NICE National Institute for Health and Care Excellence

Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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Bone and joint infections: are oral antibiotics safe and effective compared with intravenous antibiotics?

A UK multicentre trial including 1,054 adults with acute or chronic bone or joint infections found that using oral antibiotics in the first 6 weeks of treatment did not increase the risk of treatment failure within 1 year, compared with using intravenous antibiotics. People in the intravenous group experienced more intravenous catheter complications and had longer hospital stays than people in the oral group. There was no significant difference between the groups in the incidence of *Clostridium difficile* diarrhoea or the percentage of participants reporting serious adverse events. The potential for a difference in the longer-term outcomes of the two groups beyond the 1-year study duration warrants further work.

Overview and current advice

Bone and joint infections are usually treated with a prolonged course of intravenous antibiotics. However, intravenous therapy can be associated with risks, can be inconvenient for the person receiving it and is often more costly than oral treatment (Li et al. 2019).

A Cochrane review (Conterno and Turchi, 2013) investigated the effects of different systemic antibiotic treatment regimens for treating chronic osteomyelitis in adults. The review found that there was no difference in the rate of disease remission between oral and parenteral antibiotics if the bacteria are susceptible to the antibiotic used. However, the findings were based on limited and low-quality evidence. Many of the included studies were more than 20 years old, and currently there is a far higher prevalence of bacteria that are resistant to many of the available antibiotics. Bacterial resistance represents another challenge in the choice of antibiotics for treating chronic osteomyelitis.

The NICE guideline on antimicrobial stewardship recommends that where intravenous antimicrobials are required, prescriptions should be reviewed at 48 to 72 hours in all health and care settings. Response to treatment and microbiological results should be included in the review, to determine if the antimicrobial needs to be continued and, if so, whether it can be switched to an oral antimicrobial.

New evidence

An open-label, multicentre, randomised controlled trial (RCT) investigated whether oral antibiotics were non-inferior to intravenous antibiotics for treating complex bone and joint infections (Li et al. 2019).

The RCT included 1,054 adults from 26 UK sites with acute or chronic bone or joint infections including:

- osteomyelitis of the extra-axial skeleton
- joint infection requiring excision arthroplasty
- prosthetic joint infection
- orthopaedic fixation-device infection
- vertebral osteomyelitis with or without associated discitis or soft-tissue infection.

Nearly two-thirds (60.6%) of participants had infections that were related to prosthetic joint implants or orthopaedic devices. Few participants (7.6%) were treated for their infection without surgery.

Participants were randomised 1:1 to receive either oral or intravenous antibiotics to complete the first 6 weeks of treatment for their infection. Randomised treatment began within 7 days of surgical intervention for the infection or, if the infection was being managed without surgery, from the start of antibiotic therapy for that clinical episode. The study did not use a standard antibiotic regimen. The choice of antibiotic was determined by infection specialists and was based on factors including local epidemiology, antimicrobial susceptibility, bioavailability, previous infections, contraindications, allergies and drug interactions. Up to 5 consecutive days of intravenous antibiotics for unrelated intercurrent infections were allowed in the oral group. Adjunctive oral antibiotics were allowed in the intravenous group, and rifampicin could be added to treatment in either group at any time after randomisation, at the infection specialists' discretion. Follow-on antibiotics after the randomised treatment phase were allowed in both groups and 76.7% of participants continued antibiotics beyond 6 weeks. The median duration of antibiotic therapy was 78 days in the intravenous group, and 71 days in the oral group.

Definite treatment failure (defined according to clinical, microbiological or histological criteria) within 1 year after randomisation (the primary outcome) occurred in 13.2% (67/509) of people in the oral group and 14.6% (74/506) of people in the intravenous group. The difference in risk between the oral and intravenous groups in the intention-to-treat population was −1.4% (90% confidence interval [CI] −4.9% to 2.2%). Oral treatment was shown to be non-inferior to intravenous treatment because the upper limit of the 90% CI was within the prespecified margin of 7.5%. Sensitivity analyses in the modified intention-to-treat and per-protocol populations were consistent with the main findings.

More people in the intravenous group discontinued their treatment early compared with the oral group (18.9% compared with 12.8%, p=0.006), and intravenous catheter complications were more common in the intravenous group compared with the oral group (9.4% of people compared with 1.0%, p<0.001). However, there was no significant difference between the intravenous and oral groups in the incidence of *Clostridium difficile* diarrhoea (1.7% compared with 1.0%, p=0.30) or the percentage of participants reporting 1 or more serious adverse events (27.7% compared with 26.2%, p=0.58). The median length of hospital stay was significantly longer in the intravenous group compared with the oral group (14 days compared with 11 days, p<0.001).

Commentary

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Antibiotic therapy, with or without surgical debridement, is the mainstay of treatment for clinically important orthopaedic infections. Antibiotics are generally given intravenously, with many UK trusts recommending a 4 to 6-week course, guided by individual case-by-case microbiology advice. Intravenous antibiotic therapy can be more inconvenient and costly than oral antibiotics and carries with it the associated risks of cannula use and a potentially longer hospital stay.

The evidence for the use of oral over intravenous therapy is limited and largely based on the documented difficulty of achieving the required concentration in the bone or spine of certain antibiotics, for example, flucloxacillin and erythromycin.

The paper by Li et al. lends support to using oral antibiotics, having found oral therapy to be non-inferior to intravenous therapy when used during the first 6 weeks for complex orthopaedic infection. Using oral therapy in these situations will likely improve patient reported experience and is potentially cost-saving for the NHS. However, it is worth noting that these findings were based on treatment failure at 1 year. Therefore, they may not fully reflect the longer-term implications to the patient, as some complex orthopaedic infections are known to have quiescent periods of several years. The potential for a difference in the longer-term outcomes of the two groups must therefore be considered and warrants further work.

Giving consideration to switching from intravenous to oral antibiotics after 48 to 72 hours is a general antimicrobial stewardship measure recommended in Public Health England's 'Start smart - then focus' antimicrobial stewardship toolkit for English hospitals, and NICE's guideline on antimicrobial stewardship.

Going forward, while cases must continue to be considered on an individual basis and managed with a multi-disciplinary approach (between surgeons, microbiologists and specialist pharmacists), clarity in the form of further research and robust guidance on the ever-increasing challenge of complex orthopaedic infection management would be welcomed.

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Marieta Franklin declared no interests.
Nikhil Pradhan declared no interests.

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References

Li H-K, Rombach I, Zambellas R et al. (2019) Oral versus intravenous antibiotics for bone and joint infection. New England Journal of Medicine 380: 425−36
Conterno LO and Turchi MD (2013) Antibiotics for treating chronic osteomyelitis in adults. Cochrane Database of Systematic Reviews 2013, Issue 9. Art. No.: CD004439. DOI: 10.1002/14651858.CD004439.pub3.

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