■ ANNOTATION

The length of antibiotic treatment in patients with periprosthetic joint infection

BALANCING EVIDENCE AND EXPERIENCE

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Periprosthetic joint infection (PJI) remains a severe complication after arthroplasty, with rates expected to rise given the ageing population and their increasing rates of comorbidity. Management is challenging due to the interplay between surgical strategies, antibiotic treatment, and patient-specific factors. Traditionally, prolonged courses of antibiotics were used; however, extending therapy may not improve outcomes, and raises risks such as toxicity and antimicrobial resistance. Recent evidence suggests that shorter antibiotic regimens and early transition to oral antibiotics can be equally effective in some circumstances. For patients managed with debridement, antibiotics, and implant retention, a six- to eight-week systemic course of antibiotics may be sufficient when combined with thorough debridement and the use of biofilm-active agents. In two-stage revision, the use of antibiotic-loaded cement spacers permits even shorter lengths of antibiotic treatment, while single-stage revisions may also require shorter regimens under favourable conditions. Early transition to oral antibiotics can also be equally effective compared with prolonged intravenous therapy across all surgical procedures with advantages for patients and healthcare systems. Despite these promising findings, the heterogeneity of studies (including variable definitions of infection and outcome, small sample sizes and diverse surgical techniques) limits the generalizability of the results. Further high-quality, standardized research is required to determine the optimal length of antibiotic treatment in different surgical strategies. Meanwhile, a multidisciplinary approach which carefully balances the efficacy of antibiotic treatment with potential risks is essential for improving outcomes in these patients. The aim of this annotation was to review the current literature dealing with the length of antibiotic treatment in the management of PJI, and to consider the avenues that should be investigated in the future.

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Introduction

Periprosthetic joint infection (PJI) represents a devastating complication following arthroplasty. The incidence is reported to be between 0.79% to 2.0% for hip and knee arthroplasty,[1,2] and is higher after complex primary, revision, and oncological arthroplasties.[3–5] With the ageing population, increasing rates of comorbidity such as obesity and diabetes, and a continuing increase in the number of arthroplasties being performed, it can be expected that the burden of PJI will continue to increase.[6,7] Management decisions are often challenging due to the varying patient, implant, and organism factors involved. The resulting complex interplay between surgical intervention, antimicrobial therapy, and host issues necessitates collaboration in a multidisciplinary team setting to improve outcomes.[8,9] Despite extensive research, many aspects of the treatment of PJI, such as the length of antibiotic treatment which is required, remain poorly understood.

While surgical intervention is an essential component of PJI management, antibiotics significantly augment infection control by reducing bacterial load and preventing systemic spread. Historically, long postoperative courses of antibiotics, often of greater than three months, have been used.[10] However, there is a point at which extending antibiotic treatment no longer improves the rate of successful treatment but becomes counterproductive. Adverse reactions, patients' comfort, cost and length of stay (LOS) in hospital, and the rise in antibiotic resistance must all be considered.[11–13] In the Prosthetic joint Infection in Australia and New Zealand, Observational (PIANO) study,[14] at least one adverse

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event occurred with parenteral antibiotic treatment in 18.2% of patients, resulting in a change of therapy in 104 patients. Antibiotic resistance is rapidly becoming a global crisis, with recent data published in *The Lancet* suggesting that approximately five million deaths worldwide were attributable to this issue in 2019.[15] This number has been projected to rise and outstrip cancer as a cause of death by 2050.[16] Such considerations have led to many investigators to evaluate the outcomes of both short and long courses of antibiotics. The summation of the available evidence in four recent meta-analyses has been supportive of short courses.[17–20] However, the largest randomized controlled trial (RCT) dealing with this issue offers conflicting evidence.[13] The combination of many heterogenous, small studies into a meta-analysis must also be considered when interpreting their findings. As differing surgical strategies including debridement and implant retention (DAIR), single- and two-stage exchange arthroplasty are often grouped in these studies, further caution must be exercised when applying their conclusions to clinical practice.

In order to identify relevant articles, a PubMed search was conducted using the keywords 'antibiotic duration', 'antibiotic length', 'antimicrobial duration', 'antimicrobial length', 'periprosthetic joint infection', 'prosthetic joint infection', and 'arthroplasty infection'. After screening abstracts, studies which involved the evaluation of the impact of length of the course of antimibiotics on clinical outcomes were selected. A manual review of the reference lists from these studies was then performed. Exclusion criteria included studies involving antibiotic prophylaxis, investigations of fungal infections, research involving orthopaedic hardware other than arthroplasties, and non-English-language publications. Included studies were those deemed most relevant by the authors.

DAIR

When compared with staged revision arthroplasty, DAIR offers the advantage of reducing surgical morbidity and maintaining joint function, when used in appropriately selected patients.[21] The evolution of the length of antibiotic treatment in these patients reflects a shift from traditional recommendation of four to six weeks of intravenous treatment, often followed by a long period of oral treatment, towards shorter courses.[10,22] A RCT from Zimmerli et al[23] in 1998 started this process by supporting regimens of three and six months for patients with staphylococcal infections involving the hip and knee, respectively. Whether this course could safely be shortened to six or eight weeks has been subsequently investigated in several case series, observational studies, and RCTs.

Bernard et al[24] conducted a prospective trial of six weeks versus 12 weeks of antibiotics and identified no improvement in the success of treatment with longer courses. However, this study included a combination of DAIR, exchange or excision arthroplasty and fusion, with lower rates of success in the DAIR group. These authors also conducted a multicentre retrospective study involving PJI of the hip or knee in 87 patients who underwent DAIR, and again found no benefit of the longer courses of antibiotics.[25] Finally, Bernard et al[13] conducted the Duration of Antibiotic Treatment in Prosthetic Joint Infection (DAPITO) trial, a multicentre, noninferiority RCT comparing six with 12 weeks of postoperative antibiotics. This included 410 patients who underwent DAIR, single-stage, and two-stage revision arthroplasty. There was persistent infection in 18.1% of patients in the six-week group and 9.4% in the 12-week group. Most of the failures of treatment in the six-week group were in the DAIR group. The difference was less marked in single- or two-stage revision, highlighting implant removal as a critical factor influencing the outcome of treatment.

A further multicentre RCT was undertaken by Lora-Tamayo et al,[26] comparing an eight-week regimen of levofloxacin plus rifampicin with three- or six-month courses in the treatment of staphylococcal PJIs of the hip and knee, respectively, using DAIR. The shorter regimen was found to be noninferior in terms of the rate of clinical cure; however, there are caveats to note. Firstly, the study was underpowered, which may explain the higher rates of polymicrobial infections in the long-course group. Patients deemed to be at high risk of early failure were also excluded, introducing a selection bias, and the need for supplementary DAIR was not considered to be a failure.

The role of suppressive antibiotic therapy (SAT) following DAIR has also been investigated. In a multicentre retrospective review of 510 patients treated using DAIR,[27] treatment failure occurred in 39 of 167 patients (23.3%) who received SAT, compared with 27 of 343 patients (7.9%) who did not receive SAT, indicating no significant benefit. In the sub-group analysis, the patients least likely to benefit from SAT were those without high-risk features, specifically *Staphylococcus aureus* infection, PJI of the knee, late-acute infection, chronic kidney disease, revision arthroplasty, and a cemented arthroplasty. SAT is therefore best reserved for patients with limited surgical options, a recurrent infection, difficult-to-treat pathogens, or those receiving immunosuppressive treatment.[28]

Ultimately, based on the available evidence, selected patients being treated with DAIR could be managed with course of antibiotics for less than three months. However, six weeks should be a minimum, and consideration should be given to other risk factors for the failure of treatment.[29] Finally, the importance of patient selection and surgical principles, including adequate debridement and exchange of modular components, must not be forgotten.

Single-stage revision

Single-stage revision arthroplasty is growing in popularity, particularly given the higher rates of patient satisfaction and lower healthcare costs compared with two-stage exchange.[30,31] However, evidence is still emerging as to the optimal length of antibiotic treatment for these patients, as uptake of this approach has not been as widespread as DAIR or two-stage revision. The 2012 guidelines from the Infectious Diseases Society of America recommended two to six weeks of intravenous (IV) antibiotics followed by three months of oral suppression, ideally with a biofilm active agent for patient undergoing a single-stage revision.[7] In contrast, the Endo-Klinik reported on their extensive single stage revision experience using a ten- to 14-day IV course only, with reinfection rates of 15%.[32] The authors noted that their approach included a radical debridement, exceeding that commonly seen in a two-stage approach, which must be considered if adopting shorter courses. The length of antibiotic

treatment in single-stage revision was recently considered in a systematic review using three separate groups: 1) short IV treatment (< 2 weeks), 2) short IV treatment plus oral treatment, and 3) long IV treatment (> six weeks).[33] Short IV plus oral treatment had the highest rate of successful treatment, particularly when combined with antibiotic loaded cement. However, when only considering studies with > five years of follow-up, there was no significant difference in the success rates between groups. As with other meta-analyses in PJI, the included studies were almost exclusively retrospective in design with small samples sizes, varied surgical procedures and antibiotics, and inconsistent reporting of outcome. The DAPITO trial,[13] which favoured 12 over six weeks of antibiotics, mainly involved patients treated with DAIR. The results for single-stage revision identified three failures of treatment in the six-week group, and two in the 12-week group, suggesting that prolonged courses may not be advantageous.

Overall, the weight of evidence leans towards supporting shorter IV courses, particularly when oral alternatives are available and combined local delivery.[34] This trend was seen in a recent systematic review,[35] in which a gradual reduction in the length of IV treatment following single-stage revision between 2000 and 2015, without any change in the rates of successful treatment which were reported. The topic of the length of IV antibiotic treatment was covered more broadly in the Oral Versus Intravenous Antibiotics for Bone and Joint Infection (OVIVA) trial,[36] in which patients treated for bone or joint infection at 26 UK centres were randomly assigned to receive either IV or oral antibiotics in the first six weeks of treatment. Treatment failed in 14.6% of patients in the IV group and 13.2% in the oral group. Early transition to oral antibiotics has advantages, including lower healthcare costs, greater patient comfort, and fewer complications related to IV therapy. However, compared with DAIR and two-stage revision arthroplasty, the evidence dealing with the length of antibiotic treatment following single-stage revision remains limited. As adoption of the single-stage approach has increased, high-quality studies are needed to define the optimal antibiotic regimen.

Two-stage revision

Two-stage revision arthroplasty remains the standard form of treatment for the management of PJI in many centres.[37] As with DAIR and single-stage revision, there has been a trend towards shorter courses of antibiotics following the first-stage, and the role of antibiotic-loaded spacers to deliver high local concentrations may help support this shift.[38] Promising outcomes with lengths of systemic antibiotic treatment between 24 hours and 14 days, when combined with local antibiotic treatment, have been reported in retrospective studies.[39,40] The use of local antibiotics was further supported in a prospective study by Cabrita et al[41] who compared two-stage revision arthroplasty of the hip with and without a vancomycin-loaded spacer. Infection control was significantly better in the antibiotic spacer group (89.1% vs 66.7%; $p < 0.05$) combined with improved functional outcomes. Accordingly, local antibiotic delivery is recommended in addition to systemic treatment in some guidelines.[7,42]

A recent systematic review reviewing nine studies on two-stage revision arthroplasty found no significant difference in the rates of infection control between prolonged (≥ four weeks) and shortened (≤ two weeks) courses of IV antibiotic treatment, with or without subsequent oral treatment.[43] The weighted mean rates of success were 90.0% for prolonged IV treatment, 91.9% for shortened IV treatment, and 96.1% for shortened IV treatment followed by oral antibiotics, with no significant differences between groups. As the authors noted, their study had limitations, including different definitions of infection, and the predominance of small retrospective studies introduced potential bias. Some patients also had previously undergone surgery, had a reinfection or died before follow-up, potentially affecting the rates of successful treatment.

In a further meta-analysis, Olearo et al[19] compared the outcomes of short and long courses of antibiotics in DAIR and single- or two-stage revision, with short treatment defined as four to 12 weeks. They found that shorter courses were not associated with a significantly higher risk of failure in any of the surgical procedure groups. It is important to note that the short duration of up to three months is the same period of time which was associated with a significantly higher raate of successful treatment in the DAPITO trial.[13] Interestingly, the authors also found that in observational studies published before 2015 (compared with those published after), there was a 52% lower risk of failure of treatment with shorter courses. The cause of this disparity is unclear, but may be related to shifting patient demographics, differing definitions of infection, or transparency in the reporting of outcomes. Ultimately, despite providing evidence supportive of shorter courses of antibiotics, the authors still advocate for a length of treatment of > 12 weeks despite the paucity of high-quality supporting evidence.

Another separate area in two-stage revision is the use of antibiotics following the second stage. Currently, no definitive guidelines exist. Many assume that the absence of positive cultures obtained at the time of the second stage confirms that the infection has been cleared, negating the need for further postoperative antibiotics.[44] However, two previous observational studies and one recent RCT showed that extended periods of oral antibiotics following the second stage improves the rate of success.[45–47] However, as most recurrent infections in these studies were caused by different pathogens, it is possible that further antibiotics treated new organisms rather than solely targetted residual infection. The RCT only included patients with negative culture at the time of the second stage, which may have introduced selection bias.[47] It also fell short of its intended sample size due to exclusions and loss to follow-up. The small sample size may explain the relative high reinfection rate of 29% for those who did not receive antibiotics. In the largest cohort study on this topic in the literature, Ryan et al[48] reviewed 444 two-stage revisions showing that a short course (≤ two weeks) of oral antibiotics following the second stage had the same effect as prolonged treatment in reducing reinfection rates at one year. The issue of drug resistance must also be considered. It has recently been shown that patients who receive extended prophylaxis after the second stage are far more likely to develop a subsequent further PJI with bacteria resistant to the agents which they were prescribed. Kelly et al[49] found that 67% of recurrent infections in an extended-therapy group had drug-resistant strains, compared with none in those

who did not continue to take antibiotics. Given the common practice of indefinite oral suppressive treatment in patients with recurrent PJI, this risks fostering resistant organisms which will interfere with future options for treatment. Similarly, PJI caused by *Candida* spp. is most frequently seen in patients who have undergone several revision procedures with prolonged courses of antibiotics.[50,51] Moreover, the prolonged use of antibiotics is associated with adverse systemic effects, including gastrointestinal and neurological disturbances, nephrotoxicity, and hepatotoxicity, which may affect tolerance and compliance.[52] Thus, widespread adoption of these antibiotic protocols must be approached with caution.

While the current evidence suggests that shortening systemic antibiotic regimens to < 12 weeks may be as effective as prolonged treatment in selected patients, this is largely based on retrospective observational studies, many of which have small sample sizes, potential treatment allocation bias, and differing definitions of infection. Further high-quality studies are required to determine optimal protocols of treatment. The use of local antibiotic strategies, such as antibiotic-impregnated spacers, remains a key adjunct in the management of patients with PJI and may allow the systemic use of antibiotics to be reduced.

Conclusion

Recent studies from a range of medical disciplines increasingly support the use of shorter courses of antibiotics.[53] Given this trend, in part driven by the need for general antibiotic stewardship and concerns regarding the rise of resistant organisms, it is natural that shorter courses have been investigated in studies of patients with PJI. Extended IV treatment is not only associated with increased costs, but also heightens the risk of adverse events, and it is therefore encouraging that trials such as OVIVA have shown that oral antibiotic regimens can be just as effective.[36] Most recently, the Short or Long Antibiotic Regimes in Orthopaedics (SOLARIO) randomized, multicentre study compared a short course (≤ seven days) with a prolonged course (≥ four weeks) of systemic antibiotics in patients who also received local antibiotic treatment.[54] Patients included those with a broad spectrum of musculoskeletal infections, including fracture-related infection, and PJI. Publication of the results is awaited.

Systematic reviews and meta-analyses comparing short with extended courses of antibiotics have shown similar rates of the control of infection.[17–19,33,43] However, variations in the definitions of infection, surgical techniques and antibiotic protocols complicate these comparisons. For PJI managed with DAIR, a six- or eight-week systemic course may be sufficient for some patients.[25,26] However, patient selection, thorough debridement with exchange of modular components, and the use of a biofilm-active agent all may help in achieving a successful outcome.[55] Similarly, shortened systemic courses may be used in single- and two-stage revision arthroplasty. However, consideration must be given to local antibiotic delivery, patient-related factors, and microbiology data to provide bespoke decision-making for each patient.

In general, observational studies lean toward supporting shorter courses, whereas RCTs support longer courses. This may simply reflect methodological differences between these designs of studies. In observational series, the clinician can tailor the length of antibiotic treatment to individual patient factors, such as soft-tissue compromise, comorbidities, immunosuppression, the infective organism, and the method of fixation of the implant, reserving prolonged treatment for patients with more complex presentations. Because these clinical judgments are not always captured in retrospective datasets, good outcomes with abbreviated regimens may be reported by selecting patients with a lower-risk of recurrent infection.[19] By contrast, RCTs enforce strict criteria and protocols, and patients are randomly allocated to different lengths of treatment regardless of the perceived complexity. For example, the DAPITO trial did not alter the length of antibiotic treatment, regardless of whether the patients were treated with DAIR or single- or two-stage revision.[13] In order mitigate this, future research should incorporate more detailed, prospective phenotyping of patients with PJI so that observational analyses can adjust for these confounders. Similarly, pragmatic RCTs stratified by complexity and host factors are needed to ensure that the findings translate to the great variety of clinical presentation in patients with PJI.

Ultimately, at present there is no one-size-fits-all approach to the antibiotic treatment of PJI. The heterogeneity of the patients, causative organisms, surgical techniques and local practices all contribute to complexity of the management. Future research must strive for comprehensive reporting, encompassing the functional state of the patients, the microbiology, and operating details to be of value. Using a core outcome set for PJI would assist in this regard.[56] Similarly, without consensus on what constitutes 'success', our ability to grade treatments remains fundamentally limited. Adopting a universally accepted (or, at a minimum, explicitly detailed) set of criteria for success would improve our ability to compare studies and strengthen the synthesis of evidence. Until then, a collaborative multidisciplinary team approach which balances evidence and expert opinion remains important, enabling nuanced decision-making which provides the best possible outcomes for these patients.

Take home message

- Recent evidence suggests that in periprosthetic joint infection, shorter systemic antibiotic courses, and early transition to oral therapy can be as effective as prolonged treatment.
- However, current studies are heterogeneous and limited, so decisions must be individualized within a multidisciplinary team while high-quality, standardized trials are pursued to define optimal durations across surgical strategies.

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