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Review

Antibiotic penetration into bone and joints: An updated review

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ABSTRACT

Treatment of bone and joint infections can be challenging as antibiotics should penetrate through the rigid bone structure and into the synovial space. Several pharmacokinetic studies measured the extent of penetration of different antibiotics into bone and joint tissues. This review discusses the results of these studies and compares them with minimum inhibitory concentrations (MIC) of common pathogens implicated in bone and joint infections in order to determine which antibiotics may have a greater potential in the treatment of such infections. Clinical outcomes were also evaluated as data were available. More than 30 antibiotics were evaluated. Overall, most antibiotics, including amoxicillin, piperacillin/tazobactam, cloxacillin, cephalosporins, carbapenems, aztreonam, aminoglycosides, fluoroquinolones, doxycycline, vancomycin, linezolid, daptomycin, clindamycin, trimethoprim/sulfamethoxazole, fosfomycin, rifampin, dalbavancin, and oritavancin, showed good penetration into bone and joint tissues reaching concentrations exceeding the MIC_{90} and/or MIC breakpoints of common bone and joint infections pathogens. Few exceptions include penicillin and metronidazole which showed a lower than optimum penetration into bones, and the latter as well as flucloxacillin had poor profiles in terms of joint space penetration. Of note, studies on joint space penetration were fewer than studies on bone tissue penetration. Although clinical studies in osteomyelitis and septic arthritis are not available for all of the evaluated antibiotics, these pharmacokinetic results indicate that agents with good penetration profiles would have a potential utilization in such infections.

Contents

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Introduction

Bone and joint infections are major health problems and considered a significant cause of morbidity and mortality (Boselli and Allaouchiche, 1999). Moreover, treatment can be challenging and requires prolonged courses as it depends on the penetration of antibiotics to the infection site (Boselli and Allaouchiche, 1999; Fraimow, 2009). Two published reviews on antibiotics penetration into bones only have been published. The first by Boselli et al. included studies published between 1978–1997 (Boselli and Allaouchiche, 1999). The second review was published in 2009 by Landresdrofer et al. and included studies between 1998–2007 (Landersdorfer et al., 2009a). Moreover, the recommendations of antibiotic therapy in current treatment guidelines were based mainly on clinical studies, as well as the high bioavailability of recommended oral antibiotics (Berbari et al., 2015; Osmon et al., 2013; Korean Society for Chemotherapy et al., 2014). However, with the knowledge of the penetration profiles of different antibiotics into bone and joint tissues, upcoming guidelines are assumed to make recommendations consistent with the findings of the pharmacokinetic studies discussed in this review which can offer a surrogate for clinical utility.

Since many antibiotics have been approved after the last review and given the availability of new data for older antibiotics, it was prudent to provide an updated review evaluating these data in line with previously published studies to produce a comprehensive informative resource for healthcare providers caring for patients with bone and joint infections.

Search strategy

A literature search was performed using MEDLINE and SCOPUS databases for the period from January 1976 to November 2018. Keywords included 'antibiotics'; 'antibacterials'; 'bone penetration'; 'joint penetration'; 'synovial fluid'; as well as the name of each antibiotic searched and included in this review. Conference proceedings and abstracts were searched using SCOPUS databases.

Penetration of antibiotics into bones and joints

The concentrations reported in the summarized studies were either mean, range, or peak concentrations (C_{max}) and were compared to the most recently reported MIC_{90} of the most common Gram-positive pathogens associated with bone and joint infections from two global surveillance studies (Jones et al., 2017; Pfaller et al., 2018). For pathogens or antibiotics where MIC_{90} data were not available, results were compared with the latest MIC susceptibility breakpoints (Clinical and Laboratory Standards Institute, 2018). Table 1 summarizes pertinent mean antibiotics concentrations along with MIC_{90} and susceptibility breakpoints. For studies reporting bone concentration values using bone weight as the denominator (e.g., μg/g), concentrations were converted to μg/mL using a conversion factor of 1.9 g/mL for the bone density (Cameron et al., 1999).

Penicillin G

In one study, penicillin G was given to three patients undergoing total hip or knee arthroplasty (THA or TKA) (Smilack et al., 1976). After 2 MU q4 h were given preoperatively, cancellous bone concentrations were measured 0.5–1 h after the last dose. Although penicillin G was detectable in serum at 0.5–9.4 μg/mL, it was undetectable in bone, which may indicate its poor usability in bone infections.

Amoxicillin/clavulanate

Weismeier et al., measured bone penetration of 2/0.2 g IV amoxicillin/clavulanate in 20 THA patients (Weismeier et al., 1989). Amoxicillin penetration into cortical and cancellous bones was similar. In cortex and spongy layers, mean concentrations were 49.4/4.4 and 34.6/3.04 μg/mL, 45.2/4.6 and 37.6/3.04 μg/mL, and 17.5/1.9 and 11.2/1.3 μg/mL at 1 h, 1–2 h, and 2–5 h, respectively. In a similar study where 1/0.2 g of amoxicillin/clavulanate was given preoperatively to 21 THA patients, both components demonstrated excellent penetration into synovial fluid where concentrations were almost equivalent to serum concentrations (Grimer et al., 1986). Conversely, amoxicillin concentration ratio in serum to bone was 10:1. Concentrations reported in these studies exceed the MIC_{90} of osteomyelitis and septic arthritis organisms (Pfaller et al., 2018).

Antistaphylococcal penicillins

All 39 patients in a study received 2 g of flucloxacillin before THA/TKA (Torkington et al., 2017a). In TKA, mean femoral and tibial bone concentrations were 8.1 ± 6.8 and 7.2 ± 5.5 μg/mL, respectively. On the other hand, mean femoral head, neck, and acetabulum concentrations in THA were 11.7 ±7.7, 10.1 ±4.9, and 27.1 ± 15.9 μg/mL, respectively. Another study compared the

Table 1
Antibiotic penetration into bone and joint tissues and MIC_{90} of common bone and joint infections pathogens.

Antibiotic	Average cancellous bone concentration, μg/mL	Average cortical bone concentration, μg/mL	Average joint concentration, μg/mL	MIC_{90} (Jones et al., 2017; Pfaller et al., 2018) (Susceptibility Breakpoint (Clinical and Laboratory Standards Institute, 2018)), μg/mL							
				S. *aureus*	CoNS	*Enterococci*	BHS	VGS	Enterobacteriaceae	*P. aeruginosa*	Anaerobes
Penicillin G	Undetectable		NA	NA (≤0.12)	NA (≤0.12)	≤0.06 (≤8)	NA (≤0.12)	1 (≤0.12)	NA	NA	NA
Amoxicillin/ clavulanate	27.8/2.5	37.4/3.6	NA	NA	NA	2–8 (≤8)[a]	NA (≤0.25)[a]	NA (≤0.25)[a]	NA (≤8/4)	NA	NA (≤4/2)
Oxacillin	NA	4	3.4	>2 (≤2)	>2 (≤0.25)	NA	NA	NA	NA	NA	NA
Cloxacillin	NA	3.8[b]	0.5	NA	NA	NA	NA	NA	NA	NA	NA
Dicloxacillin	NA	3.8[b]	NA	NA	NA	NA	NA	NA	NA	NA	NA
Flucloxacillin	89.5	Detectable	NA	0.25	NA	NA	NA	NA	NA	NA	NA
Piperacillin/ tazobactam	40.5/detectable	35.5/detectable	69.9/7.7	NA	NA	NA	NA	NA	NA (≤16/4)	NA (≤16/ 4)	NA (≤32/ 4)
Cefazolin	75.4	Detectable	112.2	NA	NA	NA	NA	NA	NA (≤2)	NA	NA
Cephalexin	4.2[b]		15.8	12.5	12.5	NA	NA	NA	NA	NA	NA
Cefadroxil	5.1		NA	NA	NA	NA	NA	NA	NA	NA	NA
Ceftriaxone	10.7		NA	NA	NA	0.12	NA (≤0.5)	1 (≤1)	NA (≤1)	NA	NA
Ceftazidime	32.1[b]		NA	NA	NA	NA	NA	NA	NA (≤4)	NA (≤8)	NA
Cefepime	99.8	67.6	NA	NA	NA	NA	NA (≤0.5)	NA (≤1)	NA (≤2)	NA (≤8)	NA
Imipenem	NA		13.8	NA	NA	NA	NA	NA	NA (≤1)	NA (≤2)	NA (≤4)
Meropenem	10.6[b]		12.5	NA	NA	NA	NA (≤0.5)	NA (≤0.5)	NA (≤1)	NA (≤2)	NA (≤4)
Ertapenem	9.9	6.1	19.8	0.5	NA	NA	NA (≤1)	NA (≤1)	NA (≤0.5)	NA (≤4)	NA (≤4)
Aztreonam	16[b]		83	NA	NA	NA	NA	NA	NA (≤4)	NA (≤8)	NA
Amikacin	Detectable		Detectable	NA (≤16)	NA	NA	NA	NA	NA (≤16)	NA (≤16)	NA
Gentamicin	Detectable		Detectable	≤1 (≤4)	> 8	NA	NA	NA	NA (≤4)	NA (≤4)	NA
Ciprofloxacin	13.8[b]		NA	NA (≤1)	NA	NA (≤1)	NA	NA	NA (≤1)	NA (≤1)	NA
Levofloxacin	10	4.6	8.9	>4 (≤1)	>4	>4 (≤2)	1 (≤2)	2	NA (≤2)	NA (≤2)	NA
Moxifloxacin	2.8[b]		3.4[c]	0.125 (≤0.5)	NA	NA	NA	NA	NA	NA	NA (≤2)
Doxycycline	3[b]		NA	≤0.5 (≤4)	>8	>8 (≤4)	>8 (≤2)	>8 (≤2)	NA (≤ 4)	NA	NA
Vancomycin	3.8	4.5	NA	1 (≤2)	2 (≤4)	2-> 16 (≤4)	0.5 (≤1)	0.5–1 (≤1)	NA	NA	NA
Daptomycin	21.4[b]		21.6	0.5 (≤1)	0.5	0.25 (≤4)	1–2 (≤1)	1 (≤1)	NA	NA	NA
Linezolid	6.4[b]		> 4	1-2 (≤4)	1	1 (≤ 2)	1–2 (≤2)	1 (≤2)	NA	NA	NA
Clindamycin	6.9[b]		2	>2 (≤0.5)	>2	>2	NA (≤0.25)	>2 (≤0.25)	NA	NA	NA (≤2)
TMP/SMX	6.8/35.8[b]		Detectable	≤0.5–1 (≤2/38)	>4	≤0.5	NA	2	NA (≤2/38)	NA	NA
Fosfomycin	NA		NA	NA	NA	NA (≤64)	NA	NA	NA (≤64)	NA	NA
Rifampin	6.5	1.3	NA	NA (≤1)	NA	NA (≤1)	NA	NA	NA	NA	NA
Metronidazole	5.6[d]	5.7[d]	5.6	4.9	NA	NA	NA	NA	NA	NA	NA (≤8)
Dalbavancin	13.4[d]	4.2[d]	NA	0.06 (≤0.25)	0.06	0.12 (≤0.25)	≤0.03 (≤0.25)	≤0.03	NA	NA	NA
Oritavancin	27[c,d]	65.6[c,d]	NA	NA (≤0.12)	NA	NA (≤0.12)	NA (≤0.25)	NA (≤0.25)	NA	NA	NA

BHS, β-hemolytic *Streptococcus* (*S. pyogenes*), NA, not available; VGS, Viridans group *Streptococcus*, CoNS, Coagulase-negative *Staphylococci*; TMP/SMX, Trimethoprim/sulfamethoxazole.
[a]This is the MIC_{90} of ampicillin which can be a surrogate for amoxicillin MIC (Conceicao et al., 2012).
[b] Values that show no distinction between cortical and cancellous bones are from studies that reported overall bone concentrations without such distinction.
[c] C_{max} (mean was not available).
[d] From *in vivo* studies.

penetration of oral versus IV formulations of flucloxacillin in 20 TKA/THA patients (Ferrero et al., 1993). Bone concentration was detected only after the 2 g IV dose with mean concentration of 14.1 ± 7.2 μg/mL. Parsons et al. measured the concentration of flucloxacillin in seven patients undergoing THA (Parsons et al., 1978). Each patient received 2 g of flucloxacillin plus 2 g ampicillin preoperatively followed by 2 g postoperatively q6 h for up to 72 h. Mean plasma concentration was 137.2 ± 28.4 μg/ mL while mean concentration in cancellous bone was 89.5 ± 18.1 μg/mL. Despite achieving high concentrations in bone, flucloxacillin failed to achieve similar results in synovial fluid as reported in a small study of six patients who received 250 mg of flucloxacillin followed by synovial fluid aspiration over 36 h (Sattar et al., 1983a). A study involving 60 patients undergoing oral surgery was conducted to evaluate the concentration of cloxacillin, dicloxacillin and flucloxacillin (Köndell et al., 1982). Each 20 patients received one of the previous antibiotics at 500 mg. Mandibular bone concentration was 3.8 ± 0.8 μg/mL for cloxacillin whereas both dicloxacillin and flucloxacillin achieved similar concentrations of 3.8 ± 1 μg/mL.

In a study of oxacillin, 1 g was administered to 28 patients where oxacillin achieved a mean concentration of 18.9 μg/mL in serum, 4 μg/mL in cortical bone (22/28 patients), and 3.4 μg/mL in synovial fluid (Fitzgerald et al., 1978). In 26 rheumatic patients who received oral ampicillin or cloxacillin, synovial fluid concentration of ampicillin was found close to its counterpart in the serum unlike cloxacillin that showed much lower concentration than in the serum (Howell et al., 1972). Of note, most antistaphylococcal penicillins such as cloxacillin and flucloxacillin are highly protein-bound which may affect their penetration ability (Sattar et al., 1983a; Howell et al., 1972).

Piperacillin/tazobactam

A dose of 4.5 g of piperacillin/tazobactam (4/0.5 g) reached mean bone concentrations of 17.1/2.3 ± 22/2.5 μg/mL with a mean ratio to serum concentration of 0.15 for piperacillin and 0.13 for tazobactam (Al-Nawas et al., 2008). Another study in ten THA patients given 3.375 g (3/0.375 g) dose preoperatively showed mean concentrations of piperacillin in cancellous and cortical bones of 40.5 ± 19.2 and 35.5 ± 14.8 μg/mL, respectively (Incavo et al., 1994). In synovial fluid, 1 h after dosing of 4.5 g in six healthy participants resulted in mean concentrations of 69.9 ± 4.9 and 7.7 ± 0.3 μg/mL for piperacillin and tazobactam, respectively (Boselli et al., 2002). These findings demonstrate the usefulness of this combination in the treatment of bone and joint infections.

Cefazolin

Yamada et al. administered 2 g of IV cefazolin to 43 THA/TKA patients preoperatively (Yamada et al., 2011). Mean concentration in serum 1 h after dosing was 170.3 ± 51.3 μg/mL. In cancellous bone, the concentration was 42.6 ± 28.1 μg/mL in hip and 30.4 ± 19.8 μg/mL in knee. Another study in coronary artery bypass graft (CABG) patients showed mean cefazolin C_{max} in the sternal cancellous bone of left and right sides of 112 ± 59 μg/mL and 159 ± 118 μg/mL, respectively, following the administration of 6 g (4 g preoperatively and 2 g during the operation) (Andreas et al., 2015). A third study demonstrated a variable cefazolin penetration profile, where it was detected in the femoral bone in only one of four patients at 19.9 μg/mL versus >50 μg/mL in serum (Smilack et al., 1976). A single 1 g dose given to 48 joint replacement patients achieved mean concentrations of 10.8 and 24.4 μg/mL in bone and synovial fluid, respectively (Schurman et al., 1978a). Also in synovial fluid, a preoperative 2 g of cefazolin resulted in an estimated concentration of about 200 μg/mL (Dastgheyb et al., 2015). In another study, cefazolin concentration in synovial fluid ranged from equal to higher than its counterpart in serum (Schurman et al., 1978b). Cefazolin concentrations in these studies exceeded the MIC_{90} of *Staphylococci*.

Cephalexin

Oral 1 g of cephalexin q6 h resulted in bone and synovial fluid concentrations of 2.5 and 5.7 μg/mL, respectively, in 13 TKA patients (Jalava et al., 1977). Concentrations increased to 5.9 and 10.1 μg/mL, respectively, on the next day. In another study and after a single oral 500 mg of cephalexin, mandibular bone showed mean C_{max} of 4.03 ± 0.63 μg/mL in 36 patients (Akimoto et al., 1990).

Cefadroxil

Akimoto et al. administered oral 250 mg of cefadroxil to 52 patients preoperatively to an impacted third molar extraction (Akimoto et al., 1994). Mean C_{max} in the mandibular bone and its ratio to the plasma were 5.1 ± 0.5 μg/mL and 0.2 ± 0.03, respectively. This concentration exceeded α-hemolytic streptococci MIC_{90} reported in this study of 1 μg/mL.

Ceftriaxone

Eleven patients undergoing surgical debridement for the tibia were given 2 g IV ceftriaxone daily for a mean of 15.8 days (Garazzino et al., 2011). In this study, Garazzino et al reported AUC/plasma ratios of 9.32 in cortical bone and of 24.1 in cancellous bone. Another study treated 13 THA patients with 1 g ceftriaxone either at the time of the operation or 8 h prior (Lovering et al., 2001). Ceftriaxone mean concentration preoperatively was 5.8 μg/mL compared with 15.6 μg/mL in patients who received it immediately before the surgery. Both studies support the use of ceftriaxone in bone infections which has been proven clinically as its concentrations reach beyond the MIC_{90} of potential pathogens (Eron et al., 1983).

Ceftazidime

A study of 10 patients undergoing amputation of lower extremities involved administering 2 g of ceftazidime 0.5 h before the procedure (Raymakers et al., 1998). Most of the samples collected from gangrenous areas showed at least 3.4 μg/mL indicating good penetration profile into areas with severe ischemia. Another study of 43 THA/TKA patients who received 1 g preoperatively plus two 500 mg doses 6 h and 12 h later showed mean serum and femoral bone concentrations of 64.8 and 32.1 μg/mL, respectively (Leigh et al., 1985). A study involved measuring ceftazidime perfusion in lower limb ischemia in amputation candidates found mean concentrations of 22 μg/mL in serum and 4.9, 7, and 6.5 μg/mL in bones with low, moderate, and high ischemia, respectively (Lozano-Alonso et al., 2016). Although these results demonstrate that ceftazidime concentration could exceed the MIC breakpoint against *P. aeruginosa* (of ≤8 μg/mL) in the absence of ischemia, it was not associated with high cure rate in a clinical study of patients with bone and/or joint infections (cure rate = 57.4%) (Gentry, 1985).

Cefepime

In 10 patients given 2 g of cefepime before THA, mean concentration in cancellous and cortical bones were 99.8 and 67.6 μg/mL, respectively (Breilh et al., 2003). This dose led to a bone/plasma mean concentration ratio of 1.06 in cancellous bone compared with 0.9 in cortical bone. Additionally, the combination

of cefepime fluoroquinolones resulted in 79% recovery rate in the treatment of Gram-negative bacilli bone and joint infections (Legout et al., 2006).

Imipenem

In synovial fluid, mean concentrations at 1, 2, and 3 h after administering 1 g of imipenem to six patients (two patients for each time point) were 20.4, 13 and 7.9 μg/mL, respectively, compared with 42.5, 20.1, 9.3 and 5.7 μg/mL in blood at same points, respectively (Pechinot et al., 1991). Although MIC90 of imipenem against bone and joint infections are not available, concentrations reported in these studies exceed the MIC susceptibility breakpoint of *Streptococcus pneumoniae* and *Pseudomonas aeruginosa* (≤0.12 and ≤2 μg/mL, respectively). (Jones et al., 2017; Pfaller et al., 2018; Clinical and Laboratory Standards Institute, 2018)

Meropenem

Administering 500 mg of meropenem prior to orthopedic surgery in adult patients resulted in mean bone marrow concentration of 15.4 μg/mL that was >50% the serum C_{max} (Sano et al., 1993). In bone and synovial fluid, concentrations ranged between 10.9–0.8 and 20.3–4.6 μg/mL. A study on 11 patients with lower limb ischemia, mean serum concentration was 29.6 ± 24.8 μg/mL (Lozano-Alonso et al., 2016). In bone, the concentrations were 64.6 ± 76, 58.9 ± 115.3, and 36.5 ± 38.6 μg/mL in tissues with low, moderate, and high degrees of ischemia, respectively. These concentrations reached above the MIC breakpoint for *Streptococci* (≤0.25–0.5 μg/mL) and *P. aeruginosa* (≤2 μg/mL) (Clinical and Laboratory Standards Institute, 2018).

Ertapenem

Boselli et al. administered of 1 g of ertapenem to 18 patients before THA (Boselli et al., 2007). Median serum concentrations at 1.6, 12.4, or 23.8 h after administration were 70.1, 10.0, and 2.6 μg/mL respectively, whereas those in cancellous bone were 25.1, 3.6, and 1.1 μg/mL, respectively. In cortical bone, median concentrations were 15.2, 2.5, and 0.6 μg/mL, respectively. Synovial fluid concentrations were 49.8, 7.6, and 1.9 μg/mL, respectively. Ertapenem concentrations in this study exceeded the MIC_{90} for Enterobacteriaceae, methicillin-susceptible *Staphylococcus aureus* (MSSA), and anaerobes (0.25–1 μg/mL) (Wexler, 2004).

Aztreonam

In a study of 12 patients requiring maxilla-facial surgery, 1 g of aztreonam was administered preoperatively as IV bolus or infusion (Fracasso et al., 1989). Interestingly, bone concentrations were detectable only in patients who received the bolus injection. In another study, 18 THA/TKA patients who received 2 g of aztreonam had mean bone and synovial fluid concentrations of 16 ± 4.3 and 83 ± 9.2 μg/mL, respectively (MacLeod et al., 1986). Both studies indicate good bone and joint penetration profiles for aztreonam.

Aminoglycosides

Administering 5 mg/kg of gentamicin achieved therapeutic concentrations in vertebral discs of all ten patients who received the antibiotic (Tai et al., 2002). Gentamicin also demonstrated a similar penetration profile in bone of THA/TKA patients in a study by Torkington et al. (Torkington et al., 2017b). In synovial fluid, both amikacin and gentamicin achieved concentrations that were equal or higher than serum concentrations (Schurman et al., 1978b). Despite their hydrophilic nature, aminoglycosides proved their ability to penetrate into bone and joint tissues representing a reasonable option for treatment of infections at these sites.

Ciprofloxacin

Ciprofloxacin penetration into turbinate bone was studied in eight patients undergoing turbinectomy. Concentrations were measured 3 h after an oral dose of 250 mg, and authors report that concentrations exceeded the reported MICs by several folds (Esposito et al., 1987). Another study assessed ciprofloxacin concentration in sternal bone marrow in patients received a single 400 mg IV dose (group 1) or 750 mg oral dose q12 h for two days (group 2). Mean concentrations were 14.8 ± 14.4 and 12.7 ± 6.46 μg/mL 1 h after dosing in group 1 and group 2, respectively (Mertes et al., 1990). A third study assessed ciprofloxacin tissue penetration in skull bone of 14 patients undergoing brain tumor excision to whom a 200 mg single IV dose was given 0.5 h before skin incision (Leone et al., 2002). Ratio of skull bone/serum concentration during skin closure was 1.8 ± 3. These concentrations exceed the MIC breakpoints against Gram-positive and Gram-negative pathogens of bone and joint infections.

Levofloxacin

In one study, 500 mg of IV levofloxacin was given to 12 THA patients (Rimmele et al., 2004). Levofloxacin concentrations, collected about 1.2 h after administration, were 7.5 ± 1.3, 7.4 ± 4.2, 3.9 ± 1.2, and 8.9 ± 2.1 μg/mL, in plasma, cancellous bone, cortical bone, and synovial fluid, respectively. Another study measured levofloxacin concentrations in 21 adult patients undergoing bone surgery at about 1.5 h after IV dosing of 500 mg (von Baum et al., 2001). Cancellous and cortical bone concentrations were 12.5 ± 6.8 and 5.3 ± 2.1 μg/mL, respectively. The extent of diffusion of levofloxacin into bone in the presence of ischemia was measured in patients who were candidates for amputation (Lozano-Alonso et al., 2016). Mean concentrations were 14.7 μg/mL in serum and 7.8, 12.2, and 11.6 μg/mL in bones with low, moderate, and high degrees of ischemia, respectively. Comparing these findings with the findings of the previous two studies indicate that levofloxacin diffusion into bone can remain similar regardless of ischemia. These concentrations are greater than the MIC_{90} of *Streptococci* and MSSA (≤2 and 0.5 μg/mL, respectively) (Jones et al., 2017; Pfaller et al., 2018).

Moxifloxacin

A Monte Carlo simulation for 10,000 patients was conducted based on data from 24 patients given oral 400 mg 2–7 h before THA (Landersdorfer et al., 2009b). Median concentration in both cortical and cancellous bones was about 2.5 μg/mL. Another study on eight CABG patients who received 400 mg of IV moxifloxacin detected mean serum concentrations of 3.4 and 2.9 μg/mL at 2 and 5 h following the infusion, respectively (Metallidis et al., 2006). In the body and manubrium of sternal bone, mean concentrations were 3.2 and 3 μg/mL at 2 h and 2.7 and 2.9 μg/mL at 5 h, respectively. In synovial fluid, moxifloxacin achieved C_{max} of 3.4 ± 0.5 μg/mL compared with 3.5 ± 0.8 μg/mL in serum (Dan et al., 2004). These concentrations exceed the MIC_{90} of *S. aureus* reported in the first study of 0.125 μg/mL (Landersdorfer et al., 2009b).

Doxycycline

After the administration of 200 mg of IV doxycycline to 25 patients undergoing orthopedic surgery, bone concentration

ranged 1–1.1 μg/mL (Dornbusch, 1976). In another study, mean mandibular bone concentration of six patients was 4.9 ± 3.8 μg/mL 3 h after administering doxycycline 200 mg oral dose (Bystedt et al., 1978). These concentrations exceed the MIC_{90} of doxycycline against *Staphylococci*(Pfaller et al., 2018).

Vancomycin

Massias et al. studied IV vancomycin penetration into the sternal bone of 10 patients undergoing cardiac surgery (Massias et al., 1992). Patients were treated with 10 mg/kg q8 h for 48 h preoperatively. Mean concentration in bone was 17.7 ± 5.7 μg/mL while the concentration ratio of bone to plasma was 0.57 ± 0.20. In another study in 14 THA patients (group 1) and 5 with osteomyelitis (group 2) (Graziani et al., 1988), group 1 received 15 mg/kg IV 1 h preoperatively which resulted in mean concentrations in cancellous and cortical bones of 4.4 ± 7.6 and 2.1 ± 1.5 μg/mL, respectively. On the other hand, group 2 received multiple 15 mg/kg doses that were detectable in only two of five cortical bone specimens at 11.2 ± 6.7 μg/mL with cortical bone/serum ratio of 0.3 ± 0.12. Cancellous bone specimen was obtained from only one patient in group 2 in which concentration equalled 6.8 μg/mL with a ratio to serum concentration of 0.21. This good penetration profile was also seen in sternal bone after administration of 15 mg/kg to patients undergoing cardiac surgery (Martin et al., 1994). Conversely, a study in TKA 10 patients given 1 g of vancomycin showed a weaker penetration pattern where mean concentration in cancellous and cortical bones were 0.1 ± 0.3 and 0.1 ± 0.1 μg/mL, respectively (Bue et al., 2018). In a study of lower limb ischemia, mean concentrations were 17 μg/mL in serum and 11.6, 13.7, and 8.8 μg/mL in bones with low, moderate, and high levels of ischemia, respectively (Lozano-Alonso et al., 2016). Thus, vancomycin diffuses into bone more poorly when ischemia is present. Collectively, these studies show that vancomycin reaches concentrations that exceed the MIC_{90} against *S. aureus* (1 μg/mL) and *Streptococci* (≤2 μg/mL) and the MIC_{50} of *Enterococci* (1 μg/mL), but perhaps not the MIC_{90} of *Enterococci* of >16 μ/mL (Jones et al., 2017; Pfaller et al., 2018).

Daptomycin

Montange et al. reported mean daptomycin bone penetration rate of 14.1 ± 11.9% in 16 arthroplasty patients after 8 mg/kg dose with mean concentrations of 36.3 ± 2.9, 6.5 ± 3.6, and 21.6 ± 6.8 μg/mL in shinbone, thighbone, and synovial fluid, respectively (Montange et al., 2014). In another study, when 4–5 doses of 6 mg/kg/day of daptomycin were given to 9 patients with diabetic foot infection, mean C_{max} in metatarsal bone was 4.7 μg/mL (Traunmuller et al., 2010). Daptomycin concentrations highly exceed the MIC_{90} of Gram-positive pathogens of osteomyelitis and septic arthritis, thus it represents a reasonable treatment option (Jones et al., 2017; Pfaller et al., 2018).

Linezolid

In ten TKA patients, oral linezolid was given at 600 mg q12 h for two days preoperatively and 1 h before anesthesia (Rana et al., 2002). Mean concentrations in cancellous bone, synovium, and synovial fluid were >4 μg/mL that are at least double the MIC_{90} for both *Staphylococci* (2 μg/mL) and *Streptococci* (1 μg/mL) (Jones et al., 2017; Rana et al., 2002). In another study, 13 implant-associated MRSA infected patients received preoperative 600 mg of IV linezolid (Kutscha-Lissberg et al., 2003). Linezolid concentrations in the joints exceeded 10 μg/mL and reached 3.9 ± 2.0 μg/mL in the bone. Lovering et al administered 600 mg of IV linezolid to 12 THA patients and found mean concentrations in bone of 9.1, 8.6, and 6.3 μg/mL at 10, 20, and 30 min after starting the infusion, respectively (Lovering et al., 2002). In ischemic limbs, linezolid achieved mean concentrations of 20, 29.1, and 40.1 μg/mL in bones with low, moderate, and high ischemia, respectively, versus 65.7 μg/mL in serum. These findings indicate that linezolid diffuses well regardless of perfusion level (Lozano-Alonso et al., 2016).

Clindamycin

A study on 31 patients of oral and maxillofacial surgery involved administering 600 mg of IV clindamycin preoperatively (Mueller et al., 1999). At the end of the infusion, mean plasma concentration was 12.7 ± 4.5 μg/mL while bone concentration at 0.5 h post-infusion ranged between undetectable to 3.4 μg/mL. In another study, 13 joint replacement patients were given 300 mg of intramuscular (IM) clindamycin 1 h before surgery followed by a 30-min IV of another 300 mg given concurrently with bone exposure until its removal (Baird et al., 1978). Mean concentrations in bone and joint capsule were 5 ± 1.2 and 3.3 ± 0.7 μg/mL, respectively. Another study involved administering 300 mg of IM clindamycin to 30 THA patients q8 h and found mean concentration in bone of 4.9 ± 3.4 μg/mL versus 7.3 ± 3.4 μg/mL in serum (Nicholas et al., 1975). A similar study of THA patients found that serum and bone concentrations exceeded the MIC of most of the Gram-positive pathogens of surgical orthopedic infections (Schurman et al., 1975). In 8 rheumatoid arthritis patients, clindamycin achieved a mean concentration of 0.5 μg/mL in synovial fluid after a 300 mg dose (Deodhar et al., 1972). A study in THA/TKA patients demonstrated significant uptake of clindamycin in non-inflamed human bone where mean plasma and bone concentrations in two of three patients were 11.3 and 15.8 μg/mL, respectively (Smilack et al., 1976). In critical lower limb ischemia, mean clindamycin concentrations were 2.3, 1.9, and 1.5 μg/mL in bones with low, moderate, and high ischemia, respectively, while serum concentration was 3.8 μg/mL. Findings indicate that clindamycin could reach the susceptibility breakpoint of Gram-positive cocci in ischemic tissues (≤0.25 μg/mL for *Streptococci* and ≤0.5 μg/mL for *Satphylococci*), but less likely that of anaerobes (≤2 μg/mL) (Clinical and Laboratory Standards Institute, 2018).

Trimethoprim/sulfamethoxazole (TMP/SMX)

A study on 14 THA patients given 3.2 g SMX and 640 mg TMP for two days preoperatively found that TMP reached 4.2–9.4 μg/mL in all bone types compared with SMX (26.3–45.3 μg/mL) (Saux et al., 1982). Additionally, the former demonstrated bone/serum ratio concentration that is 6 times higher than the latter. TMP/SMX concentration ratio in cortical bone, cancellous bone, and bone marrow to serum were 0.2, 0.3, and 0.3, respectively. A similar finding in synovial fluid was reported by Sattar et al where TMP achieved concentration close to that in serum compared with SMX (Sattar et al., 1983b). As these concentrations exceed the MIC_{90} of Gram-positive pathogens, this profile confirms the clinical efficacy of TMP/SMX in bone and joint infections reported in clinical trials (Jones et al., 2017; Pfaller et al., 2018; Nguyen et al., 2009; Stein et al., 1998).

Fosfomycin

No studies have yet evaluated fosfomycin penetration into bone; however, *in vivo* efficacy was assessed in three MRSA osteomyelitis studies. The first study involved 11 rats and found eight of ten bone cultures showed no bacterial growth (Poeppl et al., 2014). A similar finding was seen with seven of nine cultures in the second study (Poeppl et al., 2011). The third study demonstrated no growth in all cultures of both the fosfomycin and fosfomycin/daptomycin groups (Lingscheid et al., 2015).

Rifampin

An oral 600 mg of rifampin given q12 h was shown to be effective in the treatment of staphylococcal bone and articular infections in a small clinical study (Cluzel et al., 1984). In this study, the ranges of the concentration ratio of cancellous bone to serum were 0–41 and 0–39 at 3 h and 12 h, respectively whereas cortical bone to serum concentration ratio was 0–20 at 3 h. Roth et al. administered 600 mg of IV rifampin to 32 patients where the dose was divided into 300 mg IV bolus followed by an infusion of 300 mg over 1 h (Roth, 1984). After 2.5–3.5 h from treatment initiation, bone concentration ranged 2.7–16.7 μg/mL. Another study of 68 patients demonstrated that a 600 mg dose given q12 h achieves a higher concentration ratio of cancellous bone to serum compared with 300 mg dose given q12 h or 600 mg given q24 h (Sirot et al., 1983). In 13 THA patients, 600 mg of rifampin was given orally daily (Sirot et al., 1977). Mean bone concentrations 1–3 days later were 1.3 ± 1 and 6.5 ± 1.3 μg/mL in cortical and cancellous bones, respectively. Collectively, these studies indicate excellent penetration of rifampin into bone tissues at levels higher than the MIC susceptibility breakpoint of rifampin against *S. aureus* of ≤1 μg/mL (Clinical and Laboratory Standards Institute, 2018).

Metronidazole

In a study of six patients who received three doses of metronidazole of 400 mg q8 h, C_{max} in serum and synovial fluid were 9.6 and 5.6 μg/mL, respectively, at 12 h after the first dose (Sattar et al., 1982). An *in vivo* study of 15 rats given metronidazole (15 mg/kg) involved sampling from compact femoral and cancellous scapular bone (Summersgill et al., 1982). Concentrations were 5.7 and 5.1 μg/mL, respectively. Concentrations reported in these studies were slightly below the MIC breakpoint of metronidazole against anaerobes (≤8 μg/mL) (Clinical and Laboratory Standards Institute, 2018).

Dalbavancin

Penetration of 20 mg/kg of IV dalbavancin was studied in noninfected bone and joint tissues of rabbits (Solon et al., 2007). Concentrations were above the MIC for common Gram-positive pathogens when measured 12–336 h after dosing. Concentrations were the highest in bone marrow with a mean of 13.4 μg/mL and reached the lowest in cortical bone with a mean of 4.2 μg/mL. Moderate-to high concentrations were reached in synovial space and surrounding tissues.

Oritavancin

In an *in vivo* study, 21 rabbits were administered 20 mg/kg of oritavancin (Lehoux et al., 2015). C_{max} in tibia, bone matrix, and bone marrow were 38.8, 65.6, and 27 μg/mL, respectively. Calculated AUC in were 1,792.1, 2,779.5, and 5,136.3 g h/g, respectively, which were 1.1, 1.7, and 3.1-fold higher than that in the serum, respectively. Oritavancin concentration in bone remained above the MIC_{90} against *S. aureus* throughout the 168 h study duration.

Discussion and conclusion

Overall, most antibiotics discussed in this review have the ability to penetrate into rigid bone tissues, as well as the synovial fluid. Antibiotics that showed good penetration profiles into bone tissues include amoxicillin, piperacillin/tazobactam, flucloxacillin, cloxacillin, cephalosporins (all four generations), carbapenems (no data for imipenem), aztreonam, aminoglycosides, fluoroquinolones, doxycycline, vancomycin, linezolid, daptomycin, clindamycin, trimethoprim/sulfamethoxazole, fosfomycin, rifampin, dalbavancin, and oritavancin. Few exceptions include penicillin and metronidazole which showed a lower than optimum penetration into bones. The good profile seen with bones was similar with joint tissue penetration except for flucloxacillin and metronidazole. In addition, data for joint space penetration were lacking for penicillin, cloxacillin, second, third, and fourth generation cephalosporins, ciprofloxacin, moxifloxacin, doxycycline, fosfomycin, rifampin, and oritavancin. Notably, the extent and rate of penetration vary between different agents probably due to variations in pharmacokinetic characteristics. Fortunately, despite the variation in penetration extent, all agents with reported good penetration profiles achieve concentrations that are sufficient for antibacterial activity as demonstrated by the comparison with the MIC_{90} or the MIC breakpoints of various organisms implicated in bone and joint infections. Interestingly, results from a recent study by Li et al that showed non-inferiority of oral antibiotics versus IV antibiotics for bone and joint infections were consistent with the pharmacokinetic findings of the antibiotics reported in this review (Li et al., 2019).

While the studies summarized in this review provide an insight into the usefulness of tested antibiotics for the treatment of bone and joint infections, many suffered from some limitations. First, the small sample size of participants was a common limitation. Such limitation probably can be overcome either by enrolling a larger number of participants or simply by performing a Monte Carlo simulation when all pharmacokinetic parameters data are available from enrolled participants as in the case with the study by Landersdorfer et al that assessed the penetration of moxifloxacin into bone tissues (Landersdorfer et al., 2009b). Second, a variation in the doses given to participants was observed between some studies evaluating the same antibiotic. In some cases, however, lower or higher doses than those approved by the US Food and Drug Administration were evaluated. Third, the presence of certain conditions that limit the blood flow, such as ischemia, may affect the extent to which some antibiotics diffuse into bone and joint tissues resulting in presumably lower concentrations than what could have been achieved in normal tissues. Nonetheless, the antibiotics studied by Lozano-Alonso and colleagues in the presence of various levels of ischemia (ceftazidime, meropenem, levofloxacin, and linezolid with the exception of vancomycin) showed good bone penetration profiles despite vascular insufficiency (Lozano-Alonso et al., 2016). Fourth, many of the included studies in this review were old, hence, lacking sufficient details about the characteristics of enrolled participants and methodologies. In addition, as technologies in drug concentration measurement have advanced, such studies if replicated may show some differences in the results. Last, in cases with some new antibiotics (such as fosfomycin, dalbavancin, and oritavancin), only results from animal studies were available and reported. Therefore, for such antibiotics, studies in human subjects would be needed to confirm results seen *in vivo*.

In conclusion, while clinical studies in osteomyelitis and septic arthritis are not available for all of the evaluated antibiotics, pharmacokinetic results reported in this review indicate that agents with good penetration profiles would have a potential utilization in such infections.

Conflict of interest

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Ethical approval

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