Table 2. Characteristics of included population pharmacokinetic studies.

Study (publication year)	Country (single/multiple Centers)	Type of study	Patient characteristics	Number of subjects (Male/ Female)	Number of observations[a]	Sampling time	Age (years) Mean ± SD Median [Range]	Weight (kg) Mean ± SD Median [Range]	Dosage regimen[b]	Bioassay [LOQ] ($mg \cdot L^{-1}$)
Meagher AK (2003) [44]	USA (Single)	Prospective	Patients treated in a compassionate use program	318 (166/152)	1930	C_{min}[c], 2, 4, and 8 h post dose for single-interval sampling; or C_{max}[d] and C_{min} for split-interval sampling	Male: 55 ± 16.5 [14-88] Female: 56 ± 16.2 [16-88]	Male: 80 ± 22.4 [40-200] Female: 74 ± 22.2 [37-142]	600 mg q12h i.v. gtt. over 0.5 to 2 h and/or orally; If weight < 40 kg, then 10 mg/kg q12h	HPLC [0.01]
Whitehouse T (2005) [45]	UK (Dual)	Prospective	Critically ill patients	28 (17/11)	595	IS[a]	59 [19-90]	NR BMI: 25.0 [19.0-38.1]	600 mg q12h i.v. gtt. over 30 min for the first three doses and then 600 mg q24h iv	HPLC [0.1]
Abe S (2009) [7]	Japan/UK/ USA Caucasian[e] (Multiple)	Prospective	Patients with infectious disease	455 (265/190)	2539	intensive sampling within 18 h and sparse sampling within 18-60 h after last dose	58.6 ± 18.3 [18-98]	73.1 ± 24.4 [30-190.5]	600 mg q12h for Japanese and primarily 600 q12h for Caucasian both by i.v. gtt and / or orally[f];	HPLC [0.01]
Swoboda S (2010) [40]	German (Single)	Retrospective	Septic patients with and without extended dialysis	15 (10/5)	NR	IS[b]	on dialysis: 57.2 ± 11.9; not dialysis: 68.6 ± 4.2	on dialysis: 97.4 ± 19.4; not dialysis: 88.8 ± 9.1	600 mg q12h i.v. gtt for 60 min	HPLC [0.1]

Table 2 (continued)

Study (publication year)	Country (single/multiple Centers)	Type of study	Patient characteristics	Number of subjects (Male/ Female)	Number of observations[a]	Sampling time	Age (years) Mean ± SD Median [Range]	Weight (kg) Mean ± SD Median [Range]	Dosage regimen[b]	Bioassay [LOQ] ($mg \cdot L^{-1}$)
Sasaki T (2011) [35]	Japan (single)	Prospective	Patients with infectious disease	50 (36/14)	135	pre-dose, 1.5, 2, 4, 5, 8, and 9 h post dose at steady state	69.1 ± 12.8 [32-92]	57.3 ± 12.1 [38.4-100]	300 to 600 mg q12h orally and/or i.v. gtt. over 1 to 2 h.	HPLC [0.1]
Tsuji Y (2013) [36]	Japan (single)	Retrospective	Low body weight patients with renal dysfunction	14 (9/5)	68	elimination phase and many near trough concentrations	67 ± 12 [42-84]	53.4 ± 12.0 [32.5-69.7]	600 mg q12h i.v. gtt over 60 to 90 min	HPLC [NR]
Matsumoto K (2014) [37]	Japan (single)	Prospective	Adult patients	44 (34/10)	88	C_{min} and C_{max}	70.6 ± 10.3 [34.0-86.0]	57.1 ± 13.2 [36.0-95.3]	300 mg or 600 mg q12h i.v. gtt or orally	HPLC [0.2]
Luque S (2014) [18]	Span (single)	Prospective	Neurosurgical critically ill patients	11 (7/4)[g]	plasma: 46; CSF: 45	pre-dose, 1, 3, 5, 8, 12 h post dose at steady state	51.9 ± 10.3	76.8 ± 13.1	600 mg q12h i.v. gtt for 1 h	HPLC [plasma 0.5 CSF 0.1]
Dong HY (2016) [17]	China (single)	Retrospective	Critically ill patients with staphylococcal infections	27 (21/6)	133	pre-dose, 0.5, 1, 2, 3, 6, 8, 10 and 12 h post dose	60.6 ± 19.9 [17-91]	63.2 ± 11.6	600 mg q12h i.v. gtt over 30 to 60 min	HPLC [0.31]

Table 2 (continued)

Study (publication year)	Country (single/multiple Centers)	Type of study	Patient characteristics	Number of subjects (Male/ Female)	Number of observations[a]	Sampling time	Age (years) Mean ± SD Median [Range]	Weight (kg) Mean ± SD Median [Range]	Dosage regimen[b]	Bioassay [LOQ] ($mg \cdot L^{-1}$)
Taubert M (2016) [41]	German Single	Prospective	Critically ill patients	52 (33/19)	NR	intensive sampling over 4 days after 0 to 4 administrations	58 [28-84]	76 [44-120]	600 mg q12h i.v. gtt over 10-120 min or orally	LC-MS/MS [NR]
Minichmayr IK (2017) [11]	USA / German / Austria (Multiple)	Prospective	Septic patients, patients with diabetic or cystic fibrosis, healthy	51 (32/19)	plasma: 1598; ISF_A: 1430; ISF_M: 1089	IS[c]	61.0 [24.0-78.0][h]	69.5 [48.1-123][h]	600 mg q12h i.v. gtt for 30 min or orally[i]	HPLC [0.2/0.8][j]
Tsuji Y (2017) [38]	Japan (Multiple)	Retrospective	Hospitalized patients	81 (51/30)	493 total; 380 unbound[k]	basically, in the elimination phase, and many near-trough concentrations	69 [8-85][h]	53.2 [21-99.5][h]	10 mg kg^{-1} q8h (paediatrics) or 300 mg q24h to 600 mg q12h (adult) i.v. gtt. over 1 to 2 h and/or orally.	HPLC [0.1]
Wicha SG (2017) [22]	German (Single)	Prospective	Patients with different degrees of liver failure	28 (NR)	serum: 51; urine: 48; dialysis: 11	C_{min} at steady state	62.6 ± 13.4 62 [33-82]	81.0 ± 21.7 80 [46-150]	600mg q12h i.v. gtt for 30 min	HPLC [serum 0.2 urine and dialysis 1.0]

Table 2 (continued)

Study (publication year)	Country (single/multiple Centers)	Type of study	Patient characteristics	Number of subjects (Male/ Female)	Number of observations[a]	Sampling time	Age (years) Mean ± SD Median [Range]	Weight (kg) Mean ± SD Median [Range]	Dosage regimen[b]	Bioassay [LOQ] ($mg \cdot L^{-1}$)
Ide T (2018) [24]	Japan (Single)	Prospective	Sepsis patients with and without continuous renal replacement therapy	27 (NR)	NR	pre-dose, 1, 1.5, 2, 3, 5, 12 h post dose on day 3 or later	RP: 65.1±14.5 RD: 74.3±11.3 CRRT: 60.2±16.1	RP: 57.8 ± 7.54 RD: 53.4 ± 10.2 CRRT: 58.7 ± 15.7	600 mg q12h i.v. gtt over 60 min	HPLC [NR]
Allegra S (2018) [43]	Italy (Single)	Prospective	Critically ill patients	27 (15/12)	159	pre-dose, 0.5, 2, 3.5, 5.5, 7.5, 11 h post dose at steady state	63.1 ± 15.4 [68.0]	67.5 ± 11.9 [64.0]	600 mg q12h i.v. gtt. over 30 min	UPLC [0.12]
Strydom N (2019) [46]	Korea (Single)	Prospective	Tuberculosis patients undergoing lung resection surgery	9 (5/4)	plasma: 44; tissue lesion: 156[l]	sparse sampling within 31.5 h post dose at steady state	40.3 ± 12.7 43 [23-58]	BMI: 22.9 ± 3.7 22.2 [18.8-29.4]	300 mg q12h orally	LC/MS-MS [plasma:0.001] [tissue lesion: 10 ng/g]
Crass RL (2019) [4]	Italy (Single)	Retrospective	Patients with and without renal impairment	603 (409/194)	1309	C_{max} and C_{min}	62 ± 15	76 ± 19	600 mg q12h orally or i.v. gtt. over 1 hour initially and adjust later when necessary	HPLC [0.2]

Table 2 (continued)

Study (publication year)	Country (single/multiple Centers)	Type of study	Patient characteristics	Number of subjects (Male/ Female)	Number of observations[a]	Sampling time	Age (years) Mean ± SD Median [Range]	Weight (kg) Mean ± SD Median [Range]	Dosage regimen[b]	Bioassay [LOQ] ($mg \cdot L^{-1}$)
Xie FF (2019) [47]	Greece (Multiple)	Prospective	Obese patients with pneumonia	15 (9/6)	NR	pre-dose, 0.5, 0.75, 1, 1.25, 1.5, 2, 4, 6, 8, 10, 12 h post 6th dose	64.5 [IQR: 56.2-71.0]	125 [IQR: 112.5-133.0]	600 mg q12h i.v. gtt. over 30 min	LC-MS [0.05]
Thibault C (2018) [25]	Canada (Single)	Retrospective	Premature infants	26 (15/11)	78	0.5, 2-3 h post dose at steady state	24 [8-88] days	1.423 [0.81-3.256]	GA ≤ 34 wk, PNA ≤ 7 d, 10 mg/kg q12h, i.v. gtt.; GA ≤ 34 wk, PNA > 7 d, 10 mg/kg q8h, i.v. gtt.; GA > 34 wk, 10 mg/kg q8h, i.v. gtt..	HPLC [0.78]
Li SC (2019) [30]	China (Single)	Prospective	Pediatric patients	112 (65/47)	135	opportunistic sampling at steady state	2.9 ± 3.4 1.6 [0.03-11.9]	13.9 ± 10.2 11.0 [2.1-46.0]	10 mg/kg q8h i.v. gtt. over 1 hour	HPLC [0.4]

Table 2 (continued)

Study (publication year)	Country (single/multiple Centers)	Type of study	Patient characteristics	Number of subjects (Male/ Female)	Number of observations[a]	Sampling time	Age (years) Mean ± SD Median [Range]	Weight (kg) Mean ± SD Median [Range]	Dosage regimen[b]	Bioassay [LOQ] ($mg \cdot L^{-1}$)
Garcia-Prats AJ (2019) [48]	South Africa (single)	Prospective	Children with multidrug-resistant tuberculosis	48 (24/24)	196	MDRPK1: 0, 1, 2, 4, 8 and either 6 or 11 h post dose at steady state; MDRPK2: 0, 1, 4, 10 h post dose	4.6 [0.6-15.3]	13.9 [7.15-57.6]	< 10 years, 10 mg/kg q 12h orally; > 10 years, 10 mg/kg q 24h orally[m]; up to maximum daily dose of 600 mg.	LC-MS/MS [0.1]
Ogami C (2019) [39]	Japan (single)	Prospective	Pediatric patients 15 (10/5)	48 (24/24)	total concentrations : 92; unbound concentrations : 70	sparse sampling within 28 h post dose	24 [2-156][n] months	9.9 [3.0-49.7][n]	10 mg/kg q 8h orally and/or i.v.gtt	HPLC [0.1]
Wang DD (2019) [31]	China (single)	Retrospective	Patients with different types of shock	37 (27/10)	90	0, 1, 2, 3, 4, 5 and 6 h post dose	59.5 ± 16.3 62.0 [29.0-89.0]	NR	600 mg q 12h, i.v.gtt	NR

Table 2 (continued)

Study (publication year)	Country (single/multiple Centers)	Type of study	Patient characteristics	Number of subjects (Male/ Female)	Number of observations[a]	Sampling time	Age (years) Mean ± SD Median [Range]	Weight (kg) Mean ± SD Median [Range]	Dosage regimen[b]	Bioassay [LOQ] ($mg \cdot L^{-1}$)
Alghamdi (2020) [50]	Brazil/Georgia /USA (Multiple)	Brazil/Georgia : Prospective; USA: retrospective	Tuberculosis patients	104 (78/26)	508	Brazil: pre-dose and at 1, 2, 4, 8, 12, 18 and 24 h post dose; Georgia: pre-dose and at 2, 4 to 6, 8 to 10, 12, and 24 h post dose; USA: sparse sampling mainly at 2 h post dose	37.1 [IQR:27.3-49.0]	60.0 [IQR:54.2-69.8]	Brazil: 600 mg q 24h or q 12h orally; Georgia: 600 mg daily (except one received 300 mg daily) orally; USA: 300 to 600 mg q 24h orally	Brazil: HPLC [NR] Georgia/USA:LC-MS [0.3]
Soraluce A (2020) [51]	Spain (Multiple)	Prospective	Critically ill patients undergoing CRRT and patients with preserved renal function	40 (29/11)	311	pre-dose, 1, 2, 3, 6, 8 to 10 and 12 h post dose	70 [22-85]	73 [55-110]	600 mg q 12h i.v. gtt over 30 min (one received an infusion of 60 min)	HPLC [plasma: 0.5] [effluent: 0.2]
Zhang SH (2020) [32]	China (Single)	Prospective	Patients with liver dysfunction	45 (39/6)	63	sparse sampling within 12 h post dose at steady state	47 [28-68]	65.5 [45.5-95]	600 mg q 12h i.v. gtt between 1 and 2h	HPLC [0.22]
Ehmann L (2020) [42]	German (Single)	Prospective	Obese and non-obese patients30	30 (4/26)	239[o]	Blood samples: 0, 0.5, 1, 2, 3, 4, 5, 6 and 8 hours post dose Tissue samples: 0-0.5, 0.5-1, 1-1.5, 1.5-2, 2-3, 3-4, 4-5, 5-6, 6-7, and 7-8 hours post dose	51.5 [30.0-65.0]	101 [52.0-230]	600 mg q 24h i.v. gtt over 30 min	HPLC [NR]

Table 2 (continued)

Study (publication year)	Country (single/multiple Centers)	Type of study	Patient characteristics	Number of subjects (Male/ Female)	Number of observations[a]	Sampling time	Age (years) Mean ± SD Median [Range]	Weight (kg) Mean ± SD Median [Range]	Dosage regimen[b]	Bioassay [LOQ] ($mg \cdot L^{-1}$)
Wang XP (2020) [33]	China (Multiple)	Prospective	Critically ill patients	117 (34/83)	241	C_{max} and C_{min} in patients administered at least one dose.	62 [19-90]	63.0 [43.8-115.0]	600 mg q 12h i.v. gtt	LC-MS/MS [0.05]
Blackman AL (2021) [49]	USA (Single)	Prospective	Critically ill obese patients with severe skin and soft tissue infections	11 (6/5)	44	Sparse sampling at 1, 3, 5 h post infusion and pre-dose at steady state	59.6 ± 13.0	141.3 [99.9-188.0]	600 mg q 12h i.v. gtt within 30 min	HPLC [0.1]
Yang M (2021) [34]	China (Single)	Prospective	Critically ill pediatric patients	63 (43/20)	246	C_{min}, C_{max} and another two sampling at elimination phase	5.21 ± 4.22	22.28 ± 15.00	10 mg/kg q 8h for age < 12 years, 600 mg q 12h for age between 12 and 18 years, i.v. gtt within 1-2h	UPLC-MS/MS [0.078]

Abbreviations: BMI, kg/m^2, body mass index; CRRT, patients on continuous renal replacement therapy (800 ml/h); RD: patients with renal dysfunction (CL_{CR} < 50 ml/min); HPLC, high performance liquid chromatography; IQR, inter-quartile range; i.v. gtt, intravenous infusion; IS: intensive sampling; LLOQ, lower limit of quantification; NR, not reported. RP: patients with preserved renal function ($CL_{CR} \geq 50$ ml/min); UPLC, ultra-performance liquid chromatography.

[a] Plasma samples were collected, unless otherwise specified.[b] The intravenous infusion time was not listed if it was not reported.

[c] C_{min}: 0-0.5 h before administration.

[d] C_{max}: at the end of linezolid infusion or 1-2 h after the oral administration.

[e] Four Caucasian phase II/III studies were conducted in UK and USA.

[f] One sample of 1 patient and 16 samples of 9 patients were collected after 400 mg and 200 to 580 mg, respectively. Those data were included in modelling because of no significant deviation from linear PK at doses up to 625 mg.

[g] Eleven patients were included for the study but only 8 patients were used for modelling as 3 patients did not have enough data points.

[h] Fifth - 95th percentiles.

[i] For patients with sepsis and healthy volunteers, the first dose was 600 mg administered as a 30-min intravenous infusion. Patients with sepsis continued to receive 600 mg q12h i.v. gtt while healthy volunteers were given orally as 600 mg tablet q12h. Five patients with diabetic foot infection received a single dose [600 mg] and five patients received multiple doses (600 mg q12h) for at least 3 days; All doses were intravenously administered as an infusion over 30-min. Patients with cystic fibrosis were randomized to initially receive oral/IV linezolid at 600 mg bid for 9 doses; after at least 9-day washout period, patients were crossed over to receive the alternate formulation; intravenous infusion lasted over 30 min.

[j] 0.2 mg/L for plasma and 0.8 mg/L for microdialysate / retrodialysate / perfusate / ultrafiltrate.

[k] Samples were from either serum or plasma.

[l] samples from tissue lesions included: lung (41), cavity wall (24), small nodule (8), caseum from cavity (29), closed nodule caseum (4), caseous fibrotic nodule (9), necrotic nodule (37) and fibrotic tissue (4).

[m] the dosage regimen for ten-year-old children was not specified.

[n]: 2.5th-97.5th percentiles.

[o]: total plasma concentrations (n=239), unbound plasma concentrations (n=90), tissue concentration (n=591), retrodialysate concentrations (n=89).

IS[a]: 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2.25, 2.5, 4, 6, 12 h post the first dose; C_{min}, 1 h post dose on day 1, 2, 3, 5, 7, and every third day thereafter if needed.

IS[b]: C_{min}, 1, 1.5, 2, 3, 4, 6, 8, 11.9, 13, 13.5, 14, 15, 16, 18, 20, and 23.9 h post-dose (on day 2-day 4), linezolid infusions were administered at t = 0 and 12 h.

IS[c]: For septic patients and healthy volunteers, samples were collected at 0, 0.33, 0.66, 1, 1.33, 1.66, 2, 2.33, 2.66, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8 h; Visit 1 started at first dose (all IDs); Visit 2 for patients start 45.2-117 h after first dose (n = 18 IDs); Visit 2 for healthy volunteers started 69.2-95.2 h after first dose (n = 9 IDs). For all patients with diabetic foot infection, samples were collected at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8 h after the first dose; For patients with cystic fibrosis, samples were also collected at the same time points after multiple administrations (600 mg bid for at least 3 days, n = 5 IDs). For patients with cystic fibrosis, samplings were collected at 0, 0.5, 0.75, 1, 1.25, 1.5, 2, 4, 6, 8, 12 h after the first and ninth doses.