Infection and Drug Resistance

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REVIEW

Model-Informed Precision Dosing of Antibiotics in Osteoarticular Infections

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Abstract: As a heterogeneous and wide inflammation, osteoarticular infection (OAI) shows an increasing incidence in recent years. *Staphylococcus aureus* is the most important pathogen causing OAI. The antibiotic treatment will affect the outcomes of OAI patients, and the drug selection and dosage regimen highly rely on patients' variability, pathogen susceptibility, and drug property like bone permeability. Model-informed precision dosing (MIPD) provides options to describe and quantify the pharmacokinetic (PK) variability of the OAI population using different models, such as the population pharmacokinetic (PPK) model and physiological-based pharmacokinetic (PB/PK) model. In the present review, we highlighted that the MIPD of antibiotics played a critical role in OAI and listed the dose regimen recommended by the model. Collectively, our current study provided a valuable reference for the treatment of patients and improved the safety and efficiency of drug use.

Keywords: osteoarticular infection, antibiotic, PPK, PBPK, dose

Background

As a wide inflammation resulting from microbial invasions of bone and/or joint structures,[1] osteoarticular infection (OAI) is a heterogeneous disease in its pathophysiology, clinical presentation, and treatment, which is frustrating for both patients and their doctors.[2] OAI includes osteomyelitis, spondylodiscitis, septic arthritis, and prosthetic joint infection (PJI). With the rapid economic development, severe social aging problems, and the increase in artificial joint replacements, the incidence of OAI is rising worldwide.[3–5] For example, the diagnosis of PJI has been steadily increasing in 2009–2018,[6] which is associated with a 1-year mortality rate of 8–25.9%.[7–9] For osteomyelitis, such rate is increased with the calendar year from 11.4 cases per 100,000 person-years in 1969–1979 to 24.4 per 100,000 person-years in 2000–2009 in the United States.[10]

The most common infection-causing pathogen for OAI is *Staphylococcus aureus*, including methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA).[4,11–13] Other pathogens that cause OAI, such as coagulase-negative staphylococci (CoNS) and aerobic Gram-negative bacilli, cannot be ignored.[14,15] The resistances of CoNS isolated from OAI to vancomycin, teicoplanin, and linezolid are increased by 0–2.3%, 3.8–22%, and −3.5% between 2002 and 2011, respectively, while *S. aureus* is still sensitive to the above-mentioned antibiotics.[16]

The treatment of OAI requires antimicrobial therapy and surgical intervention, such as debridement and joint drainage.[12,17–19] Infectious Diseases Society of America

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Received: 5 August 2021
Accepted: 11 November 2021
Published: 11 January 2022

(IDSA) recommends vancomycin in combination with a third- or fourth-generation cephalosporin to cover the pathogens, including MRSA, streptococci, and Gram-negative bacilli, for patients with vertebral osteomyelitis as empirical administration.[19] Insufficient antimicrobial treatment may induce secondary infections, deep vein thrombosis, and even secondary surgery.[20,21] The success of antibiotic therapy depends on their permeability in bone tissue, the susceptibility of infected bacteria, and host-related factors.[22] IDSA has issued the guidelines for the diagnosis and treatment of PJI in 2013 and native vertebral osteomyelitis in adults in 2015,[19,23] which provide general antibiotic choices and dose regimens mainly based on experiences from cohort or case-controlled analytic studies. Notably, some essential oils can be a new antimicrobial frontier against multidrug-resistant bacteria, although most of the studies are still in the laboratory research stage.[24,25]

Model-informed precision dosing (MIPD) uses mathematical methods to integrate and quantitatively analyze information, such as physiology, pharmacology, and disease processes, through model simulations based on statistical principles, finally realizing the quantitative or at least semi-quantitative guidance for drug dosage individualization and increasing the safety and efficiency of drug use. Commonly used methods of models include the population pharmacokinetic (PPK) model, population pharmacodynamic (PopPD) model, pharmacokinetic/pharmacodynamic (PK/PD) model, physiological-based pharmacokinetic (PB/PK) model, and so on.[26,27] PPK model can identify sources and correlates of PK variability in a target patient population receiving an agent of interest.[28,29] PB/PK model uses "physiology room" to replace the compartmental model, and simulates the circulatory system blood flow to connect the body's various tissues or organs, allowing simulation of the time course of drug concentrations in plasma and tissues, such as bone tissue.[30,31]

In the present work, we summarized the recently published studies to emphasize the potentiality of MIPD of antibiotics in individualization and precision medicine for OAI treatment.

MIPD of Antibiotics Against Gram-Positive Bacteria-Caused OAI

Penicillin

Cloxacillin is a time-dependent antibiotic against staphylococcal infections,[32,33] with a plasma protein-binding (PB) rate of around 94% and a half-life ($T_{1/2}$) of nearly 45 min.[34] Its PK/PD target is the time above the MIC of greater than 50% of the dosing interval (50% fT>MIC). The label recommended dose of cloxacillin in OAI is 4–6 g/day, iv, divided into 2–4 times. A retrospective study[35] included 82 patients with severe septic bursitis receiving cloxacillin (2 g, q4 h, iv until improvement, afterward 1 g, q6 h, po until resolution) alone or in combination with gentamicin 240 mg/day, iv or rifampicin 600 mg/day, po. They concluded that cloxacillin alone might be sufficient for patients without extensive cellulitis, and cloxacillin in combination with gentamicin seemed to be appropriate for the majority of severe patients.

Courjon et al[36] recruited 11 patients with OAI caused by MSSA who received continuous infusion (CI) or intermittent infusion (II) of cloxacillin using a prospective crossover design and developed a PPK model. Tables 1 and 2 summarize the demographic data of patients and model parameters. They used a two-compartment model to describe the data, performed PK/PD simulations, and calculated the probability of target attainment (PTA) for several II and CI dosing regimens. Moreover, they suggested a prolonged infusion or CI of cloxacillin, ie, 2–3 g, q6 h, 2–4 h of infusions; 2 g, q4 h, 1–2 h of infusions; 6–12 g/day, and CI would achieve a PTA of 90% based on the PK/PD target of 50% fT>MIC against *S. aureus* at a MIC up to 0.5 mg/L. Those two studies both showed insufficient label dose in OAI.

Cephalosporin

Cephalexin shows a time-dependent bactericidal activity against MSSA, its oral bioavailability (F) is close to 100%, and its $T_{1/2}$ is 49.5–76.5 min,[37] with a PB of 10–15%[34] and a PK/PD target of 40% fT >MIC. The recommended dose in the instruction is 250–500 mg, qid, po for adults and 25–50 mg/kg, qid, po for children.[38] Moreover, the guideline also recommends cephalexin 500 mg, q6 h, as a followed-by oral therapy for an additional 7–14 days after parenteral antibiotics for at least 14 days in adults with MSSA septic arthritis.

One study[39] showed that after a single dose of 1 g cephalexin orally, the samples of two patients were collected after 3–4 h, the bone concentrations were 1.3 and 3.1 μg/g, while the serum concentrations were 37.7 and 27.9 μg/mL, respectively. Given that the frequency of four times daily would lower treatment compliance with higher frequency in clinical practice, one PK/PD study[40] showed the safety and efficiency of cephalexin at a median dose of 40 mg/kg, q8 h,

Table 1 Overview Characteristics of Included Studies

Drug	First Author (Year)	Number of Patients (Male/ Female)	Age (y)[a]	Weight (kg)[a]	Total Number of Samples	Pathogens	Model	Modeling Approach	Number of Compartments	Retained Covariates in Final Model	
										Covariates ~CL	Covariates ~Vc
Cloxacillin	Johan Courjon (2020)[36]	11 (8/3)	53 (21–65)	Cl/Il: 83 (52–95) Il/Cl: 70 (60–97)	84	MSSA	PPK	NPAG	Two	None	BSA
Cephalexin	Amanda Gwee (2020)[41]	12 (7/5)	7.6 (1.2–16.7)	25 (10.0–78.8)	53	MSSA	PPK	NONMEM	One	Weight	Weight
Clindamycin	Naïm Bouazza (2012)[44]	50 (30/20)	56.7 ± 3.0	69.9 ± 2.7	122	MSSA	PPK	NONMEM	One	Weight,	None
Ciprofloxacin	Cornelia B. (2020)[49]	37 (12/25)	66 ± 9	74 ± 20	/	MSSA	PBPK	NONMEM	Five[b]	/	/
	Noël Zahr (2021)[50]	92 (57/35)	59.8 ± 32.9	79.6 ± 23.9	397	G^+ (7.6%) G^- (92.4%)	PPK	NONMEM	Two	Fat-free mass, eGFR, rifampicin co-administration	Fat-free mass,
Levofloxacin	Gauthier Eloy (2020)[55]	59 (28/31)	57.5 ± 20.1	72.1 ± 15.9	197	*S. aureus*	PPK	NONMEM	One	Age, eGFR	None
Rifampicin	Amélie Marsot (2017)[57]	62 (46/16)	57.4 (20–89)	72.3 (46–119)	103	Staphylococci	PPK	NONMEM	One	Fusidic acid co-administration	Fusidic acid co-administration
Rifampicin	Amélie Marsot (2020)[58]	83	51.9 (19–82)	81.4 (57–100)	129	Staphylococci	PPK	NONMEM	One	Fusidic acid co-administration	Fusidic acid co-administration

(*Continued*)

https://doi.org/10.2147/IDR.S332366 DovePress

Table 1 (Continued).

Drug	First Author (Year)	Number of Patients (Male/ Female)	Age (y)[a]	Weight (kg)[a]	Total Number of Samples	Pathogens	Model	Modeling Approach	Number of Compartments	Retained Covariates in Final Model	
										Covariates ~CL	Covariates ~Vc
Dalbavancin	Michael W. (2015)[63]	18 (9/9)	38.1 (21–55)	/[c]	/	*S. aureus*	PPK	NONMEM	Three	CL_{CR}	BSA
	Michael W. (2015)[63]	31 (14/17)	66.7 (47–82)	/[d]	/	*S. aureus*	PPK	NONMEM	Four	/	/
	Pier Giorgio (2021)[64]	15 (8/7)	60 (51–72)	71 (66.5–82.5)	120	*S. aureus*	PPK	NONMEM	Two	None	None
Daptomycin	Sylvain Goutelle (2016)[68]	23 (14/9)	68 (19–84)	72 (47–140)	203	*S. aureus*	PPK	NONMEM	Two	Sex	Sex
	Romain Bricca (2019)[69]	81 (47/34)	60 ± 18	79 ± 20	577	*S. aureus*	PPK	NONMEM	Two	CL_{CR}, sex	Weight, CGC
	Romain Garreau (2021)[70]	183 (106/ 77)	60.5 ± 16.0	79.2 ± 20.2	1303	*S. aureus*	PPK	NONMEM	Two	CL_{CR}, sex	Weight, age, sex, rifampicin co-administration.
Ertapenem	Jonathan Chambers (2019)[72]	10 (8/2)	64 [57–74]	112.3 (79–188)	69	Enterobacteriaceae	PPK	NONMEM	Two	CL_{CR}	CL_{CR}
	Sylvain Goutelle (2018)[73]	31 (21/10)	58 (19–87)	75 (50–136)	133	Enterobacteriaceae	PPK	NPAG	Two	/	/
Fosfomycin	Matteo Rinaldi (2021)[80]	48 (34/14)	56.4 [42.9–66.7]	80 [68–90]	116	G^+ and G^-	PPK	NPAG	Two	CL_{CR}	Weight

Notes: [a]mean ± SD or median (range) or median[IQR]; [b]The PB/PK model of ciprofloxacin included a central (blood) compartment, two peripheral tissue compartments, and compartments for the organic and inorganic (hydroxyapatite) matrix in cortical and cancellous bone; [c]no data of weight, but BMI of subjects is 27 (22–32) $kg/m^{2;}$ [d]no data of weight, but the BMI of subjects is 32.1 (22.4–43.4) kg/m^2; /: not stated;

Abbreviations: PB/PK, physiological-based pharmacokinetic model; PPK, population pharmacokinetic model; NONMEM, non-linear mixed-effects model; NPAG, the non-parametric adaptive grid algorithm; BSA, body surface area; CL_{CR}, creatinine clearance; eGFR, estimated glomerular filtration rate.

Table 2 Summary of Drug PK Parameters and Dosing Recommendations for OAI Patients

Drug	Mean of PK Parameters		Dosing Recommendations for OAI Patients		Target
	CL (L/h)	Vd (L)	From Label or Guideline	Proposed by the Model	
Cloxacillin[36]	16.2	V1:16.0 V2:2.7	4–6 g/d, iv	6–12 g/d, 3 h infusions or CI against *S. aureus* at MIC ≤ 0.5 mg/L	50% fT>MIC
Cephalexin[41]	CL/F:8.21	V/F:15.9	25 mg/kg, qid, po	22–45 mg/kg, bid, po or 15–25 mg/kg, tid, po against MSSA at MIC of 1–2 mg/L; 80 mg/kg, bid, po or 45 mg/kg, tid, po against MSSA at MIC of 4 mg/L	40% fT > MIC
Clindamycin[44]	15.2	66.2	600–900 mg, q8 h, iv	600 mg, tid, iv/po for patients ≤ 75 kg against *S. aureus* at MIC ≤ 0.125 mg/L; 900 mg, tid, iv/po for patients >75 kg against *S. aureus* at MIC ≤ 0.125 mg/L	$C_{min\ (plasma)}$ ≥ 2 mg/L
Ciprofloxacin[49]	20.7	V1:5.85	400 mg, q8 h/q12 h, iv	400 mg, q8 h, iv against *S. aureus* at MIC ≤ 0.75 mg/L; 400 mg, q12 h, iv against *S. aureus* at MIC ≤ 0.5 mg/L	fAUC/MIC ≥ 40
Ciprofloxacin[50]	CL/F:44	V1/F:56.5	1583±430 mg/d, po	1375 mg/d, poor 500 mg, q8 h, po, for a patient with 70 kg, eGFR = 100 mL/min/1.73 m^2 and no rifampicin against *P. aeruginosa* with a MIC of 0.25 mg/L. 2200 mg/d, po for same patient but co-administration of rifampicin	fAUC/MIC≥125,110,35[c]
Levofloxacin[55]	CL/F:6.10	V/F:90.6	500–750 mg, qd, iv/po	750 mg, qd, iv/po against *S. aureus* at MIC<1 mg/L	AUC/MIC ≥ 100
Rifampicin[58]	CL/F:5.1[a] CL/F:12.8[b]	V1/F:39.8[a] V1/F:74.0[b]	300 mg, tid, po	900–1200 mg/d, po with fusidic acid against Staphylococci at MIC ≤ 0.064 mg/L	$AUC_{0\text{-}24h}$/MIC ≥ 952
Dalbavancin[63]	/	/	1500 mg, single, iv; 1000 mg followed one week later by 500 mg, iv	Two 1500mg dosing regimen one week apart, iv against S. aureus at MIC ≤ 0.12 mg/L	$fAUC_{0\text{-}24h}$ /MIC: 265 ±143
Dalbavancin[64]	0.106	V1:17.40 V2:15.10	1500 mg, single, iv; 1000 mg followed one week later by 500 mg, iv	Two 1500mg dosing regimen one week apart, iv against MSSA and MASA at MIC ≤ 0.125 mg/L	$fAUC_{0\text{-}24h}$/MIC > 27.1, 53.3 and 111.1
Daptomycin[69]	0.585	V1:10.1 V2:3.39	6 mg/kg, qd, iv	10 mg/kg, qd, iv against *S. aureus* at MIC ≤ 1mg/L	$fAUC_{0\text{-}24h}$/MIC > 66
Daptomycin[70]	0.365	V1:3.59 V2:4.71	6 mg/kg, qd, iv	10 mg/kg, qd, iv for male against *S. aureus* at MIC ≤ 1 mg/L; 8 mg/kg, qd, iv for female against *S. aureus* at MIC ≤ 1 mg/L	$fAUC_{0\text{-}24h}$/MIC > 66
Ertapenem[72]	1.34	V1:5.72 V2:4.77	1 g, qd, iv	1 g, qd, iv against Enterobacteriaceae at MIC ≤ 0.064 mg/L	50%fT > MIC
Ertapenem[73]	0.055	V1:6.091	1 g, qd, iv	1 g, bid, iv/sc against Enterobacteriaceae at MIC ≤ 1 mg/L	40%fT > MIC

(*Continued*)

Table 2 (Continued).

Drug	Mean of PK Parameters		Dosing Recommendations for OAI Patients		Target
	CL (L/h)	Vd (L)	From Label or Guideline	Proposed by the Model	
Fosfomycin[80]	1.31	V1:6.4	4–12 g/d, iv	2g, q6 h, iv against *S. aureus, E. coli*, ESBL-producing *E. Coli* and MRSA; 8g/d, CI against CoNS, *K.pneumoniae*, ESBL-producing *K.pneumoniae*; 12g/d, CI against *P. aeruginosa*; 16g/d, CI against KPC-producing *K. pneumoniae*	70%T> MIC

Notes: [a]With fusidic acid; [b]Without fusidic acid; [c]The PK/PD target for ciprofloxacin is AUC/MIC≥125 for Gram-negative aerobic bacteria,≥110 for staphylococcus infections and ≥35 for Gram-positive bacteria, respectively. /: not stated;

Abbreviations: CL, clearance; V1, apparent volume of distribution of the central compartment; V2, apparent volume of distribution of the peripheral compartment; qd, once a day; bid, twice a day; tid, three times a day; qid, four times a day; q6 h, every 6 h; q8 h, every 8 h; q12 h, every 12 h; CI, continuous infusion; iv, intravenous injection; po, oral administration; sc, subcutaneous injection; (f)$AUC_{0\text{-}24h}$/MIC, (free) drug area under the concentration-time curve over 24 h divided by the MIC; %(f)T>MIC, time that the (free) drug concentration exceeds the MIC for at least % of the dosing interval.

po in 12 children with OAI, and the PTA was 100%, 90%, and 80% for MSSA with MICs at 0.25, 2, and 4 mg/L, respectively.

In 2020, Gwee et al[41] established the first PPK model of cephalexin to optimize the dosing regimen, such as twice-daily and thrice-daily, with 12 OAI children caused by MSSA. Due to the delay in oral absorption, one compartment with a transit compartment model was used to fit the data of cephalexin adequately. They concluded that 22–45 mg/kg, bid, or 15–25 mg/kg, tid, po for MSSA with a MIC of 1–2 mg/L; 80 mg/kg, bid, or 45 mg/kg, tid, po for MSSA with a MIC of 4 mg/L could achieve a PTA of 90% at the target of 40% fT>MIC. They developed a more detailed and specific dosing regimen of cephalexin, showing the superiority of the PPK model.

Lincosamide

Clindamycin is a time-dependent killing antibiotic against anaerobic bacteria, Gram-positive cocci and bacilli, and Gram-negative bacilli,[42] with a PB of 92–94% and a $T_{1/2}$ of 2.5–3 h. The label recommended dose of clindamycin for adults' infection is 600–2700 mg/day, divided into 2 or 3 times, iv; 150–300 mg, q6 h or q8 h, po. IDSA recommends it to treat native vertebral osteomyelitis in adults at a dose of 600–900 mg, q8 h, iv as a parenteral treatment.[19] An observational study included 61 OAI patients receiving a median dose of 600 mg, q8 h. The measured median $C_{min(plasma)}$ was 1.39 mg/L, with 58% of patients below the target of 1.7 mg/L (due to C_{bone} /MIC > 2 at the MIC of 0.25 mg/L based on the penetration of 30% to bone), suggesting this dose regimen was not sufficient.[43]

In 2012, Bouazza et al[44] developed a PPK model consisting of 50 osteomyelitis patients receiving clindamycin at a median dose of 26.0 mg/kg/d, iv/po, and these data were adequately described by a one-compartment model. F was estimated to be 87.6%. They chose a PK/PD target of $C_{min\ (plasma)} \geq 2$ mg/L due to C_{bone} /MIC > 5 at the MIC of 0.125 mg/L for S. *aureus* based on the penetration of 30% to the bone. Besides, Monte Carlo simulations showed that 600 mg, q8 h, iv/po was enough for patients with a bodyweight ≤75 kg. For those with a bodyweight >75 kg, the dose should be raised to 900 mg, q8 h, iv/po as the clearance was significantly increased with bodyweight. Adjusting the dose regimen according to the patient's bodyweight may be more proper to ensure efficiency.

Fluoroquinolone

Ciprofloxacin produces its concentration-dependent activity against many Gram-negative and Gram-positive bacteria,[45,46] including intracellular *S. aureus*,[47,48] and its PK/PD target is $fAUC_{0\text{-}24\ h}$ /MIC ≥ 40. With a PB of about 25% and a $T_{1/2}$ of 4 h,[34] FDA recommends 400 mg, iv,q8 h or q12 h, with a duration of 4 to 8 weeks for OAI patients. In 2020, Landersdorfer et al[49] developed a PB/PK model consisting of 39 patients with a single dose of 400 mg, iv, at 0.5–20 h before orthopedic surgery to study the complete time-course of ciprofloxacin in bone. It included a central (blood) compartment, two peripheral tissue compartments, and compartments for the organic and inorganic (hydroxyapatite) matrix in cortical and cancellous bone. They found that at 0.5–2 h and 13–20 h, the average observed cortical bone/plasma concentration ratio

(C_{cort}/C_{plasma}) was 0.67 and 5.1, and that for cancellous bone (C_{canc}/C_{plasma}) was 0.77 and 4.4, respectively. Moreover, at the steady-state, AUC_{cort}/AUC_{plasma} and AUC_{canc}/AUC_{plasma} were 1.62 and 2.53, respectively, with higher concentrations detected in bone compared with plasma. Monte Carlo simulations showed that with the maximum approved daily dose of 400 mg, q8 h, reverse engineered PK/PD breakpoints for plasma and bone were 0.75 mg/L and 0.5 mg/L, respectively, which was lower than the MIC of S. *aureus* (1 mg/L) based on the PK/PD target of AUC_{cort}/MIC of ≥86 and AUC_{canc} /MIC of ≥135. Therefore, the currently approved dose regimen would not be sufficient, and it suggests that a combination with other classes of antibiotics would be more efficient for treating S. aureus osteomyelitis. Recently, Zahr et al[50] developed a PPK model of ciprofloxacin with 92 OAI patients, which was fitted to a two-compartment. They made a specific dosing regimen according to the patient's bodyweight, eGFR, co-administration of rifampicin, the PK/PD target for different infectious pathogens. For example, a patient with 70 kg, eGFR = 100 mL/min/1.73 m^2 and no rifampicin, the corresponding dose is 1375 mg/d, po, based on the target of AUC/MIC ≥125 for *P. aeruginosa* with a MIC of 0.25 mg/L. Moreover, co-administration of rifampicin increases this dose by 60% (namely 2200 mg/d, po). Although the specific values of PK/PD target, the PK parameters, the probability of target attainment (PTA) of simulations have certain deviations in two model studies, and the dose of ciprofloxacin (400 mg, iv, q8 h) is a bit lower in the treatment of OAI.

Levofloxacin has a similar action mechanism as ciprofloxacin, its F is about 99%, and PK/PD target is $AUC_{0\text{-}24\ h}$/MIC ≥100, with a PB of 24–38% and a $T_{1/2}$ of approximately 6–8 h.[51,52] As for the penetration into bone, one study encompassed 12 subjects undergoing total hip replacement who received a single dose of levofloxacin 500 mg, iv. After 1.2 h, the samples were collected and analyzed. Results showed that the C_{plasma} was 7.5 ± 1.3 mg/L. The mean C_{cort}/C_{plasma} and C_{canc}/C_{plasma} were 0.5 and 1.0, respectively, which achieved greater concentrations in cancellous and cortical bone tissues compared with the breakpoint of MIC ≤ 2 mg/L for susceptible organisms, such as *S. aureus*.[53] The recommended dose of levofloxacin is 250–750 mg, qd, iv/po, while IDSA recommends 500–750 mg, qd, po for native vertebral osteomyelitis caused by MSSA in adults.[19] A patient of periprosthetic knee infection caused by *Streptococcus anginosus*, was successfully treated by vancomycin (1 g, q12h, iv) and levofloxacin (750 mg, qd, iv) for 4 weeks, and then levofloxacin (750 mg, qd, po) for 2 weeks.[54]

In 2020, Eloy et al[55] developed a PPK model of levofloxacin with 59 OAI patients, and the model consisted of a one-compartment model with first-order absorption and elimination. Monte Carlo simulations evaluated the PTA of levofloxacin at a dose of 750 mg, qd, with different ages and renal functions. They found that 750 mg, qd would provide an optimal exposure at the target of $AUC_{0\text{-}24\ h}$ /MIC ≥100 for *S. aureus* at a MIC of <1 mg/L. If the patients were older than 60 years old with an eGFR <70 mL/min/1.73 m^2, the dose should be decreased. Therefore, levofloxacin 750 mg, qd, iv/po seemed to be appropriate for most OAI patients.

Rifampicin

Rifampicin inhibits DNA-dependent RNA polymerase activity, which concentration-dependently kills most intracellular and extracellular Gram-positive and Gram-negative bacteria,[34] with a PB of 89%. The PK/PD target of rifampicin is $AUC_{0\text{-}24\ h}$/MIC ≥952. One study demonstrated that the C_{cort}/C_{serum} and C_{canc}/C_{serum} at 3 h after 600 mg, bid, po were 0.20 and 0.41, respectively, showing a good bone penetration of rifampicin.[56] Moreover, rifampicin was recommended by IDSA to treat Staphylococcal OAI at a dosing regimen of 300–450 mg, bid, po.[23]

In 2016, Marsot et al[57] established the first rifampicin PPK model consisting of 62 OAI patients, and this model was composed of a one-compartment model and a transit absorption model. They found that fusidic acid led to potential high drug exposure of rifampicin, presenting a decrease of CL (5.1 L/h vs 13.7 L/h) and Vd (23.8 L vs 61.1 L). Since fusidic acid inhibits the transporter OATP1B1, of which rifampicin is a sensitive substrate. In 2020, they[58] enrolled 21 new patients to rebuild a PPK model, and this new dataset consisting of 83 patients used the same compartment model. They confirmed this drug-interaction by Monte Carlo simulations that rifampicin co-administration with fusidic acid achieved the target of $AUC_{0\text{-}24\ h}$/MIC ≥952 for staphylococci at a MIC of 0.004–0.064 mg/L with all tested dosing regimens (600 and 900 mg, qd; 450 and 600 mg, bid; or 300 mg, tid), except for 600mg, qd for *Staphylococcus epidermidis* OAI, whereas none of the tested dosing regimens achieved this target in the absence of fusidic acid. Those two studies showed that the co-administration of fusidic acid might improve the PTA of rifampicin in OAI.

Glycopeptide

As a second-generation lipoglycopeptide antibiotic, dalbavancin's $T_{1/2}$ is 346 h at a once-weekly dosing regimen, with a PB of 93%.[34] Dalbavancin exhibits a dose-dependent activity, with a target of mean $fAUC_{0\text{-}24\ h}$/MIC 265 ± 143 against *S. aureus*, and it shows increased activity against Gram-positive bacteria, including MRSA, compared with natural glycopeptides, such as vancomycin and teicoplanin.[59] FDA label recommends a single infusion dosage of 1500 mg or a two-dose regimen of 1000 mg followed by 1 week of 500 mg for patients with acute bacterial skin and skin structure infections with normal renal function.[60] A retrospective cohort study of adults with OAI, or other infections receiving dalbavancin (1500 mg for two doses 1 week apart) or SOC (vancomycin 17.1 mg/kg and daptomycin 7.4 mg/kg) showed that compared with SOC, dalbavancin was related to a lower 90-day infection-related readmission, a shorter hospital stay before therapy, and a longer time to infection-related readmission.[61] In a case-control study of prosthetic joint infections, 1500 mg for two doses with a 3-week interval showed no significant difference in efficacy and reduced toxicity compared with other drug combinations.[62]

In 2015, Dunne et al[63] conducted two phase-I studies of dalbavancin. They developed a PPK model to describe the time course of dalbavancin in plasma with 18 healthy volunteers using a three-compartment model with zero-order iv input and first-order elimination. Subsequently, a four-compartment PPK model was expanded for the dalbavancin transfer between plasma and bone tissue with 31 healthy volunteers to characterize the bone penetration. They found that after a single dose of 1000 mg, iv, the dalbavancin concentrations in cortical bone were 6.3 and 4.1 μg/g at 12 h and 14 days, respectively, while those in plasma were 85.3 and 15.3 μg/mL, respectively. Moreover, the AUC_{bone}/AUC_{plasma} penetration ratio was 0.131. Besides, they concluded that two 1500 mg dosing once-weekly regimens provided tissue exposure over the MIC_{99} for *S. aureus* of 0.12 mg/L for 8 weeks and were well tolerated based on the target of $fAUC_{0\text{-}24\ h}$/MIC of 265 ± 143. In 2021, 15 Gram-positive OAI adult patients were recruited to develop another PPK model of dalbavancin using a two-compartment model with linear elimination to fit the data.[64] Results showed that two licensed dosages granted an extension of desirable PTA up to 3 weeks at the target of $fAUC_{0\text{-}24\ h}$/MIC >27.1 or 53.3. Two 1500 mg dosing once-weekly regimens granted an extension of desirable PTA up to 5–7 weeks, 3–4 weeks, and 3 weeks at the target of $fAUC_{0\text{-}24h}$/MIC >27.1, 53.3, and 111.1, respectively, against *S. aureus*. Finally, they concluded that two 1500 mg dosing once-weekly regimens might be continuously effective for up to 5 weeks against MSSA and MRSA in OAI patients. Studies of PPK models showed the potency of two 1500 mg dosing once-weekly in OAI.

Lipopeptide

Daptomycin is a concentration-dependent killing antibiotic against Gram-positive bacteria, and its PK/PD target is $AUC_{0\text{-}24\ h}$/MIC >666 against *S. aureus*.[65] As a high plasma PB drug (90–93%),[66] daptomycin's bone penetration percentage is 9.0%.[67] Moreover, its recommended dose is 6 mg/kg, qd for MRSA OAI patients in the guideline published by IDSA in 2013.[23] In 2016, one PPK model consisting of 23 OAI patients described the data by a two-compartment model.[68] The model showed that the CL of daptomycin was significantly higher in males compared with female patients, and suggested that $C_{max(plasma)}$>50 μg/mL and $C_{min\ (plasma)}$< 24 μg/mL could be considered as targets for TDM. Bricca et al made a series of studies for the PPK of daptomycin in OAI patients,[69,70] both using a two-compartment model. They concluded that sex difference, rifampicin co-administration, and P-gp gene polymorphism might affect the probability of $AUC_{0\text{-}24\ h}$/MIC target attainment. Interestingly, contrary to clindamycin, the rifampicin co-administration improved daptomycin exposure, showing the decrease of the volume of distribution of the central compartment (V1) due to the P-gp induction effect of rifampicin. Besides, they recommended a dosing regimen of 8 mg/kg/d in women and 10 mg/kg/d in men by PK/PD simulations at the target of $fAUC_{0\text{-}24\ h}$/MIC >66 for *S. aureus* at a MIC ≤ 1 mg/L.

MIPD of Antibiotics Against Gram-Negative Bacteria-Caused OAI

Carbapenem

Ertapenem shows a time-dependent killing activity against Gram-negative bacteria, which is stable against hydrolysis by extended-spectrum beta-lactamases (ESBL), while it can be hydrolyzed by Metallo-beta-lactamases. With a PB of 85–95% and a $T_{1/2}$ of 2.5–4 h, its PK/PD target is defined as 40% fT>MIC.[71] The label recommended dose and guideline recommendation for Enterobacteriaceae-caused native

vertebral osteomyelitis in adults are both 1 g, qd, iv. A PPK model of ertapenem[72] performed a two-compartment model and showed a bone to plasma ratio of 0.025 over 24 h after a single dose of 1 g, iv in 10 obese OAI patients, and the PTA of bone is ~90%, ~80%, ~65%, ~45%, and ~30% for MICs of 0.064, 0.125, 0.25, 0.5, and 1.0 mg/L, respectively. Therefore, ertapenem is recommended to treat OAI at a dose of 1 g, qd, iv against Enterobacteriaceae at a MIC ≤ 0.064 mg/L. Another PPK model[73] consisting of 31 subjects used a two-compartment model to compare subcutaneous injection (sc) with intravenous injection (iv) of 1 g, bid/qd of ertapenem. They found that sc administration lowered the peak concentration but prolonged the action of ertapenem, with a higher value of fT>MIC. For example, the regimen of 1 g, qd, iv failed to achieve 90% PTA for a MIC of 1 mg/L, whereas 1 g, qd, sc achieved this goal. Moreover, 1 g, bid, iv/sc provided 90% PTA for a MIC of 2 mg/L, which could achieve the PK/PD target for OAI patients.

MIPD of Broad-Spectrum Antibiotics in OAI

Fosfomycin

Fosfomycin is a time-dependent bactericidal antibiotic disrupting the first step of bacterial cell wall synthesis,[74] and its PK/PD target is 70% T>MIC. With a wide range of bactericidal activity against Gram-positive bacteria and Gram-negative bacteria, including MRSA and MDR-enterobacteria,[74,75] fosfomycin is also active against biofilms.[76,77] With a PB of <5% and a $T_{1/2}$ of 3–5 h, the label recommended dose of fosfomycin is 4–12 g/day, divided into 2–3 times for adults. Fosfomycin shows a good penetrating ability to the bone, and its ratio of the $AUC_{0-6\ h}$ for the bone to plasma is 0.43±0.04 after a single intravenous dose of 100 mg/kg for diabetic patients presenting with bacterial foot infection.[78] The available data suggested that 93.7% OAI patients (343/365) used fosfomycin (4–24 g/d) as a part of combination therapy showing well safety.[79]

In 2021, Rinaldi et al[80] conducted a prospective study with 48 OAI patients and developed a PPK model of fosfomycin. A two-compartment open model with infusion input and first-order elimination best fitted the data. Monte Carlo simulations showed a daily dosage of 2 g, q6 h by II against *S. aureus, E. coli*, ESBL-producing *E. Coli*, and MRSA; 8 g by CI against CoNS, *K. pneumonia*, and ESBL-producing *K. pneumoniae*; 12 g by CI against *P. aeruginosa*, and 16 g by CI against KPC-producing *K. pneumonia* would achieve the optimal PTA of 70% T>MIC and the cumulative fraction of response (CFR) (≥90%).

Conclusions

In the present study, we summarized the characteristics of the relevant study population, model parameters, and recommended dosing regimens of the PPK and PBPK models of antibiotics in OAI patients. MIPD takes account of the individual characteristics adequately, and tailors antibiotic dose recommendations for each patient instead of the "one-dose-fits-all-approach". The model achieves stratification of dose regimen based on the types of infectious pathogens and their respective susceptibility to different antibiotics. Moreover, it identifies other risk factors influencing treatment efficacy and safety of OAI, like drug bone permeability, $T_{1/2}$, drug–drug interactions, and administration route. Although MIPD extrapolation should match the intended population and monitor dynamically, this review optimized antibiotic dose administration for OAI patients and advanced relevant information for the clinicians.

Data Sharing Statement

All data analyzed are included in this published article.

Funding

This work was supported by the National Natural Science Foundations of China (81770004 and 82073894) and the Cultivation Project of PLA General Hospital for Distinguished Young Scientists (2020-JQPY-004).

Disclosure

The authors declare no competing interests.

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