Antimicrobial stewardship: Comparative efficacy of antibiotics for *Clostridium difficile* infection

A meta-analysis considering the efficacy of antibiotics for adults with confirmed *C. difficile* infection found that for symptomatic cure, teicoplanin and fidaxomicin were better than vancomycin, and vancomycin was better than metronidazole. Public Health England is currently updating its guidance on the management and treatment of *C. difficile* infection and prevention through effective antimicrobial stewardship as recommended by NICE, is critical.

Overview and current advice

Use of broad-spectrum antibiotics is associated with an increased incidence of *C. difficile* infection. NICE guidance on antimicrobial stewardship recommends that antibiotics should be used only when indicated by the person's clinical condition, and their use should be reviewed after the results of microbiological testing or based on the sensitivities of causative bacteria where appropriate. Public Health England (PHE) report that between 2007/08 and 2012/13 rates of *C. difficile* infection fell rapidly and since 2013 have fluctuated around the same rate. Community-onset cases constitute 64% of all cases with rates of *C. difficile* infection highest in people aged 75 years or older.

The Department of Health and Social Care and PHE's report *C. difficile* infection: how to deal with the problem recommends that trusts should develop restrictive antibiotic guidelines that use narrow-spectrum agents alone or in combination as appropriate. Such guidelines should avoid recommending those antibiotics most commonly reported as being associated with *C. difficile* infection for example clindamycin and second and third generation cephalosporins and should also recommend minimising the use of quinolones, carbapenems and prolonged courses of aminopenicillins. PHE guidance on the management and treatment of *C. difficile* infection (currently being updated) recommends suitable treatment options. Oral metronidazole is the recommended antibiotic for non-severe *C. difficile* infection. For people with severe *C. difficile* infection, oral vancomycin is the first line antibiotic or alternatively consider oral fidaxomicin for people with multiple co-morbidities who are receiving concomitant antibiotics.

Appropriate use of antimicrobials is important to reduce the serious threat of antimicrobial resistance. NICE, in collaboration with PHE, is developing antimicrobial prescribing guidelines to help manage common infections and tackle antimicrobial resistance across all care settings. The NICE antimicrobial evidence summaries provide commissioners, providers and health professionals with a summary of the best available evidence for antimicrobials. The NICE Pathway: antimicrobial stewardship brings together all related NICE guidance and associated products on this topic in a set of interactive flowcharts. NICE has also published a key therapeutic topic antimicrobial stewardship: prescribing
New evidence

A systematic review and meta-analysis of 24 randomised controlled trials (RCTs) by Beinortas et al. 2018 investigated the comparative efficacy of antibiotics for *C. difficile* infection. The meta-analysis involved 5,361 adults with confirmed *C. difficile* infection. The mean age was 63 years and 53% of participants were female. Study follow-up time was typically between 21 to 30 days, with the exception of 2 RCTs which reported outcomes at 56 and 90 days (median 28 days).

The majority of studies investigated vancomycin (21 RCTs, n=2,107), metronidazole (7 RCTs, n=563) and fidaxomicin (6 RCTs, n=881). The final analysis include 13 different antibiotics, 5 of which are not currently available in the UK. The duration of treatment ranged from 4 to 25 days. All the included studies had an active comparator. Every antibiotic had at least 1 direct comparison with vancomycin. The primary outcome of interest was sustained symptomatic cure. Secondary outcomes included primary cure and recurrence rate.

In the final analysis, teicoplanin (odds ratio [OR] 0.37, 95% confidence intervals [CI] 0.14 to 0.94) and fidaxomicin (OR 0.67, 95% CI: 0.55 to 0.82) were significantly better than vancomycin for the primary outcome of sustained symptomatic cure. The authors reported that the overall consistency of the network meta-analysis for the primary outcome was good because there was no significant heterogeneity. However, the included teicoplanin trials were unblinded and the authors considered that confidence in the effects of teicoplanin was very low. Confidence in the treatment effect was only considered high for fidaxomicin. Vancomycin was better than metronidazole for symptomatic cure (OR: 0·73, 95% CI: 0·56 to 0·95). For the secondary outcome of primary cure, no treatment was significantly better than vancomycin. There were significantly fewer recurrences of infection with fidaxomicin compared with vancomycin and metronidazole. The authors reported significant heterogeneity for this outcome and stated that these results should be interpreted with caution.

This well-conducted review by Beinortas et al. is reportedly the first network meta-analysis comparing efficacy of different antibiotics for *C. difficile* infection and includes previously unpublished RCTs. The investigators did not identify any small trial or publication bias and sensitivity analyses only identified minimal changes in the results obtained from the overall network meta-analysis. The network meta-analysis also included antibiotics which are not available in some countries, resulting in more accurate estimates of treatment effect for the other antibiotics, including those generally used in clinical practice in the UK. A number of limitations with the review were identified by the authors. PHE guidance on managing and treating *C. difficile* infection recommends treatment options based on disease severity. However, in this review few of the included RCTs reported relevant data on disease severity and no consistent *C. difficile* infection severity assessment was used. The authors reported that results of subgroup analyses considering disease severity are therefore “less reliable”.

Commentary

Commentary provided by Professor Peter Wilson, Consultant Microbiologist, University College London Hospital, London UK

The meta-analysis of Beinortas et al. 2018 addresses a common problem in clinical practice, namely which treatment for *C. difficile* is likely to be most effective at reducing symptoms such as debilitating diarrhoea, as quickly as possible. Unfortunately the review does not enable clear recommendations to be made, related to choice according to severity of infection, duration of treatment or the appropriate management of recurrence. The review included over 5000 participants in 24 RCTs. Despite most trials being sponsored by manufacturers and quality at best being moderate, appropriate comparisons
were made and heterogeneity was low. Therefore the findings can be accepted with reasonable confidence.

Antimicrobial stewardship and infection control measures have resulted in considerable progress in reducing the incidence of C. difficile infection. Withdrawal of the antibiotic remains the best advice to relieve mild symptoms but, when antibiotic treatment is essential for concomitant infection or gastrointestinal symptoms are severe, existing national and European guidance relies on vancomycin or metronidazole. Fidaxomicin was significantly more effective than vancomycin in achieving sustained symptomatic cure. Recurrences were reduced with this antibiotic, although there was less confidence in the finding. The review did not undertake a cost benefit analysis, which could have helped determine whether it should be made first choice over vancomycin despite its higher acquisition cost. Currently metronidazole is the agent recommended for mild disease. While the review could not comment on efficacy by severity, vancomycin was significantly more effective than metronidazole and indeed metronidazole was ranked 11 out of the 13 antibiotics reviewed.

Teicoplanin is widely used for treatment of other Gram positive infections and various unblinded reports of its use for C. difficile infection have been published since 1989. The review by Beinortas et al. suggests it is more effective than vancomycin in symptomatic cure of C. difficile infection but higher quality studies are required before it could be recommended more widely. Ridinilazole appeared to be one of the most effective treatments but so far the number of participants treated remains low (ridinilazole does not currently have a UK or European marketing authorisation). None of the trials relating to probiotics, faecal microbiota transfer or immunotherapy met the inclusion criteria.

National recommendations by PHE are currently being reviewed and local formulary committees should take note of these when they are published. Key questions for this review by PHE are whether, despite its relatively high acquisition cost, fidaxomicin should be first line treatment of mild to moderate C. difficile infection or if oral vancomycin should now replace oral metronidazole as the standard treatment.

Declaration of interests:
Professor Peter Wilson has participated in advisory panels and lectures for MSD, Roche and 3M

Study sponsorship
None

References

About this Medicines Evidence Commentary
Medicines Evidence Commentaries form part of NICE’s Medicines Awareness Service and help contextualise important new evidence, highlighting areas that could signal a change in clinical practice. They do not constitute formal NICE guidance. The opinions of contributors do not necessarily reflect the views of NICE.