Table 3. Model strategies and final pharmacokinetic parameters of included studies.

Study (publication year)	Software / Algorithm	Structural Model	Fixed effect parameters		Between-subject variability	Residual unexplained variability	Internal validation	External validation (N=number of subjects)	Model application
Meagher AK (2003) [44]	ADAPT II (IT2S)	2 CMTs with parallel FO and MM eliminations	V_c	39.6 × TBW/65	22.7%	11%	GOF	NR	NR
			V_p	26.3 × TBW/65	41.8%	0.028 mg/L			
			V_{ss}	65.8 × TBW/65	23.4%				
			Q	9.09 × TBW/65	14.9%				
			CL_r	0.269 × CL_{CR}[a] × TBW/65	34.2%				
			CL_i[b]	43.5 × TBW/65	52.5%				
			K_m	1.46	68.1%				
			V_{max}	53.3 × TBW/65	25.8%				
			T_{lag}	0.371	97.6%				
			Ka	5.73	1.20%				
			AUC	228	584%				
			CL_{tav}	6.85 × TBW/65	50.3%				
Whitehouse T (2005) [45]	NONMEM (FO)	2 CMT[c] with FO elimination for all doses	CL	0.0487 × TBW	48.1%	19.0%	GOF	NR	AUC/MIC
			Q	7.48	/	2.34 mg/L			
			V_c	0.634 × TBW	22.4%				
			V_p	240	146%				
Abe S (2009) [7]	NONMEM (FOCE)	1 CMT with FO absorption and FO elimination	CL	$1.28 \times (TBW/69.5)^{1.91}$ + 0.0788 × (110 – AGE) (If age < 58) + 0.0788 × 52 (If age ≥ 58)	46.6%	8.14%	Bootstrap	NR	NR
			V	$47.0 \times (TBW/69.5)^{0.903}$	25.9%				
			K_a	0.583	181%				

Table 3 (continued)

Study (publication year)	Software / Algorithm	Structural Model	Fixed effect parameters		Between-subject variability	Residual unexplained variability	Internal validation	External validation (N=number of subjects)	Model application
Swoboda S (2010) [40]	NONMEM (FOCE-I)	2 CMT with FO elimination	CL	[0.159 × TBW + 3.5 (if dialysis)] × 0.4 (if liver transplantation or resection)	51%	4.13% 0.285 mg/L	GOF	NR	NR
			V_c	0.273 × TBW	21%				
			V_p	0.271 × TBW	/				
			Q	0.369 × TBW	/				
Sasaki T (2011) [35]	NONMEM (FOCE-I)	1 CMT with FO elimination	CL	2.85 × $(CL_{CR}{}^{a}/60.9)^{0.618}$ × 0.472 (if cirrhosis)	35.2%	1.43 mg/L	GOF	NR	Design dosing regimen
			V	33.6 × (TBW/57.9)	30.8%				
			K_a	0.583 fixed	/				
Tsuji Y (2013) [36]	NONMEM (FO)	1 CMT with FO elimination	CL	0.00327 × TBW × $eGFR^{0.428}$ × $HB^{0.502}$ × 0.283 (if ALT ≥ 100 IU/L)[d]	31.3%	21.7%	GOF, Bootstrap	NR	NR
			V	1.31 × TBW	33.9%				
Matsumoto K (2014) [37]	NONMEM (FOCE)	1 CMT with a FO absorption and FO elimination	K_a	0.583	/	21.4%	GOF, Bootstrap	NR	NR
			CL	0.0258 × $CL_{CR}{}^{a}$ + 2.03;	30.5%				
			V	27.6	/				

Table 3 (continued)

Study (publication year)	Software / Algorithm	Structural Model	Fixed effect parameters		Between-subject variability	Residual unexplained variability	Internal validation	External validation (N=number of subjects)	Model application
Luque S (2014) [18]	NONMEM (FOCE-I)	3 CMT with FO elimination	CL	16.6	50.2%	Plasma:	GOF, Bootstrap	NR	$AUC_{0\text{-}12h}$, C_{min}, C_{max}
			V_c	43.2	15.3%	29.8%			
			V_p	58.0	8.2%	0.03 mg/L;			
			V_{CSF}	0.11	/	CSF:			
			Q	3.1	88.9%	36.6%			
			Q_{CSF}	0.05	/	0.03 mg/L			
Dong HY (2016) [17]	NONMEM (FOCE-I)	1 CMT with FO elimination	CL	6.8 + 0.0134 × (AGE-61)	23.2%	3.6%	Bootstrap	NR	Design dosing regimen
			V	78.6	36.7%	0.227 mg/L			
Taubert M (2016) [41]	NONMEM (FOCE-I)	2 CMT with FO absorption and elimination	CL	$7.92 \times (\text{lactate}/1.91)^{-0.21}$ $\times (\text{fibrinogen}/13.0)^{0.04}$ $\times$ 1.82 (if ARDS)	58%	33.9% 0.07 mg/L	GOF, Bootstrap	NR	NR
			Q	65.59	/				
			V_c	$15 \times (\text{TBW}/76)^{1.31}$ $\times$ 1.53 (If peritonitis)	37%				
			V_p	26.55	/				
			K_a	1.72	/				

Table 3 (continued)

Study (publication year)	Software / Algorithm	Structural Model	Fixed effect parameters		Between-subject variability	Residual unexplained variability	Internal validation	External validation (N=number of subjects)	Model application
Minichmayr IK (2017) [11]	NONMEM (FOCE-I)	2 CMT with FO absorption and with concentration and time-dependent inhibition elimination	K_a	1.41 h^{-1}	118%	PL: 15.7% UF: 12.4% µDA: 33.9% µDM:27.0% rDA: 19.4% rDM: 19.4%	GOF, VPC, Bootstrap	NR	AUC
			CL	(7.67 for healthy volunteer, 11.2 for septic patients and 6.35 for diabetic patients) × (1 + 0.00835 × (CL_{CR}[a] -80.0))	40.1%				
			V_c	22.7 × (TBW/69.5)	36.6%				
			V_p	19.9 × (TBW/69.5)	39.4%				
			Q	57.9 × $(TBW/69.5)^{0.75}$	/				
			F_U	0.88	4.1%				
			TF_A	90%	21.9%				
			TF_M	86.2%	33.8%				
			K_{IC}	0.0017 FIXED	/				
			IC_{50}	0.48	/				
			$TF_{diabetic}$ (%)[e]	-34.9	/				
			RCLF [%]	51.3	6.45%				
			RR_A [%]	38.5	23.8%				
			RR_M [%]	53.9	18.2%				

Table 3 (continued)

Study (publication year)	Software / Algorithm	Structural Model	Fixed effect parameters		Between-subject variability	Residual unexplained variability	Internal validation	External validation (N=number of subjects)	Model application
Tsuji Y (2017) [38]	NONMEM (FOCE-I)	2 CMTs with FO absorption and elimination	CL	$(1.86 \times e^{-0.0205 \times (AGE-69)} + 1.44 \times CL_{CR}^{a,f}/100) \times (TBW / 70)^{0.75}$	36.9%	total: 31.8% 0.251 mg/L; free: 31.9% 0.034 mg/L	Bootstrap, pcVPC	NR	NR
			V_c	22.9 ×（TBW/70）	142%				
			V_p	24.7 × (TBW / 70)	5%				
			Q	$10.9 \times (TBW / 70)^{0.75}$	182%				
			T_{abs}	3.61	/				
			F	0.922	/				
			F_U	0.823	/				
Wicha SG (2017) [22]	NONMEM (FOCE-I)	1 CMT with FO elimination	CL_{nr}	$4.41 \times (TBW/57.9)^{0.75} \times (LiMAx/221.5)^{0.388}$	33.6% (33.3%)	10.0% 0.1 mg/L	GOF, VPC	NR	NR
			CL_r	$0.919 \times [1 + 0.0208 \times (CL_{CR}^{a} - 45.6)]$	62.2% (56.4%)				
			$CL_{dialysis}$	1.26	/				
			V	33.8 × (TBW/57.9)	/				
Ide T (2018) [24]	NONMEM (FOCE)	2 CMTs with FO elimination	$CL_{preserved}$	6.36	66.9%	5.8%	Bootstrap, VPC	NR	Design dosing regimen
			$CL_{dysfunction}$	2.06	40.1%				
			CL_{CRRT}	2.74	55.5%				
			Q	26.4	44.0%				
			V_c	19.6	56.8%				
			V_p	22.4	35.1%				

Table 3 (continued)

Study (publication year)	Software / Algorithm	Structural Model	Fixed effect parameters		Between-subject variability	Residual unexplained variability	Internal validation	External validation (N=number of subjects)	Model application
Allegra S (2018) [43]	NONMEM (NR)	1 CMT with FO elimination	CL	7.186 for *ABCB1* c.3435CT/TT × 1.969 for *ABCB1* c.3435CC	60.8%	2.59% 1.90 mg/L	GOF, pcVPC	NR	NR
			V	40.520	33.0%				
Strydom N (2019) [46]	NONMEM (FOCE)	1 CMT with FO absorption and elimination for plasma model[g]	K_a	2.13	/	40.4%	VPC	NR	Design dosing regimen
			CL	3.77	57.0%				
			V	145	/				
Crass RL (2019) [4]	NONMEM (FOCE-I)	1 CMT with FO absorption and elimination	Ka	1.40	/	27.1% 1.43 mg/L	GOF, pcVPC	NR	Design dosing regimen
			CL	3.43 + 3.49 × (BSA-1.89) + 1.77 × (eGFR[h]/80) – 0.0242 × (AGE-40) (If age > 40)	49.9%[i]				
			V	$42.9 \times e^{0.901 \times (BSA-1.89)}$	17.8%[i]				
Xie FF (2019) [47]	NONMEM (FOCE-I)	2 CMT with FO elimination	CL	$7.8 \times (1 - 0.0331 \times (AGE - 60)) \times (TBW/70)^{0.75}$	66.9%[j]	15.9%	GOF, VPC, NPDE	NR	Design dosing regimen
			V_c	$14.3 \times (TBW/70)$	43.5%[j]				
			Q	$65.1 \times (TBW/70)^{0.75}$	/				
			V_p	$23.8 \times (TBW/70)$	/				

Table 3 (continued)

Study (publication year)	Software / Algorithm	Structural Model	Fixed effect parameters		Between-subject variability	Residual unexplained variability	Internal validation	External validation (N=number of subjects)	Model application
Thibault C (2018) [25]	NONMEM (NR)	1 CMT with FO elimination	CL	$0.181 \times (TBW/1.4)^{0.405} \times (PNA/0.07)^{0.831}$	38.3%	1.13 mg/L	Bootstrap, GOF, VPC	NR	Design dosing regimen
			V	$1.17 \times (TBW/1.4)^{0.801}$	100%				
Li SC (2019) [30]	NONMEM (FOCE-ELS)	1 CMT with FO elimination	CL	$1.31 \times (\ln TBW/2.40)^{0.83} \times (\ln eGFR^{k}/4.89)^{0.60}$	39.1%	16.5% 0.02 mg/L	GOF, NPDE, VPC	NR	Design dosing regimen
			V	$4.24 \times (\ln WT/2.40)^{0.86}$	28.1%				
Garcia-Prats AJ (2019) [48]	NONMEM (FOCE-I)	1 CMT with FO absorption and elimination	K_a	0.77	/	25% 0.78 mg/L	GOF, VPC	NR	Design dosing regimen
			CL/F	$4.73 \times (TBW/70)^{0.75}$	37%				
			V/F	$54.8 \times (TBW/70)$	32%				
Ogami C (2019) [29]	NONMEM (FOCE-I)	1 CMT with FO absorption	CL	$5.82 \times (WT/70)^{0.75} \times [PNA^{46.0}/(2.06^{46.0}+PNA^{46.0})]$	52.3%	28.9% and 31.3% for total and unbound concentration respectively	Bootstrap	NR	NR
			V	$41.3 \times (WT/70)$	121%				
			Tabs	3.61 h	/				
			F	0.922	/				
			TM50	2.06	/				
			Hill	46.0	/				
			FU	0.811	/				
Wang DD (2019) [31]	NONMEM (NR)	1 CMT with FO elimination	CL	$11.8 \times (PLT/200)^{0.261}$	29.9%	102.0%	Bootstrap; VPC	NR	NR
			V	209	29.9%				
Alghamdi (2020) [50]	Monolix (SAEM)	1 CMT with FO absorption and elimination	CL	$6.32 \times (CL_{CR}^{a}/97.0)^{0.449}$	36.8%	25.9%	GOF; Bootstrap; VPC	NR	Design dosing regimen
			V	$40.6 \times (WT/63.0)$	10.9%				
			Ka	1.65	70.7%				
			T_{lag}	0.341	88.2%				

Table 3 (continued)

Study (publication year)	Software / Algorithm	Structural Model	Fixed effect parameters		Between-subject variability	Residual unexplained variability	Internal validation	External validation (N=number of subjects)	Model application
Soraluce A (2020) [51]	NONMEM (FOCE-I)	2 CMT with FO elimination	CL	2.62 + 4.35 × (CL_{CR}^{a}/44) + Sc × Qef)	61.5%	15.9% 0.266 $mg \cdot L^{-1}$	GOF, Bootstrap, VPC	11	Design dosing regimen
			V_1	16.2	65.9%				
			Q	71.7	/				
			V_2	29.0	/				
Zhang SH (2020) [32]	Phoenix NLME (FOCE-ELS)	1 CMT with FO elimination	CL	2.68 × $(PTA/48.07)^{0.84}$ × $(CL_{CR}^{a}/99.3)^{0.36}$	29.82%	18.5%	GOF, Bootstrap, pcVPC	NR	Design dosing regimen
			V	58.34	39.33%				
Ehmann L (2020) [42]	NONMEM (FO)	2 CMT with parallel linear and nonlinear MM clearance	CL_u[l]	3.32	66.7%	C_{p_tot} 4.76% C_{p_u} 4.56% C_{ud} 13.3% C_{RD} 1.9%	GOF, Bootstrap, VPC	NR	Design dosing regimen
			$V_{max,u}$	45.9	/				
			$K_{m,u}$	2.93	74.4%				
			$V_{1,u}$	17.0 × (LBW/51.9)	42.1%				
			Q_u	62.4 × $(LBW/51.9)^{0.75}$	46.8%				
			$V_{2,u}$	33.4 × (LBW/51.9)	16.7%				
			f_u	85.6	/				
			$TF_{OBE,u}$	54.1	TF_u 14.8%				
			$TF_{NOBE,u}$	69.0					
			ANAE-TF	-13.6	82.2%				
			$MAPCL_{Tot,u}$%	0.805	/				
			RR_{OBE}	37.5	$RR_{intercatheter}$ 26.1%				
			RR_{NOBE}	57.5	$RR_{intracatheter}$ 27.2%				

Table 3 (continued)

Study (publication year)	Software / Algorithm	Structural Model	Fixed effect parameters		Between-subject variability	Residual unexplained variability	Internal validation	External validation (N=number of subjects)	Model application
Wang XP (2020) [33]	NONMEM (FOCE-I)	1 CMT with FO elimination	CL	$5.6 \times (CL_{CR}{}^{a}/61)^{0.386}$	63.9%	36.2%	GOF, VPC, Bootstrap, NPDE	NR	Design dosing regimen
			V	43.4	17.6%	0.055 $mg \cdot L^{-1}$			
Blackman AL (2021) [49]	Pumas (FOCE)	1 CMT with FO elimination	CL	6.7×0.289 (if cirrhosis) $\times (TBW/140)^{1.12}$	25.0%	14.0%	GOF, QPC, VPC	NR	Design dosing regimen
			V	$64.3 \times (TBW/140)^{1.67}$	21.0%				
Yang M (2021) [34]	Phoenix NLME (FOCE-I)	2 CMT with FO elimination	CL	$2.34 \times (WT/15)^{0.8} \times (AST/45.9)^{(-0.16)}$	52.51%	29.0%	GOF, VPC, Bootstrap	NR	Design dosing regimen
			Q	$7.14 \times (WT/15)^{1.09}$	53.45%				
			Vc	5.22	55.78%				
			Vp	28.79	/				

Abbreviations: ALT, alanine amino transferase; AST, aspartate aminotransferase; ARDS, acute respiratory distress syndrome; BSA, body surface area; CIR, liver cirrhosis; CL_{CR}, creatinine clearance; CMT, compartment; CP_tot, total plasma concentrations; CP_u, unbound plasma concentrations; CRD, retrodialysate concentration; CμD, microdialysate concentration; CSF, cerebrospinal fluid; DURA, duration of administration; eGFR, estimated glomerular filtration rate; FO, first order; FOCE, FO conditional estimation; FOCE-ELS, FO estimation-extended least squares method; FOCE-I, FO conditional estimation method with the interaction option; HB, hemoglobin; IT2S, iterative two-stage analysis; LBW, lean body weight, LiMAx, the maximal liver function capacity; MAP, mean arterial pressure; MM, Michaelis-Menten; NR, not reported; OBE, obesity; PL, plasma concentration; PLT, platelets; PTA, prothrombin time activity; PNA, postnatal age (in years); Qef: effluent flow; Sc: sieving coefficient; TBW, total body weight

PK parameters: ANAE-TF, anaesthesia effect on TFu; $AUC_{0\text{-}12\ h}$, area under the concentration-time curve during 24 hours; CL, total clearance; CL_{CRRT}, clearance for patients on low-dose continuous renal replacement therapy. $CL_{dysfunction}$, clearance for patients with renal dysfunction; CL_{nr}, non-renal clearance; $CL_{preserved}$, clearance for patients with preserved renal function; CL_r, renal clearance; CL_{tavg}, the calculated average total clearance of linezolid over the first 7 days of treatment; CLTot,u, Total clearance of unbound linezolid; CLu, CL of unbound linezolid; F_U, fraction unbound; IC_{50}, concentration in inhibition compartment yielding 50 % of CL inhibition; K_a, the absorption rate constant; K_{cp}, rate constant for drug distribution from the central to peripheral compartment; K_{el}, linear elimination rate constant. K_{IC}, rate constant for the transfer into inhibition compartment; K_{pc}, rate constant for drug distribution from the peripheral to central compartment; KPL, rate of drug moving from plasma to lesion (KPL) ; K_m,

Michaelis-Menten constant; MAPCLTot,u, effect of MAP on CLTot,u; UF, unbound concentration; Q, intercompartmental (central-peripheral) clearance; Qu, intercompartmental distribution of unbound linezolid; RCLF, remaining fraction of CL at maximum CL inhibition; rD_A/rDM, mg/L, retrodialysate of subcutaneous adipose/muscle tissue; RR_A, RR_M, relative recovery of catheters located in interstitial space fluid of subcutaneous adipose/muscle tissue; RROBE, RRNOBE, relative recovery for obese and non-obese patients; T_{abs}, absorption half-life. TF_A, TF_M, factors transforming plasma to interstitial space fluid of subcutaneous adipose/muscle tissue concentrations; T_{lag}, the lag time before onset of absorption; TFOBE,u, TFNOBE,u, tissue factor of unbound linezolid for obese and non-obese patients; μD_A/ μD_M, microdialysate concentration of subcutaneous adipose/muscle tissue; V, volume of distribution; V_c, volume of distribution of the central compartment; V_{max}, maximum velocity of capacity-limited clearance; V_p, volume of distribution of the central compartment; V_{ss}, volume of distribution at steady state; V1,u, V2,u, volume of distribution parameters of central and peripheral CMTs of unbound linezolid; Vmax,u, maximum elimination rate of unbound linezolid;

[a]estimated with Cockcroft-Gault formula.

[b] intrinsic clearance, $CL_i \times K_m = V_{max}$

[c] 2 CMT was fitted to the multiple-dose data, 1CMT was fitted to single-dose data, but PK parameter in 1CMT was not reported;

[d] eGFR was calculated with revised equation for Japanese. eGFR (mL / min / 1.73 m^2) = $194 \times SCR^{-1.094} \times AGE^{-0.287} \times 0.739$ (if female).

[e] Difference in percent compared with healthy volunteers.

[f] CL_{CR}/100 was assumed to be 0.5 for the 4 youngest patients (1, 5, 8 and 13 years old).

[g] 10 CMTs with FO absorption and elimination for tissue model was developed, and the rates of drug moving from plasma to lesion were shown as follows: lung 0.152 h^{-1}; necrotic nodule 0.229 h^{-1}; caseum closed nodule 0.006 h^{-1}; caseous fibrotic nodule 0.275 h^{-1}; caseum from cavity 0.427 h^{-1}; cavity wall 0.305 h^{-1}; fibrotic tissue 1.29 h^{-1}; small cellular nodule 0.001 h^{-1}; fungal ball NA.

[h] calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

[i] The covariance between the variances of CL and V was 0.0603.

[j] The covariance between the variances of CL and Vc was 0.23.

[k] calculated by the modified Schwartz formula.

[l] Clearance was described by the parallel linear (CL_u) and nonlinear concentration-dependent Michaelis-Menten clearance (V_{max} and K_m).