Going forward, more randomised controlled trials, modelled on the trial by Ibrahim and colleagues, are needed to test whether early initiation of OPAT can be used in lieu of immediate hospitalisation for other childhood infections. Other important targets for antimicrobial stewardship research broadly include testing the premise that less is more. This research includes studying the safety and efficacy of early initiation of oral therapy in place of intravenous therapy, even for hospitalised patients. Additionally, it will be important to test outcomes of shorter versus traditional treatment durations for common infections such as pneumonia and urinary tract infections.

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A solution to the problem of antibiotic induced collateral damage to the gut microbiome

In their Article[1] in *The Lancet Infectious Diseases*, John Kokai-Kun and colleagues present new data from a phase 2 study of a promising drug for primary prevention of *Clostridium difficile* infection.

C difficile infection remains an important financial burden to most health-care systems.[2] Over the past 5 years, the reduction of disease recurrence has been facilitated by the availability of fidaxomicin and bezlotoxumab, and several other narrow-spectrum, microbiota-sparing drugs are in development.[3]

Late-stage clinical trials of vaccines are ongoing; however, there are currently no therapeutic strategies available to prevent primary *C difficile* infections, and thus novel preventative approaches are needed.[4]

The gut microbiome is said to function like a hidden or virtual organ, and it is fundamentally important in maintaining resistance against colonisation by *C difficile* and other potential pathogens, including multi-drug resistant Gram-negative organisms.[5,6]

The association between cephalosporins and other antibiotics and *C difficile* infection is well documented. A meta-analysis of six studies[7] showed that third-generation cephalosporins were among the highest risk class of antibiotics for development of *C difficile* infection, with an odds ratio of 3·2 (95% CI 1·8–5·71) relative to all other antibiotic classes that were studied. β-lactam drugs are one of the most commonly administered classes of antibiotics, making up 62% of all antibacterials that were prescribed for systemic use in the European Union-European Economic Area in 2017 (equivalent to 13·5 daily defined doses per 1000 inhabitants per day).[8] A considerable proportion of many β-lactam antibiotics are excreted in the bile and reach the intestine intact, particularly ceftriaxone, for which more than half of the intravenous dose is excreted through bile into the intestine.[9]

Recovery from the collateral damage caused by antimicrobials takes time, and some species might be lost entirely. Correction of underlying dysbiosis with faecal microbiota transplant is particularly efficacious, and it has shown a high clinical cure rate in patients


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who have had several episodes of *C difficile* infection.[10] However, the old maxim that prevention is better than cure is particularly germane in this case. Protecting the gut microbiota from the deleterious effect of antimicrobials initially, rather than seeking to restore it after the damage has been done, seems to be the most effective strategy.

Ribaxamase has a unique mechanism of action by inactivating antibiotics in the lumen of the gastrointestinal tract and preventing initial *C difficile* infection. This novel use of an orally administered β-lactamase enzyme degrades any concurrently administered residual intravenous antibiotic that enters the proximal gastrointestinal tract before it causes deleterious effects in the more distal colon.

The phase 2b study by Kokai-Kun and colleagues reports their findings in 412 patients over the age of 50 years in North America and eastern Europe who were administered ceftriaxone for a moderate or severe lower respiratory tract infection, half of whom received ribaxamase. Ribaxamase (150 mg twice a day) or similar placebo capsules were administered concurrently with the ceftriaxone and for 72 h after discontinuation of ceftriaxone for a median duration of ceftriaxone of 8 days in both groups. Kokai-Kun and colleagues found a lower incidence of *C difficile* infection of 1% in the group receiving ribaxamase, versus 3% in the group receiving placebo (risk reduction 2·4%, 95% CI −0·6 to 5·9; p=0·045).

Notably, they also found a significant reduction in new colonisation by vancomycin-resistant enterococci in ribaxamase-treated patients compared with those who received placebo. However, this finding was not replicated with regard to colonisation with extended-spectrum β-lactamase producing Gram-negative bacilli. The potential for ribaxamase to reduce colonisation by antibiotic-resistant organisms is certainly promising. Since the microbiota is associated with modulation of host immune, metabolic, neurological, and cardiovascular functions, it could also have broader, poorly understood effects.

Ribaxamase appears to be well tolerated and showed similar frequencies of adverse events to those in patients receiving placebo. This finding, and the claim that ribaxamase is not absorbed, is supported by no discernible effect of this drug on the plasma pharmacokinetics of intravenous ceftriaxone and no effect on the frequency of resolution of respiratory tract infections.[11,12]

Phase 3 studies are certainly warranted; however, it remains to be seen whether ribaxamase will be equally effective at reducing the risk of colonisation by pathogenic bacteria conferred by other β-lactams. Additionally, there is also the issue what to do with the intravenous to oral switch, which is a central tenet of good antimicrobial stewardship.

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