OPAT for avoidance of hospitalisation in children

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In an effort to combat antimicrobial overuse and resistance and improve patient outcomes, many paediatric hospitals have implemented antimicrobial stewardship programmes. The primary goal of these programmes is to ensure delivery of the appropriate antimicrobial at the right dose, via the preferred route, for the proper duration, at the right cost, and in the right environment. One area of increased focus for antimicrobial stewardship is outpatient parenteral antimicrobial therapy (OPAT).[1] OPAT is the administration of intravenous antimicrobials, often through a peripherally inserted central catheter, in the home environment. Compared with hospitalisation, OPAT reduces health-care costs and increases patient and caregiver satisfaction by accelerating return home.[2]

OPAT has traditionally been used to prevent prolonged hospitalisation in patients who continue to require intravenous antibiotics. Indeed, several studies have reported equivalent clinical outcomes for OPAT and prolonged hospitalisation for multiple types of infections.[1] However, few randomised controlled trials have compared clinical outcomes and safety of OPAT with those of prolonged hospitalisation in children. Furthermore, to date, no trial has examined the outcomes of initiation of OPAT in lieu of hospitalisation.

In *The Lancet Infectious Disease*, Laila Ibrahim and colleagues[3] describe a randomised, controlled, non-inferiority trial comparing the efficacy and safety of OPAT versus hospitalisation in children with cellulitis. The authors enrolled patients with moderate to severe cellulitis who were deemed to require intravenous antimicrobial treatment and would normally be hospitalised to start therapy. Patients were randomly assigned to receive flucloxacillin every 6 h in hospital or ceftriaxone once daily through a peripherally inserted intravenous cannula at home (OPAT group). Both groups received intravenous antimicrobials for about 2 days before transitioning to oral antibiotic therapy. In the per-protocol analysis, the OPAT group had significantly fewer treatment failures than did the hospitalised group (one [1%] of 89 children *vs* seven [8%] of 91 children; risk difference −6·5%, 95% CI −12·4 to −0·7). The OPAT group also experienced significantly fewer adverse events, such as rash, diarrhoea, and vomiting, than did the hospitalised group (two [2%] *vs* ten [11%]; p=0·048). Several secondary outcomes also favoured OPAT, including length of stay in the emergency department, containment of cellulitis spread within 24 h, and caregiver or parent satisfaction. Overall, these data suggest that OPAT can be used safely and effectively in lieu of hospitalisation to treat cellulitis in children requiring intravenous antibiotic therapy.

One potential limitation of this study is the use of different antimicrobials for the two groups. Differences between ceftriaxone and flucloxacillin in effectiveness against common pathogens causing cellulitis, burden of administration, and side-effects have the potential to contribute to differences in clinical outcomes. Although these are important considerations, the study design ensured both best practice and translatability to real-world scenarios. For example, the use of ceftriaxone in the OPAT group was a strategic choice: it is inexpensive compared with other intravenous antibiotics and administered only once per day, which maximises feasibility and adherence in the home environment. Moreover, the use of peripheral intravenous cannulas instead of peripherally inserted central catheters probably decreased costs and catheter-associated complications in the OPAT group.

Although OPAT has several benefits compared with hospitalisation, the burden of OPAT is still substantial for both patients and caregivers, especially compared with oral therapy.[5] A growing body of evidence suggests that intravenous antibiotics are overused in place of equally effective oral therapy across a variety of serious infections in children that might require hospitalisation.[6–9] In fact, a randomised controlled trial showed that conversion to highly bioavailable oral antibiotic therapy was non-inferior to continued intravenous antibiotics in the treatment of selected adult patients with endocarditis,[10] a condition often considered to be treatable only with parenteral therapy. Continued emphasis on using oral therapy whenever possible is important because oral antimicrobial therapy is associated with decreased costs and burden on caregivers compared with intravenous therapy.[5]

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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