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Is *clostridium difficile*-associated disease really changing?

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TITLE Relatively poor outcome after treatment of *clostridium difficile* colitis with metronidazole

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LIST OF ABBREVIATIONS *Clostridium difficile* (*C. difficile*)

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SUMMARY

This paper describes a study undertaken in response to a belief among some infectious diseases physicians that metronidazole is becoming less effective in the treatment of *C. difficile* colitis. This was a prospective observational study examining the rate of treatment failure and disease relapse in hospitalised patients given metronidazole for *C. difficile*-associated disease. Patients were included if they were symptomatic for *C. difficile* infection, had *C. difficile* toxin demonstrated in their faeces and received at least seven days of metronidazole treatment. During the eight-month period of the study there were 207 patients who qualified for inclusion. A cure was seen in 78% of patients while 22% were refractory to therapy. Fifty-eight (36%) of the 161 patients who responded to metronidazole suffered a recurrence of disease within 90 days of the original episode. The overall 90-day mortality was 27% and was higher in those who did not respond (33%) than in those who responded to metronidazole treatment (21%). The use of cefepime (a fourth generation cephalosporin) or parenteral vancomycin in the six weeks preceding a diagnosis of *C. difficile*-associated disease was significantly more likely to be associated with metronidazole treatment failure. For patients with refractory disease there was no difference in outcome comparing those who received prolonged metronidazole treatment (50% cured) with those given oral vancomycin (31% cured). The authors conclude that their data demonstrates the need for new treatments for *C. difficile* infection.

OPINION

The efficacy of metronidazole, in this study, is certainly less than might have been expected. Prospective studies from the 1980s and 1990s estimated response rates of 90–98%. Antibiotic susceptibility tests on *C. difficile* isolates were not undertaken here, so it is impossible to exclude metronidazole resistance as an explanation for the lack of clinical response. That said, *C. difficile* resistance to metronidazole is uncommon (around 6% of isolates in one large study in 2002) and is unlikely to be the full explanation for treatment failures. Some *C. difficile* strains implicated in recent hospital outbreaks have been identified as hyper-toxin producers that are less responsive to standard therapy. The severity of disease caused by such strains is greater with a higher case-fatality ratio but the authors here are clear that there were no outbreaks in their hospital during the eight months of their study. What then, should we take from this report? The study offers no clear evidence that we should change from metronidazole as first line therapy for *C. difficile*-associated disease. In poor responders, rates of cure did not differ between prolonged metronidazole and oral vancomycin. Importantly, metronidazole is cheaper than vancomycin and does not carry the risk of selecting out vancomycin-resistant bacteria. The likely explanation for most treatment failures with metronidazole is that we are dealing with increasingly debilitated patients who would fare little better with any other therapy – the high 90-day mortality reflects the severity of illness in the study group. We should be on the lookout for *C. difficile* outbreaks or metronidazole resistance in our hospitals but need to appreciate that existing treatments are becoming less effective even in the absence of these new threats.