Reduced susceptibility of *Clostridium difficile* to metronidazole

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Sir,

We report the first UK isolate of *Clostridium difficile* with reduced susceptibility to metronidazole in vitro. The isolate was recovered from the environment of a care for the elderly ward in Leeds, which was being surveyed as part of a longitudinal study of the molecular epidemiology of *C. difficile*. No similar isolate was recovered from any of the patients on this ward from whom diarrhoeal samples had been cultured for *C. difficile*. The origin of the isolate therefore remains obscure. It is notable, however, that the ward in question had only been converted (from a dining area for hospital staff) 3 months previously. *C. difficile* was not recovered from any environmental samples from this ward collected immediately prior to the ward opening, and therefore it is likely that the isolate originated from a patient. The isolate was examined at the PHLS Anaerobe Reference Unit (ARU) and gave no zone to a 5 μg metronidazole disc. By Etest, the MIC of metronidazole was 16 mg/L and it was typed as PCR ribotype 10, a non-toxigenic ribotype. Investigations for the *nim* genes associated with conferring resistance to metronidazole in *Bacteroides* species were negative.

Claims of metronidazole resistance in *C. difficile* have been reported rarely. Wong et al. recently reported that one of 100 *C. difficile* isolates was resistant to metronidazole (MIC 64 mg/L). Pelaez and colleagues reported apparent frequent resistance of *C. difficile* to metronidazole in Spain, particularly in isolates recovered from HIV-positive patients. Subsequently, the same group found that 9% of 469 clinically significant *C. difficile* isolates were resistant to metronidazole (MIC = 32 mg/L). Resistance to metronidazole was more common in isolates from patients with recurrences of *C. difficile* diarrhoea (14.5% versus 7.5%, *P* < 0.05), as was intermediate resistance to vancomycin (MIC 8–16 mg/L, 6% versus 1.5%, *P* < 0.05). However, these potentially important findings were reported in abstract form only, and require independent confirmation because of the problems associated with antimicrobial susceptibility testing of anaerobes. Notably, the PHLS ARU had not previously detected metronidazole resistance in any of over 1000 *C. difficile* isolates tested (unpublished data), and in a study of 50 random isolates the metronidazole MIC range was 0.094–1.5 mg/L. Finally, the MIC₅₀ and range of MICs for metronidazole for 105 equine *C. difficile* isolates were found to be 0.5, 16 and ≤0.25–32 mg/L, respectively.

The BSAC and NCCLS breakpoints for metronidazole are 8 and 16 mg/L, respectively, and therefore the isolate from Leeds may be classified as resistant or exactly on the breakpoint. Importantly, these breakpoint values do not necessarily reflect achievable faecal metronidazole concentrations. In healthy volunteers faecal metronidazole usually cannot be detected following oral administration. However, in patients with colonic disease therapeutic concentrations of metronidazole in faeces have been measured. In nine patients with *C. difficile* diarrhoea metronidazole concentrations were significantly higher in watery (9.3 ± 7.5 μg/g wet weight faeces, range 0.8–24.2) and in semi-formed stools (3.3 ± 3.6 μg/g, range 0.5–10.4) than in formed (1.23 ± 2.8 μg/g, range 0–10.2) faecal samples. Using these data, 96% (27/28) of samples had metronidazole concentrations below the MIC for the isolate reported here.

What are the implications of this finding? At this stage it is not known whether similar resistance will appear in toxigenic strains with obvious consequences for treatment. Nor is it certain whether similar examples have already gone unnoticed, particularly given the decreasing use of culture for the laboratory diagnosis of *C. difficile* infection. Interestingly, the ARU has recently examined three isolates from Paris that displayed similar levels of metronidazole resistance (MIC range 8–16 mg/L) and were also found to belong to PCR ribotype 10. In a study of 370 isolates of *C. difficile* from the community, *C. difficile* PCR ribotype 10 was the most common strain detected, most often from the stools of infants. From hospital adult in-patient stools, however, they represent only 1.4% of strains received at the ARU. Of the 30 PCR ribotype 10 *C. difficile* isolates identified to date by the ARU, all but the four isolates mentioned here were fully susceptible to metronidazole.

Vigilance is obviously required to ascertain whether
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toxigenic strains will acquire this resistance and thus compromise a cornerstone for treatment of C. difficile infection.

References


