vancomycin alone, although this has not been proved in either clinical or animal studies. Administration of cholestyramine inactivates concurrently administered vancomycin as a result of intraluminal binding and leads to a significant loss of activity of both agents. Where it is felt there may be some advantage in giving both, it seems sensible to utilise maximum doses and to administer the two drugs separately. A routine role for anion exchange resins has not been established, although they may have a place in monotherapy of milder disease or as combination treatment in relapse.

Modification of colonic flora

Biotherapy is an alternative and logical approach to treatment of *C. difficile*-associated diarrhoea, given that the disease originates from a change in bowel flora. A number of therapies have been tried with limited success. These included administration of

lactobacilli,[16] faecal streptococci,[17] non-toxicogenic ***C. difficile***,[18] and natural and synthetic faecal enemata.[19,20] Most have been used primarily in relapsing infections, often in combination with conventional treatment.

More recently, the utilisation of ***Saccharomyces boulardii*** appears to show considerable promise. This years, originally isolated from lychees and a close relative of ***Saccharomyces cerevisiae***, survives exposure to gastric acid and colonises the colon so long as daily administration is continued, but is readily cleared when treatment is ceased. Clinical success in the treatment of ***C. difficile***-associated diarrhoea has been demonstrated in a number of studies of both primary cases and relapses,[21,22] either as monotherapy or in combination with a standard antibiotic. However, apart from two double-blind placebo-controlled studies,[23,24] most evidence supporting its use comes from small open therapeutic trials.

The yeast appears to reduce the pathogenicity of ***C. difficile*** through a specific mechanism, either by interfering with the production and elaboration of specific toxins[25] or by liberating a protease that disrupts receptors for the toxins.[26] Continuing studies are required to ensure that ***S. boulardii*** treatment does provide a definitive cure and not simply extend a period of symptom-free remission.

Anti-peristaltic therapy

Anti-peristaltic agents do not reduce the time to resolution of ***C. difficile*** diarrhoea. General consensus is that they should not be used; there is anecdotal evidence that diphenoxylate (Lomotil) may be deleterious to patients with ***C. difficile*** diarrhoea and may predispose them to toxic megacolin.[27] In theory, these agents, by slowing motility, might also lead to increased absorption of metronidazole, with lower faecal concentrations and therefore poorer outcomes of treatment.

Conclusion

After 20 years of clinical experience, specific guidelines for the treatment of ***C. difficile*** infection of the gastrointestinal tract have evolved. Oral metronidazole, which may be necessary after cessation of the precipitating agent, is now regarded as an effective and inexpensive therapy for primary infection. Bacitracin is an effective alternative. The optimal treatment of relapses remains to be defined but recent research suggests biotherapy with ***S boulardii***, either alone or in combination with antibiotics, may lead to superior outcomes. New and innovative approaches are needed in this common condition, with a protective vaccine remaining a tantalising possibility in the distant future.

References

1. Batts D H, Martin D, Holes R et al. Treatment of antibiotic associated Clostridium difficile diarrhoea with oral vancomycin. J Pediatr 1990; 97: 151-53.
2. Fekety R, Shah A B. Diagnosis and treatment of Clostridium difficile colitis. JAMA 1993: 269: 71-75.
3. Hospital Infection Control Practices Advisory Committee (HICPAC). Recommendations for preventing the spread of vancomycin resistance. Infect Control Hosp Epidemiol 1995: 16: 105-13.
4. Teasley D G, Gerding D N, Olson M M et al. Prospective randomised trial of metronidazole vs vancomycin for Clostridium difficile-associated diarrhoea and colitis. Lancet 1983; 11: 1043-46.
5. Olson M M, Shanholtzer M T, Lee J T, Gerding D N. Ten years of prospective Clostridium difficile-associated disease, surveillance and treatment at the Minneapolis VA Medical Centre 1982-1991. Infect Control Hosp Epidemiol.
6. Dudley M N, McLaughlin J C, Carrington G et al. Oral bacitracin vas vancomycin therapy for Clostridium difficile-induced diarrhoea: a randomised, double-find trial. Arch Intern Med 1986; 146: 1101-04.
7. Young G P, Ward T B, Bayley N et al. Antibiotic-associated colitis due to Clostridium difficile, double-blind comparison of vancomycin with bacitracin. Gastroenterology 1985; 89: 1038-45.
8. Bartlett J G. Antibiotic-associated colitis. Disease-A-Month 1984; 30: 1-55.
9. de Lalla F, Nicolin R, Ranaldi E et al. Prospective study of oral trecopolannin vs oral vancomycin for therapy of pseudomembranous colitis and Clostridium difficile-associated diarrhoea. Antimicrob Agents Chemother 1992: 35: 2192-96.
10. Cronberg S, Castor B, Thoren A. Fusidic acid for the treatment of antibiotic-associated colitis induced by
11. Buggy B P, Fekaty R, Silva J. Therapy of relapsing of Clostridium difficile-associated diarrhoea and colitis with the combination of vancomycin and rifampin. J Clin Gastroenterol 1987: 9: 155-50.
12. Bullon R P, Culshaw M A. Faecal metronidazole concentrations during oral intravenous therapy for antibiotic associated colitis due to Clostridium difficile. J Gut 1986: 27: 1169-72.
13. Kleinfield D I, Sharpe N G, Dorta S T. Parenteral therapy for antibiotic-associated pseudomembranous colitis. J Infect Dis 1988: 157: 389-93.
14. Kreutzer E W, Milligan F T. Treatment or antibiotic-associated pseudomembranous colitis with cholestyramine resin. Johns Hopkins Med J 1978: 143: 67-72.
15. Mogg G A G, Arabi, Youngs D et al. Therapeutic trials of antibiotic associated colitis. Scand J Infect Dis 1980: (Suppl 22): 41-45.
16. Gorbach S L, Chang T W, Goldine B. Successful treatment of relapsing Clostridium difficule colitis with Lacto-bacillus G G. Lancet 1987: ii. 1519.
17. Lewenstein A, Frigerio G, Moroni M. Biological properties of SF 68, a new approach for the treatment of diarrheal diseases. Curr Ther Res 1979: 26: 967-81.
18. Seal D, Borriello S P, Barclay F et al. Treatment of relapsing Clostridium difficile diarrhoea by administration of a non-toxogenic strain. Eur J Clin Microbiol 1987: 6: 51 53.
19. Tvede M, Rask-Madsen J. Bacteriotherapy for chronic relapsing Clostridium difficile diarrhoea in six patients. Lancet 1989, 1156-60.
20. Bowden T A, Mansberg A R, Lykins L E. Pseudomembranous enterocolitis, mechanism for restoring floral haemostasis. Am Surg 1981: 47: 178-83.
21. Kimmey M B, Elmer G W, Surawitz C M, McFarland L V. Prevention of further recurrences of Clostridium difficile colitis with Sacchammyces boularrdi. Digest Dis and Sci 1990: 35: 897-901.
22. Schellenberg D, Bonington, Champion C M et al. Treatment of Clostridium difficile diarrhoea with brewers yeast. Lancet 1004: 343: 171-72.
23. Ligny G. Le traitement par l'ultra-levure des troubles intestinaux secondaires a l'antibiotherapie: etude en double aveugle et etude clinique simple. Rev Francaise Gastroenterol 1975: 14: 15-60.
24. McFarland L V, Surawicz C M, Greenberg R N et al. A randomised placebo-controlled trial of Saccharomyces boulardii in combination with standard antibiotics for Clostridium difficile disease. JAMA 1991: 271: 1913-18.
25. Elmer G, McFarland L. Suppression by Saccharnmyes boulardii of toxogenic Clostridium difficile overgrowth after vancomycin treatment in hampsters. Antimicrob Agents Chemother 1987: 31: 129-31.
26. Pothoulakis C, Kelly C, Joshi M et al. Saccharomyces boulardii inhibits. Clostridium difficile toxin. A binding and enlerotoxity in rat iteum. Gastroenterol 1993: 104: 1108-15.
27. Cone J B, Wetzel W. Toxic megacolon secondary to pseudomembranous colitis. Dis Colon Rectum 1982: 25: 4/8-82.