remains the imperative if effective diagnostic stewardship, reduction in length of stay and potentially improved patient outcomes are to be achieved.

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None declared.

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Effectiveness of early use of fidaxomicin in preventing recurrence of *Clostridium difficile* infection

Sir,

We read with interest the manuscript by Biggs and colleagues [1].

We agree with the authors that fidaxomicin is optimally used for treatment of initial *Clostridium difficile* Infection (CDI), which is consistent with our previously reported findings [2]. Since fidaxomicin has a narrow spectrum of activity and allows reconstitution of indigenous gut flora, it is logical that the most beneficial effect is obtained before further collateral damage to the microbiome has struck.

This is supported by the findings of a randomized study comparing faecal microbiota transplantation (FMT) to fidaxomicin in 64 patients with multiply recurrent CDI [3]. This study recruited patients with average of four previous episodes of CDI, so it is perhaps unsurprising that FMT was significantly better than fidaxomicin in achieving clinical cure.

However, we disagree with the authors' proposal of reserving fidaxomicin for non-severe cases. Since 2012 at Guy's and St Thomas' NHS Foundation Trust we have administered fidaxomicin to all adult patients with CDI as a first-line therapy, including those with severe disease. To date we have treated over 600 patients, with excellent clinical outcomes as evidenced by a reduction in recurrence rates from 16% to 5% during this period. Extended-pulsed dosing of fidaxomicin has been shown to be superior to vancomycin for sustained clinical cure in addition to significantly reducing rates of recurrence. This novel dosing regimen reduces recurrence rates to 7% without incurring additional cost compared with standard dosing [4].

We have also observed a significant reduction in environmental contamination in rooms of patents with CDI who have been treated with fidaxomicin, compared to those treated with vancomycin and/or metronidazole (37% vs 58%, $P=0.02$) [5]. This is presumably due to sporicidal activity of fidaxomicin and possibly also related to reduced time to resolution of diarrhoea. This finding could have significant infection-prevention benefits, reducing in-hospital transmission and new infections.

This is likely to be a contributory factor in our organization having the lowest CDI rate in the Shelford group (of 10 leading academic English healthcare organizations), a position that has been held for the last four financial years. Our organization had a rate of 16.5 infections/100,000 occupied bed days (OBD) in 2017/18, half that of the next-best-performing Shelford group organization (the National rate during this time-period was 38.3 infections/100,000 OBD) [6].

Biggs and colleagues incorrectly state that there are 'limited data on fidaxomicin and its effect/usefulness in the treatment of rCDI and severe CDI'. In fact, the two large

multicentre, international registration studies included 102 (17.1%) and 235 (39%) patients with rCDI and 76 (15.9%) and 124 (24.4%) patients with severe CDI, respectively [7,8], significantly in excess of their own uncontrolled observations in only 38 patients. Several other studies have included patients with severe, fulminant and/or life-threatening CDI and report good outcomes in fidaxomicin-treated patients [2,4,9,10].

Furthermore, their reported rates of recurrence following a first episode (35.7% and 66.6% for mild and severe cases, respectively) appear to be significantly in excess of those reported by most other authors. This is an outlier compared to the usual reported figures of 20–30% recurrence in patients treated with metronidazole or vancomycin and even more extraordinary for patients treated with fidaxomicin. The authors provide no explanation as to why their rates are so startlingly high, presumably recurrence rates for vancomycin are even higher?

Their observations suggest either selection bias (it is unclear how patients were selected to receive fidaxomicin and we note that only 38 patients (13%) received fidaxomicin), unusual epidemiology with an endemic strain more likely to cause recurrence, or an issue with the definition of recurrence and/or laboratory testing methods.

The authors state recurrence was defined on the basis of clinical symptoms and laboratory testing using glutamate dehydrogenase and a nucleic acid amplification test (NAAT). However, it is well known that diagnosis based on NAAT cannot differentiate infection from colonization. Given that diarrhoea is relatively common in hospitalized patients, and the fact that post-infectious 'irritable bowel' syndrome is frequently experienced by patients following treatment for CDI, it is possible that recurrent CDI has been over-diagnosed Biggs *et al*.

Additionally, no data is presented on the number of prior episodes in their patient group with rCDI. Clearly, it would be unrealistic to expect fidaxomicin to prevent further recurrence in patients who have had multiple episodes; FMT would be the most appropriate therapy for this group.

These concerns raise doubt over the validity of the authors' data. Our experience and that of several others suggest that fidaxomicin is effective in both severe and non-severe episodes. Furthermore, given that severe disease is itself a recognized risk factor for rCDI, these are exactly the group of patients who should be targeted to receive fidaxomicin. We agree that there is limited value in using this treatment for patients who have had multiple (e.g., three or more) episodes where FMT may be more appropriate.

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