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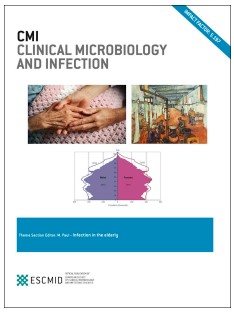

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PII: S1198-743X(23)00232-X

DOI: https://doi.org/10.1016/j.cmi.2023.05.008

Reference: CMI 3292

To appear in: *Clinical Microbiology and Infection*

Received Date: 12 February 2023

Revised Date: 25 April 2023

Accepted Date: 6 May 2023

Please cite this article as: Sendi P, Lora-Tamayo J, Cortes-Penfield NW, Uçkay I, Early switch from IV to oral antibiotic treatment in bone and joint infections, *Clinical Microbiology and Infection*, https://doi.org/10.1016/j.cmi.2023.05.008.

Theme Issue: Early Switch From IV to Orals in Infectious Diseases

Early Switch from IV to Oral Antibiotic Treatment in Bone and Joint Infections

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Word count: 169 in abstract, 2670 in main manuscript

Tables: 1

Figures: 0

References: 84 (maximum 60)

Supplementary material: None

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Background:

Objectives: The timing of the switch from intravenous (IV) to oral antibiotic therapy for orthopaedic bone and joint infections (BJI) is debated. In this narrative article, we discuss the evidence for and against an early switch in BJIs.

Sources: We performed a PubMed and Internet search investigating the association between the duration of IV treatment for BJI and remission of infection among adult orthopaedic patients.

Content: Among eight randomized-controlled trials and multiple retrospective studies, we failed to find any minimal duration of postsurgical IV therapy associated with clinical outcome. We did not find scientific data to support the prolonged use of IV therapy or to inform a minimal duration of IV therapy. Growing evidence supports the safety of an early switch to oral medications once the patient is clinically stable.

Implications: Following surgery for BJI, switch to oral antibiotics within a few days is reasonable in most cases. We recommend making the decision on the time point based on clinical criteria and in an interdisciplinary team at the bedside.

Keywords: Bone and joint infections; Osteomyelitis; Septic arthritis.

Introduction

In bone and joint infections (BJIs), traditional practice includes the administration of empiric intravenous (IV) antimicrobial agents following surgery [1]. Treatment is switched from empiric to targeted therapy once the causative microorganism is identified and, eventually, from IV to oral compounds. The best time for the switch from IV to oral therapy has been an ongoing debate for more than 50 years [2, 3]. Historically, there has been a transcontinental difference in this approach. Whereas institutions in the United States, the United Kingdom, and Australia typically considered a 6-week IV course as the gold standard [4], centres in Europe performed the switch from IV to oral antibiotics within 14 days after surgery [5]. Despite the OVIVA trial (published in 2019) [4], the discussion on this matter continues [6]. Some institutions favour IV only, others prefer a strict 6-week IV course prior to switching to orals [7, 8], and still others switch from IV to oral agents within a few days after surgery. In striking contrast to the management of BJIs in hospitalized patients undergoing surgery, initial oral antibiotic therapy is widely used by the majority of outpatient general practitioners for chronic osteoarticular infections. This is particularly true for (ischemic) diabetic foot osteomyelitis [9, 10].

"Early switch" in this narrative review refers to a time interval of ≤7 days from "definitive surgery" to the transition from IV to oral compounds, and definitive surgery refers to the final intervention for an infection episode (e.g., washout of a joint, debridement of bone) [4]. From a clinical practice point of view, the latter definition is important because the necessity of surgical intervention within the same hospitalization cannot be predicted after the first surgery (e.g., evacuation of haematoma 5 days after debridement).

In the first two sections, we review data underlying statements encountered in clinical practice that hinder the early switch from IV to oral antibiotics. We then present the data reviewed on this topic. Considering the numerous entities in BJIs, total antibiotic treatment duration and the subject of "suppressive" treatment concepts are beyond the scope of this

review. In addition, the list of possible oral antimicrobial agents (or a combination thereof) used to treat BJIs, including a discussion on bioavailability, is not an element of this review, as such lists have been published extensively elsewhere [1, 3, 6, 11-15].

Methods

In January 2023, we conducted a systematic review of the literature for studies comparing IV with oral antimicrobial therapy for BJIs. We searched PubMed by using the following keywords: *"osteomyelitis", "fracture-related infection", "arthritis", "septic arthritis", "bone infection", "joint infection", "periprosthetic joint infection", "septic surgery", "diabetic foot infection", "diabetic foot osteomyelitis", "oral", "bone penetration", "antibiotic bone concentration", "synovial fluid",* emphasizing on randomized controlled (RCT). References within these articles were evaluated to identify other relevant publications. Additional publications were identified and included manually. All types of articles were reviewed, including systematic reviews, retrospective and prospective studies, and case series.

How relevant is antimicrobial penetration into the target compartment?

One of the frequent arguments of orthopaedic surgeons and other physicians reluctant to make an early switch to oral antimicrobials – or more specifically, to a specific compound – is the belief that some antibiotics have the ability to penetrate well into the bone (e.g., fluoroquinolones), whereas others do not (e.g., beta-lactams). There are certainly differences when one compound is compared with another [16, 17]. However, caution is required when interpreting data on antibiotic bone penetration. In these studies, the drug concentration is measured in sterile bone. The permeability of infected bone for antibiotics may be increased (at least in the early stages of osteomyelitis), especially in the cancellous bone [18, 19]. Also, infected bone has a different milieu (e.g., pH) than that of sterile bone, which in turn affects

the function of bone cells and the activity of antibiotics [20, 21]. Different time intervals between antibiotic administration and harvesting of bone are used in these studies, resulting in non-comparable bone:serum concentrations. The sample (cancellous versus cortical bone) and the sample preparation and drug determination methods (e.g., HPLC, bioassay) vary among studies. Finally, in most studies only a single dose is given to estimate the bone penetration of an antibiotic, which does not reflect the steady state concentrations achieved with multiple doses per day over several weeks or months. In other words, pharmacokinetic studies of antimicrobial bone penetration cannot be relied upon to predict the outcome of subsequent clinical studies [22]. For example, penicillin derivatives have the reputation of penetrating poorly into the bone [16]. However, in a retrospective cohort including 339 cases of diabetic foot osteomyelitis, amoxicillin/clavulanate was compared with other oral regimens, with a median total antibiotic duration after surgical debridement (including partial amputation) of 30 days and switch from IV to orals almost always performed within 7 days; in this study, amoxicillin/clavulanate led to 74% remission compared with 79% with other regimens (P=0.15) [9].

Antibiotic penetration into the joint and synovia is usually excellent [23-25]. A contemporary RCT supports the efficacy of initial or immediate (ie., median IV durations of 1-2 days) switch to oral therapy in native joint septic arthritis (64% hand infections), with an overall 98% rate of cure achieved across 154 cases given 2 or 4 weeks of antimicrobials [26] .

A more detailed review on clinical pharmacological considerations in an early switch from IV to oral antibiotic is published in this theme issue [27]. Data on penetration into the bone and joint compartment have not been investigated in a clinical context, and hence, are not an indisputable counterargument for switching early from IV to oral antibiotics.

Are adverse events of oral antimicrobials more frequent than those during an outpatient parenteral antibiotic therapy?

Physicians are reluctant to prescribe certain drugs for various reasons, including clinical experience (or dogmas within teaching institutions) on adverse events or warnings from health authorities. Within this complexity of perceptions and experience, there are also inter- and intracontinental differences. For example, clindamycin for BJIs in adults is not frequently used in the United States, because of the risk of antibiotic-associated diarrhoea (AAD) and *Clostridium difficile* infection [28, 29], whereas in Europe, clindamycin is a valuable option for BJIs [30-32]. Several studies have demonstrated that the risk of AAD with clindamycin alone may not be higher than that of other agents, including penicillins, cephalosporins, and fluoroquinolones [33, 34]. The risk is mainly increased when antibiotics are combined or given over a prolonged period [34-36]. However, the risk of *C. difficile* infection is rare when clindamycin is used in combination with rifampin [37].

Another example of institutional practices is the use of fluoroquinolones for BJIs. The United States Federal Drug Administration has issued multiple warnings about the risks of fluoroquinolone-associated adverse events, including tendon rupture, aortic aneurysm, and retinal detachment [38]. Although these adverse events are not negligible, they are rare. In several orthopaedic-infectious disease specialized institutions, fluoroquinolones are successfully administered for BJIs caused by Gram-negative organisms [39, 40] or (in combination with rifampin) for *Staphylococcus* spp. infection [30, 41-43]. Indeed, the use fluoroquinolones has been identified as an independent predictor of good clinical outcome in multiple studies of orthopaedic implant-associated infections [30, 40]. Thus, while health authority warnings about fluroquinolones may be reasonable to inform a preference for other antimicrobials for common and uncomplicated infections (e.g., nitrofurantoin rather than ciprofloxacin for acute simple cystitis; amoxicillin rather than levofloxacin for community-acquired pneumonia), they should not deter physicians from prescribing fluoroquinolones for BJI, in which they are one of the most evidence-based and efficacious regimens available.

These safety concerns are examples of why some institutions and clinicians are reluctant to make an early switch to oral treatment, preferring outpatient parenteral antibiotic therapy (OPAT). However, the proportion of adverse events is not lower when IV antibiotics are given in comparison to oral treatment. A prospective multicentre cohort study investigated factors associated with AAD and *C. difficile* infection in adult patients prescribed antibiotics. Those who received IV antibiotics were more likely to develop AAD than were patients who did not (adjusted odds ratio of 2.73, 95% confidence interval, 1.38-5.43) [44]. Moreover, IV vancomycin for 7 days or longer, a regimen frequently administered for BJIs, is independently associated with *C. difficile* infection [34]. In addition, the use of IV antibiotics does not overcome the need for monitoring adverse events [45], and also requires evaluation of drug-drug interactions (e.g., vancomycin: concomitant use of nephrotoxic agents such as cyclosporine, loop diuretics, nonsteroidal anti-inflammatory drugs).

Most studies report that 5%–10% of OPAT-related complications require readmission [45-51]. These additional hospitalizations and their attendant investigations (e.g., search for thrombosis) and interventions (e.g., change of central line) increase healthcare costs [52]. Although the rate of serious complications when using OPAT is low, the independence of patients in comparison to those receiving oral antimicrobial therapy is decreased. Examples related to this issue include missed hours at work or school, greater time spent administering IV versus oral agents, and low patient and caregiver satisfaction [53, 54].

Taken together, preference for IV versus orals antimicrobials based on concerns about their relative safety profiles are not supported by the data. OPAT is more costly than oral antimicrobial therapy [55, 56], and in BJIs, oral antimicrobial therapy appears to be widely underused [57-59].

BJI studies investigating the time to switch from IV to oral antimicrobial treatment

Research groups have retrospectively evaluated the duration of IV therapy in regard to the outcome 'treatment failure', employing various oral agents. In a study on orthopaedic implant-associated infections caused by *S.aureus*, the mean duration of IV antibiotic treatment was 4.1 days (SD 4.6). The authors included 140 patients, the majority of patients (119, 85%) had ≤5 days of IV therapy. In the 2-years follow-up investigation, 12 patients (8.5%) were not cured, and treatment failure was not associated with the duration of IV therapy (≤ 5 or > 5 days) [60]. In other publications regarding native joint septic arthritis [26], implant-free osteomyelitis [61], or prosthetic joint infections [62], the duration of postsurgical IV administration was identified as an independent predictor of outcomes. Other research groups advocate for oral therapy in arthroplasty infection after surgery [63, 64]. In these retrospective studies, mostly the duration of IV therapy lasted from 2 to 8 days, typically the time interval from harvesting samples until arrival of the antibiotic susceptibility results.

Systematic reviews and meta-analyses are important tools in gathering evidence; nonetheless, they cannot overcome the heterogeneity of short or long IV treatment concepts for BJIs in clinical practice. Thus, although these analyses show no difference in outcome when antibiotic treatment is switched early from IV to oral antibiotics, they also represent the limitations of the available data and the risks of bias in selecting patients [65-67]. The latter limitation is not surprising from a physician's point of view, because not all patients encountering all clinical conditions qualify for oral antibiotic treatment, and certain clinical criteria should be fulfilled prior to considering the switch (see next section, "What to consider when choosing the time to switch from IV to oral antimicrobial treatment"). A retrospective propensity score-balanced analysis on native vertebral osteomyelitis that included 249 patients reported a failure rate of 13.3% [68]. Thirty-four patients (13.7%) required surgical intervention, and 54 patients (21.7%) received oral antibiotics for the entire treatment course. The study demonstrated a selection bias for oral treatment that was not associated with failure.

In other words, those with a good prognosis from the physicians perspective are selected for oral treatment. Also, considering that 105 patients initially received a parenteral antimicrobial regimen for a median duration of 22 days (interquartile range, 14–42), the study illustrates the potential of switching more patients earlier from IV to orals [68]. These conclusions can be extrapolated to other BJI studies [69].

Table 1 summarizes RCTs on BJIs in adults including data on early switch from IV to oral antibiotics from the last two decades. Although a few studies focused specifically on the time of the switch [4, 60], others focussed on shortening the treatment duration of BJIs [26, 70-73], or the comparison between IV and oral antimicrobials [74, 75]. In children, two RCTs revealed the efficacy of shorter treatment for BJIs [76, 77]. In both studies the switch from IV to oral antimicrobial therapy occurred between 2 and 4 days. A further prospective observational study reported excellent outcome of BJIs in 25 children treated with oral antibiotics only [69].These studies derive mainly from Europe, illustrating the influence of regional variation in institutional practices, health authority regulations, and possibly dogmas [78]. In these studies, the time of the switch ranged from 1 to <7 days, and in none of them did duration of IV therapy have a statistically significant effect on the outcome.

What to consider when choosing the time to switch from IV to oral antimicrobial treatment

No strict rule predicts a precise date for the switch and no “one-size-fits-all” rule is appropriate for all BJIs. We recommend making this decision in an interdisciplinary team at the bedside, taking into consideration numerous factors, including clinical improvement (e.g.; afebrile and haemodynamically stable, with no ongoing bacteraemia), whether the pathogens and their antibiotic susceptibility are known, whether or not the intervention was the final surgery, the ability of the patient to ingest pills, the possibility for hospital discharge, and the predicted adherence to the prescribed antibiotic regimen. Beyond these factors, the previous

duration of IV administration is of little consequence. Conversely, other factors may reasonably deter the clinician from switching to oral therapy. A high load of microorganisms at the infection site is associated with risk of a patient developing antimicrobial resistance, and theoretically the higher drug exposures with IV versus oral route for some antimicrobials may be preferable prior to reducing the microbial burden at the infection site via washout of the joint or debridement of the bone. Similarly, haematoma or poorly vascularized tissue after the first surgical intervention may be an ideal niche for microbial persistence, leading to an ongoing infection process and impaired wound healing. Therefore, it is reasonable to wait for interdisciplinary consensus at the bedside that no further surgical interventions (e.g., second look) are required prior to considering the switch from IV to oral treatment. In spine infection, surgery is infrequently performed in comparison to other BJIs. However, available data and clinical experience indicate that IV treatment can be switched to orals early in a subset of patients and when there is clinical improvement [68, 70].

Data from cardiac surgery indicate that enteral absorption of a drug may be impaired for approximately one day after the intervention due to various reasons (e.g.; paracetamol [79]). However, these data stem from investigations on drugs other than antibiotics, and the possible evidence – if at all – concerns the day of surgery or the first day after. Wound healing in orthopaedic surgery typically requires more than one day. By the time early switch is considered, other signs of enteral resorption (i.e., ingestion of food and fluid) are evident.

Conclusions and future directions

A strict minimum duration of IV treatment (minimal threshold) for BJIs is not supported by data. Early switch may not be uniformly suitable for all possible clinical conditions in BJIs. However, counterarguments against an early switch from IV to oral antimicrobial treatment, including bone penetration, concerns about adverse events, or the ease of an OPAT system, are not supported by data. Conversely, there is growing evidence

that a switch to oral compounds can be safely performed when there is clinical improvement and bacterial load reduced by surgical intervention. Such a decision should be individualized at the bedside. In addition, specialized infectious diseases and antimicrobial pharmacist knowledge is required to choose the appropriate oral antibiotic compounds.

Considering the diversity of BJI entities, there is no one-size-fits-all solution, but a switch to oral compounds within a few days after definitive surgery is reasonable for a large proportion of cases. OPAT increases healthcare costs, may be burdensome for patients and caregivers, and carries additional risk of catheter-related complications. Future studies should build on this existing evidence, and policy makers should act against regulations that do not support oral antimicrobial treatment.

Transparency declaration

The authors declare that they have no conflict of interest in relation to the topic of this review or writing the manuscript.

Authors' contributions

PS wrote the first draft, JLT, NCP and IU reviewed and edited the manuscript. All authors reviewed and approved the final version of the manuscript.

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Table 1. Randomized controlled trials (RCTs) investigating the time of early switch in bone and joint infections

Ref	Study design, Country, Years	Type of bone and joint infection (BJI)	No. of analysed patients	Time of switch from intravenous (IV) to oral treatment	Clinical Outcome
Studies investigating the time of early switch					
[4]	RCT, UK, 2010–2015	Long bone osteomyelitis, native joint infection requiring excision arthroplasty, prosthetic joint infection (45%), orthopaedic fixation device infection, vertebral osteomyelitis with or without associated diskitis	Total 1054 IV group 527 Oral group 527	As soon as possible (but no more than 7 days) after definitive surgical intervention.	Failure (1-year follow-up) IV group 74 (14.6%) Oral group 67 (13.2%)
Studies investigating antibiotic treatment duration					
[70]	RCT, France, 2006–2011	Pyogenic vertebral osteomyelitis (6 vs 12 weeks)	Total 351 6-week group 176 12-week group 175	93 patients IV for <7 days	Clinical cure 90.9% in the 6-week group 90.9% in the 12-week group Failure with <7 days IV (n=12, 13%) vs ≥7 days IV (n=20, 7%); *P*=0.204.
[71]	RCT, France, 2011–2015	Prosthetic joint infection (6 vs 12 weeks)	Total 404 6-week group 203 12-week group 201	Median duration of IV therapy in both groups 9 (interquartile range [80] 5–15) days	Persistent infection 18.1% in the 6-week group 9.4% in the 12-week group
[72]	RCT, Switzerland, 2017–2019	Diabetic foot osteomyelitis (3 vs 6 weeks)	Total 93 3-week group 44 6-week group 49	Median duration of IV therapy in 3-week group 1 day 6-week group 3 days; (*P*=0.37)	Remission 84% in the 3-week group 73% in the 6-week group
[26]	RCT, Switzerland, 2015–2018	Native joint bacterial arthritis, 64% hand arthritis (2 vs 4 weeks)	Total 154 2-week group 77 4-week group 77	Median duration of IV therapy in 2-week group 1 day 4-week group 2 days (*P*=0.01)	Cure rate 99% in the 2-week group 97% in the 4-week group
[73]	RCT, Switzerland, 2015–2018	Osteoarticular infections after implant removal (4 vs 6 weeks)	Total 123 4-week group 62 6-week group 61	Median duration of IV therapy in 4-week group 3.5 days 6-week group 5 days (*P*=0.09)	Complete clinical remission 95% in the 4-week group 95% in the 6-week group
Studies comparing IV vs oral antibiotic treatment					
[74]	RCT, Spain,	Chronic nonaxial osteomyelitis due to *Staphylococcus aureus*	Total 50 IV group 22	Median no. of days of prior empirical antibiotic therapy (IQR)	Cured IV group 90.5%

	1991–1996	(IV cloxacillin vs oral rifampin-cotrimoxazole combination)	Oral (PO) group 28	IV group 3 (2–4) PO group 5 (2–7) (*P*=0.01)	PO group 88.9%
[75]	RCT, Switzerland, published 2004	Staphylococcal infections including acute BJI and chronic osteomyelitis (OM). (IV vancomycin or flucloxacillin vs oral rifampin-fleroxacin combination)	Total 127 BJI + OM 42 IV group 20 PO group 22	The switch to the oral regimen in the PO group was done after a median of 1 day of IV therapy (IQR 1–3 days)	Cure BJI IV group 69% PO group 89%

This list is not exhaustive. RCTs that analyse the outcome of IV antibiotic treatment versus oral fluoroquinolones for osteomyelitis have been published elsewhere [3, 78, 81-84]. In the cited studies, the choice of the appropriate oral antimicrobial agent was proposed or prescribed by a team of Infectious Disease specialist, considering numerous factors within the clinical context of each case (e.g.; bioavailability, antimicrobial resistance patterns, etc.).