P0797

Efficacy of tapered fidaxomicin dosing regimens to treat simulated *Clostridium difficile* infection (CDI) in an *in vitro* gut model

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Introduction

Clostridium difficile infection (CDI) is a major burden on healthcare facilities worldwide.[1,2] Recurrence occurs in ~20% of cases.[3] Fidaxomicin is an effective treatment for CDI, associated with reduced rates of recurrence compared with vancomycin.[4] We have observed persistence of active fidaxomicin in an in vitro gut model, which may prevent recrudescence of *C. difficile* spores, reducing recurrence.[5] Modified fidaxomicin dosing may have the potential to reduce recurrence rates still further.

We have now investigated whether tapered dosing regimens can be used to treat simulated CDI in a gut model, and the effects of these regimens on gut microflora, *C. difficile* and antimicrobial persistence.

Methods

Two validated gut models were run in parallel. Models were inoculated with pooled faecal emulsion from healthy volunteers (n=5, age >60yrs). Once gut microbiota populations stabilised, models were spiked with 10^7 cfu PCR ribotype 027 *C. difficile* spores, and simulated CDI was induced by clindamycin instillation (33.9mg/L, QDS, 7days). Once high level toxin production was observed, fidaxomicin treatment commenced.

Model A was instilled with 200mg/L fidaxomicin BID for 5 days, followed by five days rest then 200mg/L fidaxomicin once daily for a further 10 days. Model B was instilled with 200mg/L fidaxomicin BID for 5 days followed by a single 200mg/L fidaxomicin dose every other day for 20 days. The models were left without further intervention for 21 days post-treatment.

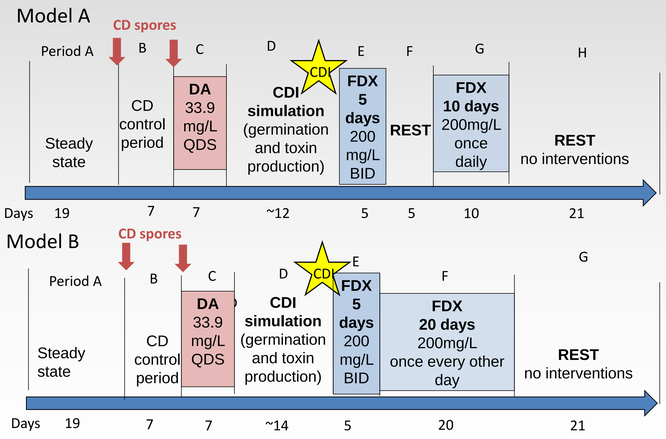

Figure 1. Experimental design of the two models
DA = clindamycin, FDX = fidaxomicin

Results

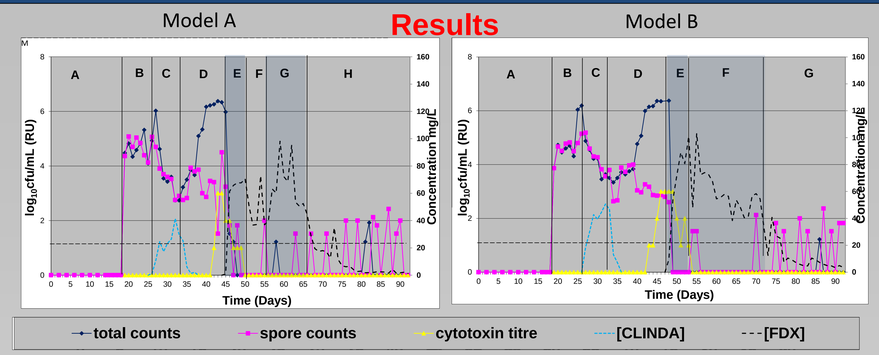

Figure 2. Mean *C. difficile* PCR ribotype 027 total viable counts and spore counts (log_{10} cfu/mL), cytotoxin titres (relative units, RU), and antimicrobial concentration (mg/L) in vessel 3 of Model A and Model B. Horizontal dotted line indicates the limit of detection

Both dosing regimens rapidly (<3 days) reduced *C. difficile* viable counts (~6 log_{10} cfu/mL), spore counts (~4 log_{10} cfu/mL) and toxin titres (3 RU) to below the level of detection. Vegetative cells and toxin remained below the level of detection for the remainder of the experiment. Spores were detected sporadically, at the limit of detection, in all three vessels of model A, but only intermittently from vessel 3 in model B. Fidaxomicin concentrations peaked at ~100mg/L in both models. Persistence of fidaxomicin activity was slightly greater in model B (5mg/L) than model A (2-5 mg/L), and remained at supra-MIC (0.25mg/L) level for the duration of the experiment in both models.

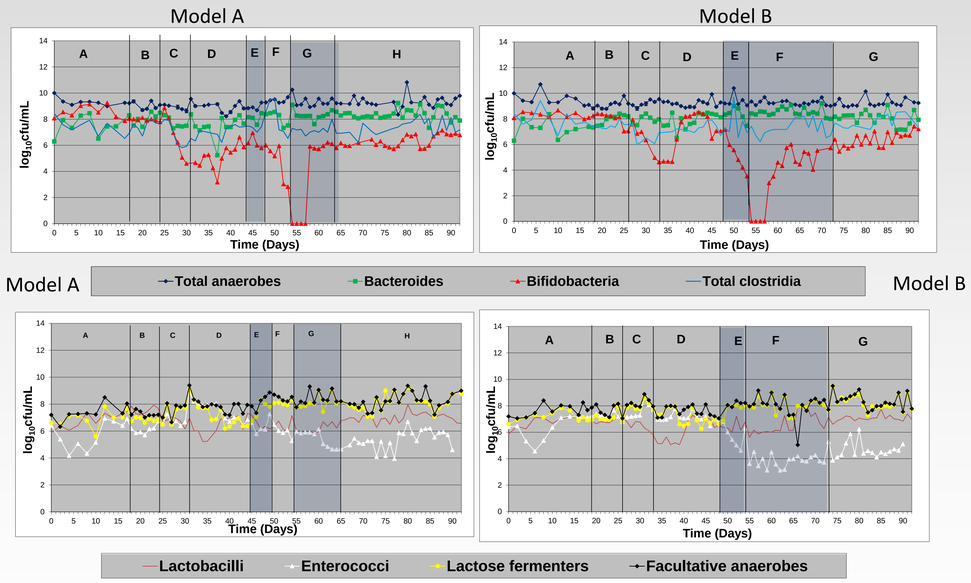

Figure 3. Mean obligate and facultative anaerobic gut microflora populations (log_{10} cfu/mL), in vessel 3 of Model A and Model B

The effects of both fidaxomicin dosing regimens on gut microflora were similarly limited, with declines in enterococci (2-5 log_{10} cfu/mL) and bifidobacteria (6-8 log_{10} cfu/mL to limit of detection). Bifidobacteria populations recovered to close to pre-fidaxomicin levels in both models by the end of the experiment.

Discussion

- Both dosing regimens rapidly reduced *C. difficile* counts to below the level of detection
- Spores continued to be detected sporadically, but no signs of recurrence of vegetative growth or toxin production were observed
- Resolution of CDI was comparable with previously investigated dosing regimens
- Effects of fidaxomicin on gut microflora populations were modest, with only bifidobacteria and enterococci populations declining.
- Although bifidobacteria declined to below the level of detection, they recovered to near pre-instillation counts.
- Effects of fidaxomicin on bifidobacteria levels in previous models have varied, likely due to variation in the composition of bifidobacteria species in the faecal samples of volunteers.
- Persistence of fidaxomicin at supra MIC level was noted (2-5 mg/L) but to a lesser extent than seen with some previous fidaxomicin dosing regimens (20 mg/L).
- Persistence of antimicrobial may prevent recrudescence of CDI spores for longer,, whilst allowing recovery of gut microflora and hence the recovery of 'colonisation resistance'

Conclusions

Both evaluated fidaxomicin tapered dosing regimens were effective for rapid resolution of simulated CDI in an in vitro gut model, and were comparable to previously evaluated standard and pulsed dosing regimens.

Persistence of antimicrobial activity and some suppression of *C. difficile* spore recovery was observed.

Tapered dosing regimens may (without necessitating increased numbers of doses) help to suppress *C. difficile* spore germination for longer periods of time than standard dosing regimens, whilst allowing recovery of the indigenous gut microflora.

References

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