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REVIEW ARTICLE

A Review of Population Pharmacokinetic Analyses of Linezolid

Enrique Bandín-Vilar[1,2,3] · Laura García-Quintanilla[1,2,3] · Ana Castro-Balado[1,2,3] · Irene Zarra-Ferro[1,2] · Miguel González-Barcia[1,2] · Manuel Campos-Toimil[4] · Víctor Mangas-Sanjuan[5,6] · Cristina Mondelo-García[1,2] · Anxo Fernández-Ferreiro[1,2]

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Abstract
In recent years, many studies on population pharmacokinetics of linezolid have been conducted. This comprehensive review aimed to summarize population pharmacokinetic models of linezolid, by focusing on dosage optimization to maximize the probability of attaining a certain pharmacokinetic-pharmacodynamic parameter in special populations. We searched the PubMed and EMBASE databases for population pharmacokinetic analyses of linezolid using a parametric non-linear mixed-effect approach, including both observational and prospective trials. Of the 32 studies, 26 were performed in adults, four in children, and one in both adults and children. High between-subject variability was determined in the majority of the models, which was in line with the variability of linezolid concentrations previously detected in observational studies. Some studies found that patients with renal impairment, hepatic failure, advanced age, or low body weight had higher exposure and adverse reactions rates. In contrast, lower concentrations and therapeutic failure were associated with obese patients, young patients, and patients who had undergone renal replacement techniques. In critically ill patients, the inter-individual and intra-individual variability was even greater, suggesting that this population is at an even higher risk of underexposure and overexposure. Therapeutic drug monitoring may be warranted in a large proportion of patients given that the Monte Carlo simulations demonstrated that the one-size-fits-all labeled dosing of 600 mg every 12 h could lead to toxicity or therapeutic failure for high values of the minimum inhibitory concentration of the target pathogen. Further research on covariates, including renal function, hepatic function, and drug–drug interactions related to P-glycoprotein could help to explain variability and improve linezolid dosing regimens.

1 Introduction

Linezolid is an oxazolidinone antibiotic used for treating serious resistant Gram-positive bacterial infections, such as methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Streptococcus*, and vancomycin-resistant *Enterococcus* [1–3], which blocks protein synthesis by binding to the 50S portion of the ribosome. Linezolid can be administered either intravenously or orally owing to its absolute bioavailability of close to 100% [4].

The labeled dosage of linezolid (600 mg every 12 h is based on several dose-finding trials that were conducted predominantly on healthy volunteers. Minimum trough concentrations (C_{min}) and mean steady-state concentrations were considered effective against Gram-positive pathogens, when taking into account their minimum inhibitory concentration (MIC). No correlation was observed between adverse effects and linezolid concentrations [5–7], nevertheless, some differences in the pharmacokinetic (PK) parameters were identified when comparing special populations, such as patients with renal impairment [8], patients with hepatic impairment [8], and elderly patients [9] to healthy subjects.

Adverse reactions related to mitochondrial toxicity, such as optic neuropathy, lactic acidosis, and in particular, hematological toxicity are the main concern. Reported rates of

Enrique Bandín-Vilar, Laura García-Quintanilla and Ana Castro-Balado contributed equally to the article.

✉ Víctor Mangas-Sanjuan
victor.mangas@uv.es

✉ Cristina Mondelo-García
crismondelo1@gmail.com

✉ Anxo Fernández-Ferreiro
anxordes@gmail.com

Extended author information available on the last page of the article

Key Points

High variability of linezolid exposure has been observed, which could result in therapeutic failure and toxicity with standard dosing.

Linezolid population pharmacokinetic models conducted in special populations are very useful for improving linezolid dosing regimens because they consider both population and pathogen characteristics.

Some covariates have been found to influence linezolid pharmacokinetics but unexplained variability still remains high, so further research is required to improve the predictive performance of these models.

hematological adverse reactions in clinical trials were significantly lower than those observed in subsequent observational studies, especially for thrombocytopenia [10, 11]. Some factors associated with higher linezolid concentrations and thrombocytopenia occurrence included renal insufficiency [12–16], hepatic impairment [13], longer treatment duration [13], low baseline platelet count [17–19], higher daily dosage [20], and high total bilirubin [19] (Table S1 of the Electronic Supplementary Material [ESM]).

Large interindividual variability has been associated with linezolid exposure, which could increase the incidence of safety issues and compromise treatment efficacy. Several authors proposed the need for linezolid concentrations to be monitored [21–23] given that some studies reported that the concentrations in almost half of patients treated with standard doses were outside the desired range [23, 24].

This percentage could be higher in special populations, which would lead to an unacceptable risk of both underexposure and overexposure. Physiological factors such as renal impairment, hepatic failure, advanced age and low body weight (WT) have been correlated with higher concentrations and adverse reaction rates. On the contrary, renal replacement techniques, younger age, excess WT, and obesity have been associated with low concentrations and therapeutic failure. There was an even higher inter-individual and intra-individual variability among critically ill patients, suggesting that this population is at an even higher risk of underexposure and overexposure [21].

In this scenario, population PK (popPK) models are a very useful tool for improving linezolid dosing regimens in special populations, maximizing the probability of target attainment (PTA) of the proposed PK/pharmacodynamic (PD) indexes. This review aims to compile all published popPK models of linezolid, focusing on dosing simulations and the influence of covariates to optimize treatment.

2 Methods

2.1 Search Strategy

The EMBASE and PubMed databases were searched from inception to February 2022 using the following terms: 'linezolid' AND ('population pharmacokinetics' OR 'pharmacometrics' OR 'pharmacokinetic model' OR 'popPK' OR 'nonlinear mixed effect model' OR 'NONMEM'). The reference lists from the relevant studies were analyzed for additional literature.

2.2 Inclusion/Exclusion Criteria

All popPK models of linezolid that met the following inclusion criteria were included in the review: (1) studied population: pediatric and adult patients; (2) treatment: linezolid administered either orally or intravenously; and (3) PK analysis: a non-linear, mixed-effect PK modeling approach was used. The following studies were excluded: (1) reviews and in vitro and animal studies; (2) papers not written in English; and (3) studies in which non-compartmental or non-parametric approaches were employed (Fig. 1).

2.3 Data Extraction

Three authors performed data extraction using a data collection form to collect the following variables: first author, year of publication, number of patients, participant characteristics (patients/healthy subjects, race/country, age, sex, WT, adult/pediatric, pathology), route of administration, number of observations, observations per patient, modeling software, structural and statistical model, tested and retained covariates, and model evaluation method. The model evaluation methods were divided into three types based on the increasing order of quality: basic internal, advanced internal, and external model evaluation [25].

3 Therapeutic Drug Monitoring

Linezolid peak plasma concentration is usually achieved within 1–2 h following oral administration [26]. The volume of distribution (Vd) is close to total body water, approximately 50–60 L [27], and its protein binding to albumin is relatively low, with a range from 10.5 to 31% [5, 28–35]. It shows good tissue distribution (Fig. 2) [Table S2 of the ESM].

Linezolid metabolism is complex as two major metabolites are formed by oxidation pathways that are not mediated by cytochrome P450 but by reactive oxygen species [36–38]. Nevertheless, interactions related to cytochrome

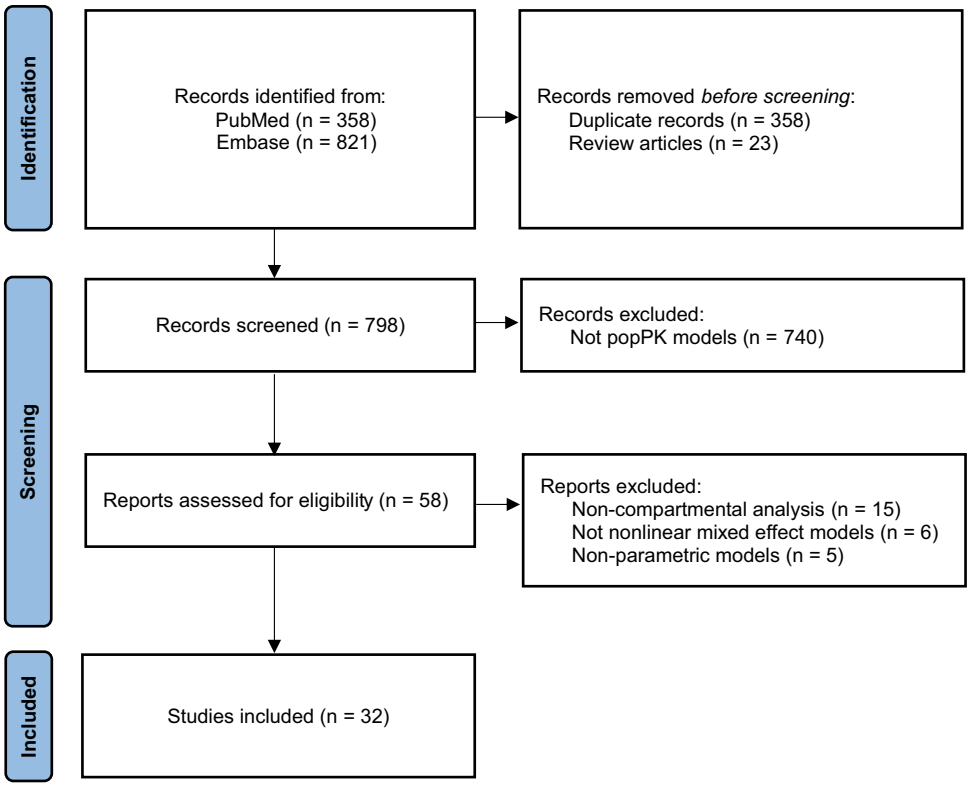

Fig. 1 Flow diagram of search results and selection process of the studies. *popPK* population pharmacokinetic

P450 3A4/3A5 and, above all, P-glycoprotein have been proposed [10, 22, 39–47] (Table S3 of the ESM) (Fig. 2).

There was a linear relationship between the C_{min} and the area under the curve in 24 h ($AUC_{0–24h}$); therefore, trough concentrations could be used as a predictor of drug exposure. The correlation between the observed and predicted AUC was high. The predicted AUC ranged from 0.7-fold to 1.3-fold and from 0.76-fold to 1.5-fold of the real AUC

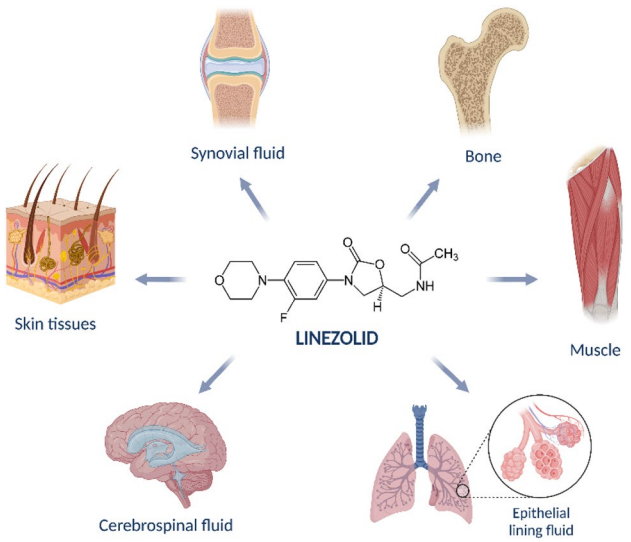

Fig. 2 Tissues in which linezolid shows good distribution properties. Created with BioRender.com [7–15]

values, respectively [48, 49]. Post-2-hour, post-5-hour, or post-6-hour sampling has also been proposed in oral administration to assess peak plasma concentration and characterize delayed absorption [24, 50].

Furthermore, it is essential to read into this value the infectious context, considering the MIC of this antibiotic against the isolated microorganism. Different PK/PD targets have been proposed as a ratio of $AUC_{0–24h}$/MIC = 50–100 [51], 80–120 [52], and a percentage of time above the MIC of greater than 85% during the entire dosing interval in order to maximize efficacy and prevent the development of antibiotic resistance [2, 51, 52]. However, a C_{min} of higher than 7.5–22.1 mg/L was significantly correlated with the occurrence of adverse effects [53–55], especially hematological toxicity, peripheral neuropathy, mitochondrial toxicity, and optic neuropathy [56]. Therefore, a target therapeutic range of C_{min} between 2 and 7 mg/L for steady-state linezolid has been proposed for treating Gram-positive bacterial infections [57]. In the case of tuberculosis (TB) infections, a C_{min} target of < 2 mg/L has also been proposed because of its lower MIC, usually ≤ 1 mg/L, even in extensively drug-resistant TB [58].

The strong correlation between exposure and efficacy and in particular toxicity supports the use of linezolid therapeutic drug monitoring with the following proposed PK/PD indexes: $AUC_{0–24h}$/MIC = 80–120, percentage of time above the MIC $\geq$85%, and C_{min} between 2 and 7 mg/L [2, 24, 51, 52, 59–61]. A recent position paper by several scientific

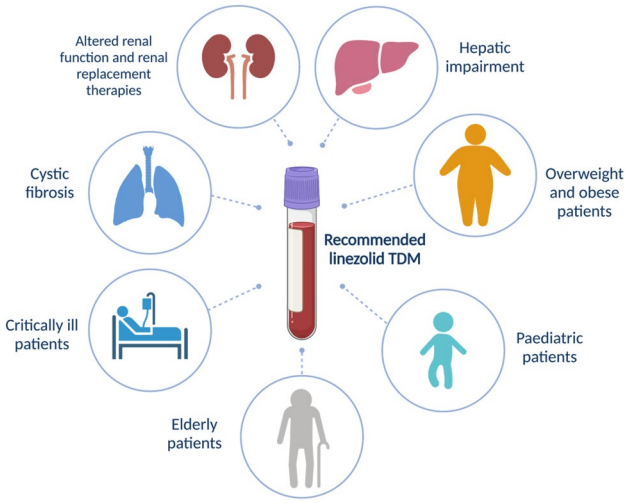

Fig. 3 Special populations in which linezolid therapeutic drug monitoring (TDM) may be warranted. Created with BioRender.com

societies (ESICM, ESCMID, IATDMCT and ISAC) pointed out that therapeutic drug monitoring is clearly recommended for linezolid in critically ill patients [57] (Fig. 3).

4 Characteristics of popPK Models

The initial database search yielded 1179 publications, of which a total of 32 studies involving 2572 participants met the inclusion criteria. The population characteristics are summarized in Tables 1 and 2, respectively. Studies were published between 2005 and 2021, and the number of subjects ranged from 5 to 603, with a median of 44.5. Of the 32 publications, 27 were conducted in adult patients [19, 34, 37, 53, 58, 62–80], four in pediatric patients [81–84] and one in both populations [33]. Intravenous administration was the only route in 16 of the publications [34, 37, 62, 65, 66, 69–72, 74, 75, 79–82, 84], while both intravenous and oral formulations were included in 11 studies [18, 19, 33, 53, 63, 64, 67, 68, 77, 78, 85]. In five studies, only oral formulations were allowed [58, 73, 76, 83, 86].

The model characteristics of the included studies are summarized in Table 3. The number of observations ranged from 44 to 2539 (median 242), and the median observations per patient was 3.9. The majority of the studies used the NONMEM software to develop the popPK model, with the exception of five studies: two used Phoenix NLME [70, 84], one used WinNonMix [65], one used Monolix [73], one used S-ADAPT [86], and one used Pumas [80]. The basic internal validation method of goodness of fit was performed in all of the included models, while bootstrapping was used in 17 of the studies [33, 53, 64, 67, 70, 71, 73–75, 77–79, 81, 82, 84–86]. The vast majority also included advanced internal validation methods, such as visual predictive check or prediction-corrected visual predictive check [18, 19, 33, 34, 37, 53, 58, 63, 68–74, 76, 77, 79, 81–86], normalized prediction distribution errors [18, 34, 72, 81], or case-deletion diagnostics [67]. In two studies, an external validation was also performed [71, 72].

Simulations were performed in 24 out of 32 studies to determine the optimal dosing regimens. Most of the studies used the ratio between $AUC_{0–24h}$ and MIC and/or the percentage of time over the MIC in a dosing interval (percentage of time above the MIC) as the PK/PD target. Several studies also used C_{min} as a surrogate marker of $AUC_{0–24h}$ [19, 37, 53, 70, 72, 73].

The final structural model, PK parameters, model variability, and tested and retained covariates are summarized in Table 4. In the studies that included the oral route of administration, absorption was described as a first-order process. The median value of the absorption rate constant was 1.22 (0.192–1.91)/h. In two studies, a fixed value of the absorption rate constant from the literature was set to 0.583/h [53, 67], and an absorption lag time parameter was included in two models [63, 73]. Oral bioavailability was > 90% regardless of the formulation, with the exception of one model developed in patients with cystic fibrosis, perhaps owing to the characteristic malabsorption, in which the bioavailability was 85.1% [68].

In adults, the population pharmacokinetics of linezolid was described by a one-compartment model in 15 studies [18, 19, 37, 53, 58, 64, 67, 69, 70, 72, 73, 75, 76, 80, 85] and by a two-compartment model in 13 [33, 34, 62, 63, 65, 66, 68, 71, 74, 77–79, 84, 86] studies. Population PK models with sparse data (mainly peak and trough sampling schema) tended to fit to a one-compartment model because of the lack of sampling points, while rich data models best fitted to a two-compartment model. The median (range) estimated value of the Vd was 45.1 L (20.2–284.4 L). Elimination was mainly described as a linear process with the exception of three studies [77, 79, 86]. Furthermore, two studies included an inhibition of clearance (CL) over time [63, 68]. The median (range) value for CL was 6.2 L/h (2.5–11.2 L/h). Typical values were reported for a patient with a total WT of 70 kg and a creatinine CL (CL_{CR}) of 80 mL/min.

In the pediatric population, three models fitted to a one-compartment with linear elimination [81–83], while one model fitted to a two-compartment model [84]. The median (range) estimated value of CL was 0.119 L/h/kg (0.0676–0.12 L/h/kg) and the V_d was 0.782 L/kg (0.385–0.836 L/kg).

Between-subject variability (BSV) was described by an exponential model in all cases, and it was relatively high. In adults, the median (range) values of BSV in CL and *Vd* (or central volumen of distribution [Vc]) were 41.7% (12.7–108.2%) and 34.9% (8.89–142.1%), respectively.

Table 1 Population characteristics of adult subjects included in the review

Study	*N* (male/female)	Participants	Race/country	Age (years[a])	Body weight (kg[a])	Subject characteristics	Type of infection	Route
Matsumoto et al. [53]	44 (34/10)	Patients	Japan	70.6 ± 10.3	57.1 ± 13.2	Adult patients	NA	IV/PO
Sasaki et al. [67]	50 (36/14)	Patients	Japan	69.1 ± 12.8	57.3 ± 12.1	Adult patients	NA	IV/PO
Tsuji et al. [33]	81 (51/30)	Patients	Japan	69 [5, 8–81]	53.2 [21–99.5]	Pediatric and adult patients	Sepsis (32%) Wound, skin, and soft tissue (31%) Pneumonia (17%) Abscess (10%) Osteomyelitis (7.5%) Undetermined (2.5%)	IV/PO
Crass et al. [19]	603 (409/194)	Patients	Black (11.4%) Caucasian (82.1%) Other (6.5%)	62 ± 15	76 ± 19	Adult patients from routine therapeutic drug monitoring with various degrees of renal dysfunction	NA	IV/PO
Zhang et al. [70]	45 (39/6)	Patients	China	47 [5, 24, 27–64]	65.5 [45.5–95]	Adult patients with liver disease	Proven or probable Gram-positive infection	IV
Xie et al. [34]	15 (9/6)	Patients	China	64.5 [56.2–71]	123.37 ± 16.77	Obese adult patients diagnosed with MRSA pneumonia admitted to ICU	Proven or probable MRSA infection	IV
Soraluce et al. [71]	No CRRT: 17 (13/4) CRRT: 23 (16/7)	Patients	Spain	No CRRT: 72 (22–85) CRRT: 68 (37–79)	No CRRT: 71 [8, 13, 24, 51, 53, 58–88] CRRT: 74 [8, 9, 13, 24, 51, 53–101]	Critically ill adult patients with or without CRRT	Probable Gram-positive infection	IV
Wang et al. [72]	117 (34/83)	Patients	China	62 [5, 19–86]	63 [43.8–115.0]	Critically ill adult patients	Proven or probable Gram-positive infection: Pneumonia (76%) Intra-abdominal infections (6%) CNS infection (4%) SST infections (3%) Bloodstream infections (2%) Bone and joint infections (1%)	IV
Alghamdi et al. [73]	104 (78/26)	Patients	Brazil (18.3%) Georgia (66.3%) USA (15.4%)	37.8 ± 16.3	61.4 ± 11.7	Adult patients routinely treated with linezolid	Pulmonary TB	PO

Table 1 (continued)

Study	*N* (male/female)	Participants	Race/country	Age (years[a])	Body weight (kg[a])	Subject characteristics	Type of infection	Route
Töpper et al. [37]	20 (10/10)	Patients	Germany	74 [5, 23–82]	70 [43–131]	Adult patients admitted to surgical and medical ICU	Hospital-acquired pneumonia (38.9%) Intra-abdominal infection (38.9%) CAP (11.1%) UTI (11.1%)	IV
Swoboda et al. [66]	Septic: 5 (4/1)	Patients	Germany	68.6 ± 4.2	88.8 ± 9.1	Critically ill septic patients with or without extended dialysis admitted to surgical ICU	MRSA or VRE post-surgical infection	IV
	Septic + ED: 10 (6/4)			57.2 ± 11.9	97.4 ± 19.4			
Fiaccadori et al. [65]	15 (7/8)	Patients	Italy	72.3 ± 10.6	69.5 ± 13.4	Critically ill patients with acute or chronic renal failure needing RRT	NA	IV
Wicha et al. [69]	LiMAx <100[b]: 11 (5/6)	Patients	Germany	72.5 ± 17	NA	Adult patients admitted to surgical ICU with or without liver dysfunction	NA	IV
	LiMAx = 100–199[b]: 14 (7/7)			66.5 ± 10.7				
	LiMAx = 200–299[b]: 9 (6/3)			61.3 ±15.7				
	LiMAx >299[b]: 17 (13/4)			57.6 ± 8.9				
Abe et al. [64]	455 (265/190)	Patients	Japanese (12.1%) Caucasian (87.9%)	58.6 ± 18.6	73.1 ± 2 4.4	Caucasian and Japanese patients from phase II/III studies	*Streptococcus pneumoniae* CAP (12.1%) Gram-positive SST infection (20.7%) Gram-positive bacteriemia (34.1%) VRE UTI, SST infection, peritonitis, or bacteriemia (13.1%) MRSA pneumonia, SST infection, or sepsis (20%)	IV/PO
Keel et al. [68]	8 (7/1)	Healthy subjects	USA	28 ± 8	67.1 ± 13.7	Healthy patients with cystic fibrosis with mild-to-moderate lung disease	NA	IV/PO

Table 1 (continued)

Study	*N* (male/female)	Participants	Race/country	Age (years[a])	Body weight (kg[a])	Subject characteristics	Type of infection	Route
Whitehouse et al. [62]	26 (17/9)	Patients	UK	59.5 [5, 17–82]	NA	Critically ill adult patients	Proven or suspected Gram-positive infection: Bacteraemia (13.5%) Wound infection (36.7%) Lower respiratory tract infection (40.8%) Pancreatic abscess (6.4%) UTI (2.6%)	IV
Plock et al. [63]	34 (NA)	24 patients/10 healthy subjects	Austria and Germany	NA	NA	Critically ill adult patients and healthy subjects	NA	IV/PO
Boak et al. [18]	41 (25/16)	Patients	Australia and USA	NA	NA	Hospitalized adult patients	NA	IV/PO
Imperial et al. [86]	88 (46/42)	Patients	South Africa Black (83%) White (1%) Mixed race (25%)	35 (17–60)	NA	Adult outpatients	XDR pulmonary tuberculosis	PO
Fang et al. [85]	152 (99/53)	Patients	China	65 [5, 8, 13–92]	64.3 ± 15.8	Hospitalized adult patients	Confirmed or suspected Gram-positive infection	IV/PO
Ide et al. [74]	Preserved renal function: 8 (NA)	Patients	Japan	65.1 ± 14.5	57.8 ± 7.54	Septic adult patients with preserved renal function, renal dysfunction or on CRRT	Respiratory tract infection (62.5%) Bacteriemia (12.5%) Mediastinitis (12.5%) Other (12.5%)	IV
	Renal dysfunction: 9 (NA)			74.3 ± 11.3	53.4 ± 10.2		Respiratory tract infection (44.4%) Bacteriemia (11.1%) Mediastinitis (11.1%) Other (33.3%)	
	CRRT: 10 (NA)			60.2 ± 16.1	58.7 ± 15.7		Respiratory tract infection (50%) Bacteriemia (20%) Septic arthritis (20%) Other (10%)	
Tietjen et al. [76]	43 (23/20)	Patients	Italy	33 [5, 14–76]	61 [8, 24, 30–86]	Adult outpatients	Proven MDR-TB	PO

Table 1 (continued)

Study	*N* (male/female)	Participants	Race/country	Age (years[a])	Body weight (kg[a])	Subject characteristics	Type of infection	Route
Tsuji et al. [75]	14 (9/5)	Patients	Japan	67 (42–84)	53.4 (32.5–69.7)	Low body weight adult patients with renal dysfunction	MRSA infection	IV
Abdelwahab et al. [58]	124 (63/61)	Patients	South Africa Black (74.2%) Mixed race (24.2%) White (1.6%)	34.3 ± 10.7	56.4 ± 9.8	Adult patients with high prevalence of HIV	MDR-TB (7.3%) Pre-XDR-TB (34.6%) XDR-TB (58.1%)	PO
Minichmayr et al. [77]	51 (32/19)	10 Healthy subjects/41 patients	Austria Germany USA	61 [5, 23–74]	69.5 [48.1–123]	Critically ill, diabetic patients with foot infections, patients with diagnosed cystic fibrosis, and healthy adult patients	Patients with sepsis (45.1%) Patients with diabetic foot infection (19.6%) Patients with cystic fibrosis (15.7%) Healthy volunteers (19.6%)	IV/PO
Taubert et al. [78]	52 (33/19)	Patients	Germany	58 [5, 24, 27–80]	76 [8, 9, 13, 24, 42–109]	Critically ill adult patients	Pneumonia (67%) Peritonitis (17%) Other (16%)	IV/PO
Ehmann et al. [79]	30 (4/26)	Patients	Germany	Obese: 52 [24, 28–61] Non-obese: 50 [24, 29–60]	Obese: 121 [96–230] Non-obese: 65 [24, 50–80]	Obese (50%) and non-obese (50%) surgical adult patients	NA	IV
Blackman et al. [80]	11 (6/5)	Patients	USA	59.6 ± 13	141.3 [99.9–188.8]	Critically ill obese adult patients	Severe SST infection (81.8% necrotizing fasciitis)	IV

CAP community-acquired pneumonia, *CRRT* continuous renal replacement therapies, *DR* drug-resistant, *ED* extended dialysis, *ICU* intensive care unit, *IAI* intra-abdominal infection, *IV* intravenous route, *LiMAx* maximal liver function capacity, *MDR* multidrug-resistant, *MRSA* methicillin-resistant *Staphylococcus aureus*, *NA* not available, *PO* oral route, *RRT* renal replacement therapies, *TB* tuberculosis, *SST* skin and soft tissue, *UTI* urinary tract infection, *VRE* vancomycin-resistant enterococci, *XDR* extensively drug-resistant

[a]Values are expressed as mean ± standard deviation, mean (range) or median [range]

[b]Number of samples in each LiMAx group and sex

Table 2 Population characteristics of the pediatric subjects included in the review

Study	*N* (male/female)	Participants	Race/country	Age[a]	Body weight (kg[a])	Subject characteristics	Type of infection	Route
Thibaut et al. [82]	26 (15/11)	Patients	France	PNA 24 days (8–88)	1.42 (0.81–3.25)	Premature critically ill infants	Mainly CoNS bloodstream infections	IV
Li et al. [81]	112 (65/47)	Patients	China	1.6 years [0.03–11.9]	11.0 [2.1–46.0]	Pediatric patients aged from 0 to 12 years	Confirmed or suspected MR Gram-positive bacterial infection	IV
Garcia-Prats et al. [83]	48 (24/24)	Patients	South Africa Black (52.1%) Mixed (47.9%)	4.6 years [0.6–15.3]	NA	HIV infected and uninfected children	MDR-TB	PO
Yang et al. [84]	63 (43/20)	Patients	China	3.85 years [0.1–15.3]	15 [4.2–70]	Critically ill pediatric patients	Staphylococcal infection	IV

CoNS coagulase-negative staphylococci, *CRRT* continuous renal replacement therapies, *HIV* human immunodeficiency virus, *IV* intravenous, *MDR* multidrug-resistant, *NA* not available, *PNA* post-natal age, *PO* oral, *TB* tuberculosis

[a]Values are expressed as mean ± standard deviation, mean (range) or median [range]

In three studies, an inter-occasion variability in CL was included with median (range) values of 33.3% (16.1–64.7%) [34, 69, 86]. In the pediatric population, BSV values were similar among the different models with median (range) values of 38.7% (37–52.5%) and 32% (28.1–55.8%) for CL and *Vd*, respectively.

With regard to residual variability, a proportional error model was used in 14 studies [34, 53, 64, 68, 70, 73–75, 77, 79, 80, 84–86] with median (range) values of 16.1% (4.76–53.9%), an additive error model was used in two [67, 82] with median (range) values of 1.28 mg/L (1.13–1.43 mg/L), and a combined error model was used in 16 studies [18, 19, 33, 37, 58, 62, 63, 66, 69–72, 76, 78, 81, 83] with median (range) values of 16.5% (4.13–56.4%) and 0.255 mg/L (0.005–1.43 mg/L) for the proportional and additive error model, respectively.

Many factors were tested as possible covariates of the PK parameters. The most commonly identified significant covariates on linezolid CL were WT, renal function (CL_{CR}), or estimated glomerular filtration rate (eGFR), renal replacement techniques and hepatic function (presence of cirrhosis, liver transplantation/resection, prothrombin activity, and LiMAx [maximal liver function capacity] value) while WT, lean body WT, body surface area, and peritonitis were identified as covariates of V_d. In the pediatric population, WT and CL_{CR} were identified as covariates of CL. Furthermore, post-natal age (PNA) was also a significant covariate on the CL in a popPK study in premature infants [82] and aspartate transaminase in critically ill pediatric patients [84].

5 Special Populations

5.1 Altered Renal Function

Initial studies of linezolid pharmacokinetics in patients with renal dysfunction or end-stage renal disease requiring hemodialysis suggested that dose adjustment was not necessary because of the similar concentration profiles observed compared to those of healthy subjects [8]. However, several subsequent studies correlated impaired renal function with increased concentrations of linezolid and its metabolites, as well as the occurrence of adverse reactions [13–16, 19, 55, 59, 87, 88].

In 2003, Meagher et al. published the first popPK model that identified renal function as a significant covariate of total linezolid CL (not included in results). They found that CL_{CR} and ideal body WT explained 16% of linezolid total average CL [89].

Despite reported renal CL of linezolid of about 30%, the impact of renal function could be more than expected a priori. According to Matsumoto et al.'s model, predicted CL ranged between 2.2 L/h up to 6.5 L/h, almost a threefold difference, from the lowest to the highest CL_{CR} value (6.3–173.1 mL/min) [53]. A target C_{min} range of 3.6–8.2 mg/L was also proposed. The lower limit was based on the trough concentration required to attain an AUC/MIC target >100 for the highest MIC observed in their hospital (2 mg/L). The higher limit was estimated based on the C_{min} associated with a 50% probability of developing thrombocytopenia, which was time dependent. Accordingly, in the model performed by Tsuji et al. [75] in low WT patients with renal dysfunction, the CL ranged from 1.8 to 3.8 L/h,

Table 3 Characteristics of the population PK models included in the review

Study	Samples (*n*)		Modeling			Simulation	
	Per subject	Total	Data	Software	Evaluation method	Results	Target
Matsumoto et al. [53]	2	88	Sparse data (peak and trough) from an observational study	NONMEM	Basic internal (GOF, bootstrap) Advanced internal (VPC)	600 mg/day: for MIC ≤ 1 mg/L or MIC = 2 mg/L and CL_{CR}< 30 mL/min Alternative agent for MIC = 4 mg/L	C_{min}: 3.6–8.2 mg/L $AUC_{0–24h}$/MIC ≥100
Sasaki et al. [67]	2.7	135	Rich data from a PK study	NONMEM	Basic internal (GOF, bootstrap) Advanced internal (case deletion diagnostics)	1200 mg/day: achieves target for MIC ≤ 2 mg/L 600 mg/day: high risk of thrombocytopenia when CL_{CR} < 10 mL/min or cirrhosis	$AUC_{0–24h}$/MIC > 100
Tsuji et al. [33]	6.1	493	Rich data from a PK study	NONMEM	Basic internal (GOF, bootstrap) Advanced internal (pcVPC)	NA	NA
Crass et al. [19]	2.2	1309	Sparse data from routine TDM	NONMEM	Advanced internal (pcVPC)	300 mg q12h for CL_{CR} < 60 mL/min 450–600 mg q8h for CL_{CR} > 90 mL/min	C_{min}: 2–8 mg/L
Zhang et al. [70]	3.6	163	Rich data from a PK study	Phoenix NLME	Basic internal (GOF, bootstrap) Advanced internal (pcVPC)	300 mg q12h for PA ≤ 40% or CL_{CR} < 10 mL/min 400 mg q24h for PA ≤ 20%	C_{min}: 2–8 mg/L $AUC_{0–24h}$/MIC = 80–100
Xie et al. [34]	NA	NA	Rich data from a PK study	NONMEM	Basic internal (GOF) Advanced internal (VPC, NPDE, SIR)	600 mg/day: low PTA with increasing WT and decreasing age even for MIC ≤ 1 mg/L	$AUC_{0–24h}$/MIC > 100 %T>MIC = 100
Soraluce et al. [71]	7.8	311	Rich data from a PK study	NONMEM	Basic internal (GOF, bootstrap) Advanced internal (VPC) External validation	1200 mg/day in continuous infusion increases PTA to > 85% for MIC ≤ 2 mg/L	$AUC_{0–24h}$/MIC > 80 %T>MIC = 100
Wang et al. [72]	1.5	241	Sparse data (peak and trough) from an observational study	NONMEM	Basic internal (GOF) Advanced internal (VPC, NPDE) External validation	CL_{CR} 40–80 mL/min: 600 mg q12h for MIC ≤ 2 mg/L CL_{CR} 80–120 mL/min: 600 mg q12h for MIC ≤1 mg/L. 900 mg q12h for MIC = 2 mg/L CL_{CR} > 120 mL/min: 600 mg q6h or 2400 mg 24-hour infusion for MIC ≤ 1 mg/L No optimal regimen for MIC = 4 mg/L	$AUC_{0–24h}$/MIC > 80 %T>MIC > 85 $C_{min,ss}$ < 10 mg/L

Table 3 (continued)

Study	Samples (*n*)		Modeling			Simulation	
	Per subject	Total	Data	Software	Evaluation method	Results	Target
Alghamdi et al. [73]	4.9	508	Rich data from a PK study	Monolix	Basic internal (GOF, bootstrap) Advanced internal (VPC)	Patients with TB: 300 mg/day for MIC = 0.125 mg/L 450–600 mg/day for MIC = 0.25 mg/L 900–1200 mg/day for MIC = 0.5 mg/L No optimal regimen for MIC > 1 mg/L	$fAUC_{0-24h}/MIC > 119$ $C_{min,ss}$ = 2–7 mg/L
Töpper et al. [37]	3.6	71	Sparse data from a PK study	NONMEM	Basic internal (GOF) Advanced internal (VPC)	NA	AUC_{0-24h} = 200–400 mg·h/L C_{min} = 2–10 mg/L
Swoboda et al. [66]	NA	NA	Rich data from a PK study	NONMEM	Basic internal (GOF)	No statistically differences between ED and non-ED patients. Low PTA for MIC = 4 mg/L	AUC_{0-24h}/MIC %T>MIC
Fiaccadori et al. [65]	44.4	222	Rich data from a PK study	WinNonMix	Basic internal (GOF)	NA	NA
Wicha et al. [69]	1.8	51	Sparse data (trough) from an observational study	NONMEM	Basic internal (GOF) Advanced internal (VPC)	NA	NA
Abe et al. [64]	5.6	2539	Rich data from phase II/III studies	NONMEM	Basic internal (GOF, bootstrap)	NA	NA
Keel et al. [68]	22	176	Rich data from a PK study	NONMEM	Basic internal (GOF) Advanced internal (VPC)	1200 mg/day achieve high CFRs for MIC < 2 mg/L Higher or more frequent dosing may be required for MIC ≥ 2 mg/L	$AUC_{0-24h}/MIC \geq 83$
Whitehouse et al. [62]	7	196	Rich data from a PK study	NONMEM	Basic internal (GOF)	600 mg q12h achieve 90% T>MIC, and AUC_{0-24h}/MIC = 100 in 76% of *S. aureus,* 75.4% of *Enterococcus* spp. *a*nd 95.8% of CoNS	AUC_{0-24h}/MIC = 100 %T>MIC
Plock et al. [63]	34.6	1176	Rich data of unbound linezolid from a PK study	NONMEM	Basic internal (GOF) Advanced internal (VPC)	NA	NA
Boak et al. [18]	3.9	161	Rich data from a PK study	S-ADAPT	Basic internal (GOF) Advanced internal (VPC, NPDE)	NA	NA

Table 3 (continued)

Study	Samples (*n*)		Modeling			Simulation	
	Per subject	Total	Data	Software	Evaluation method	Results	Target
Imperial et al. [86]	NA	NA	Rick data from a PK study	NONMEM	Basic internal (GOF) Advanced internal (VPC, bootstrap)	Patients with TB: 300 mg q12h for MIC = 0.125 mg/L 600 mg q12h for MIC = 0.5 mg/L 1200 mg q24h for MIC = 1 mg/L (PTA 86%)	fAUC/MIC >119 %fT > MIC
Fang et al. [85]	1.8	270	Sparse data from a PK study	NONMEM	Basic internal (GOF) Advanced internal (VPC, bootstrap)	NA	NA
Ide et al. [74]	NA	NA	Rich data from a PK study	NONMEM	Advanced internal (VPC, bootstrap)	600 mg q24h for MIC < 2 mg/L if renal dysfunction or CRRT, 600mg q12h if normal renal function For MIC = 2 mg/L, 600 mg q12h if renal dysfunction or CRRT, 800 mg q12h if normal renal function For MIC = 4 mg/L, no optimal dosing regimen	$AUC_{0–24h}$/MIC ≥ 80 %T>MIC = 100
Tietjen et al. [76]	6.3	244	Rich data from a PK study	NONMEM	Basic internal (GOF) Advanced internal (VPC)	TB patients: 300 mg q12h for MIC = 0.25 mg/L (PTA > 90%) 450–600 mg q12h for MIC = 0.5 mg/L (PTA ~ 90%) 600 mg q12h for MIC = 1 mg/L (PTA 72%)	$fAUC_{0–24h}$/MIC = 119
Tsuji et al. [75]	4.9	68	Sparse data (trough) from a PK study	NONMEM	Basic internal (GOF) Advanced internal (bootstrap)	NA	NA
Abdelwahab et al. [58]	3.6	444	Sparse and rich data from a PK study	NONMEM	Basic internal (GOF) Advanced internal (pcVPC)	TB patients: 300 mg q24h for MIC = 0.25 mg/L 600 mg q24h for MIC = 0.5 mg/L 1200 mg q24h for MIC = 1 mg/L	$fAUC_{0–24h}$/MIC = 119 C_{min} < 2 mg/L

Table 3 (continued)

Study	Samples (*n*)		Modeling			Simulation	
	Per subject	Total	Data	Software	Evaluation method	Results	Target
Minichmayr et al. [77]	31.3	1598	Rich data from 3 clinical trials	NONMEM	Basic internal (GOF, case-deletion diagnostics) Advanced internal (bootstrap, VPC)	Standard dosing achieves low PTA in patients with conserved renal function, foremost septic patients. High PTA with intensified regimens (loading dose, continuous infusion) for CLCR < 100 mL/min and MIC< 2 mg/L	AUC_{0-24h} = 100 %T>MIC = 99
Taubert et al. [78]	32[a]	NA	Rich data from a clinical trial	NONMEM	Basic internal (GOF) Advanced internal (bootstrap)	Standard dosing potentially insufficient for MIC = 2 mg/L, chiefly in ARDS, but also with ↑WT, ↑fibrinogen and ↓lactate	AUC_{0-12h} > 100 mg·h/L
Ehmann et al. [79]	11	329	Rich data from a clinical trial	NONMEM	Basic internal (GOF) Advanced internal (bootstrap, VPC)	↓PTA with increasing LBW 600 mg q12h for MIC ≤1 mg/L 900–1200 mg q12h for MIC = 2 mg/L No optimal regimen for MIC = 4 mg/L	%fT>MIC >95% fAUC/MIC > 80
Blackman et al. [80]	4	44	Sparse data from a PK study	Pumas	Basic internal (GOF) Advanced internal (VPC)	600 mg q12h for MIC <1 mg/L 600 mg q8/12h for MIC = 1 mg/L 600 mg q6h for MIC = 1 mg/L and TBW 140–190 kg 600 mg q8h for MIC = 2 mg/L 600 mg q12h for MIC = 2 mg/L and TBW 140–175 kg No optimal regimen for MIC = 4 mg/L	AUC_{0-24h}/MIC ≥ 100 %T>MIC > 85 C_{min} < 8.06 mg/L
Yang et al. [84]	3.9	246	Rich data from a PK study	Phoenix NLME	Basic internal (GOF) Advanced internal (pcVPC, bootstrap)	10 mg/kg q8h for MIC ≤1 mg/L 15 mg/kg q6h for MIC = 2 mg/L	AUC_{0-24h}/MIC ≥80
Thibault et al. [82]	3	78	Sparse data (trough, peak and 2–3 h post-administration) from routine TDM	NONMEM	Basic internal (GOF) Advanced internal (bootstrap, VPC)	8 mg/kg q8h for MIC = 1 mg/L 12 mg/kg q8h for MIC ≥2 mg/L No optimal regimen for MIC = 4 mg/L	AUC_{0-24h}/MIC >80 AUC_{0-24h} < 300

Table 3 (continued)

Study	Samples (*n*)		Modeling			Simulation	
	Per subject	Total	Data	Software	Evaluation method	Results	Target
Li et al. [81]	1.2	135	Sparse data (trough and peak) from a PK study	NONMEM	Basic internal (GOF) Advanced internal (bootstrap, VPC, NPDE)	10 mg/kg q8h for MIC = 0.5 mg/L 10–20 mg/kg q8h for MIC = 1 mg/L 15–20 mg/kg q8h for MIC = 2 mg/L No optimal regimen for MIC = 4 mg/L	$AUC_{0-24h}/MIC \geq 80$
Garcia-Prats et al. [83]	NA	NA	Rich data from 2 PK studies	NONMEM	Basic internal (GOF) Advanced internal (VPC)	Weight-banded dosing, 5–7 kg: 80 mg/day; 7–10 kg: 120 mg/day; 10–16 kg: 150 mg/day; 16–24 kg: 220 mg/day; 24–31 kg: 280 mg/day; 31–35 kg: 300 mg/day; 35–44 kg: 400 mg/day; >44 kg: 600 mg/day	$AUC_{0-24h} = 110$

AUC area under the curve, *CFR* cumulative fraction of response, CL_{CR} creatinine clearance, C_{min} minimum trough concentration, $C_{min,ss}$ steady-state trough concentration, *CoNS* Coagulase-negative staphylococci, *fAUC* area under the curve of unbound linezolid, *GOF* goodness-of-fit, *LBW* lean body weight, *LD* liver disease, *MIC* minimum inhibitory concentration, *NA* not available, *NPDE* normalized prediction distribution errors, *PA* prothrombin activity, *pcVPC* prediction-corrected visual predictive check, *PK* pharmacokinetic, *PTA* probability of target attainment, *q6h* every 6 hours, *q8h* every 8 hours, *q12h* every 12 hours, *q24* every 24 hours, *SIR* sampling importance resampling, *TDM* therapeutic drug monitoring, *VPC* visual predictive check, ↑ increased, ↓ decreased

[a]Median value

Table 4 Summary of structural parameter estimates, model variability, and tested and retained covariates of population PK models included in the review

Study	Structural PK model	PK parameters	Model variability	Tested covariates	Retained covariates
Matsumoto et al. [53]	One compartment with first-order absorption and elimination	$K_a = 0.583$/h $CL = 0.0258*CL_{CR} + 2.03$ L/h $V = 27.6$ L	BSV CL = 30.5% Prop REE = 21.5%	Age, WT, CR, CL_{CR}, BUN	CL: CL_{CR}
Sasaki et al. [67]	One compartment with linear elimination	$K_a = 0.583/$ h $CL = 2.85*\left(\frac{CL_{CR}}{60.9}\right)^{0.618}*0.472^{CIR}$ L/h $V = 33.6*\left(\frac{WT}{57.9}\right)$ L Where CIR = 1 if subject has cirrhosis, otherwise CIR = 0	BSV CL = 35.2% BSV V = 30.8% Add REE = 1.43 mg/L	Age, WT, CR, CL_{CR}, TBIL, CIR	CL: CL_{CR}, CIR V: WT
Tsuji et al. [33]	Two compartments with first-order absorption and elimination	$F = 0.922$ $K_a = 0.192$/h $CL = \left(1.86*e^{-0.0205*(Age-69)} + 1.44*RF\right)*\left(\frac{WT}{70}\right)^{0.75}$ L/h $V_c = 22.9*\left(\frac{WT}{70}\right)$ L $V_p = 24.7*\left(\frac{WT}{70}\right)$ L $Q = 10.9*\left(\frac{WT}{70}\right)^{0.75}$ L/h Where $RF = \frac{CL_{CR}}{CL_{CR,STD}}$ being $CL_{CR,STD}$ a standard CL_{CR} of 100 mL/min/70 kg	BSVCL = 36.9% BSVV_c = 142.1% BSVV_p = 5% BSVQ = 182.2% AddREE = 0.251mg/L PropREE = 56.4%	Age, WT, CL_{CR}, AST, ALT	CL: Age, WT, CL_{CR} Vc: WT Vp: WT Q: WT
Crass et al. [19]	One compartment with linear elimination	$K_a = 1.4/h$ $CL = 3.43 + 3.19*(BSA - 1.89) - 0.0242*(Age - 40)*Ageind + 1.77*\left(\frac{eGFR}{80}\right)$ L/h $V = 42.9*e^{0.901*(BSA-1.89)}$ L Where Ageind = 1 if subject is aged older than 40 years and Ageind = 0 if younger	BSV CL = 49.9% BSV V = 17.8% Add REE = 1.43 mg/L Prop REE = 27.1%	Age, sex, WT, BSA, HT, CR, eGFR, ICU	CL: Age, BSA, eGFR V: BSA
Zhang et al. [70]	One compartment with first-order elimination	$CL = 2.68*\left(\frac{PA}{48.07}\right)^{0.84}*\left(\frac{CL_{CR}}{99.3}\right)^{0.36}$ L/h $V = 58.34$ L	BSV CL = 15.47% BSV V = 8.89% Prop REE = 18.5%	Age, sex, WT, BMI, HT, CR_{CL}, BUN, ALT, AST, GGT, ALP, TBIL, DBIL, HB, PLT, ALB, TBA, INR, PA, UA	CL: CL_{CR}, PA
Xie et al. [34]	Two compartments with linear elimination	$CL = 7.8*(1 - 0.0331*(Age - 60))*\left(\frac{WT}{70}\right)^{0.75}$ L/h $V_c = 14.3*\left(\frac{WT}{70}\right)$ L $V_p = 23.8*\left(\frac{WT}{70}\right)$ L $Q = 65.1*\left(\frac{WT}{70}\right)^{0.75}$ L/h	BSV CL = 66.9% BSV V_c = 43.5% IOV CL = 16.1% Prop REE = 15.9%	Age, sex, WT, CR_{CL}, ALB, ALT, AST, TBIL, sepsis severity	CL: Age, WT Vc: WT Vp: WT Q: WT
Soraluce et al. [71]	Two compartments with first-order elimination	$CL = 2.62 + \left(4.35*\frac{CL_{CR}}{44}\right) + (Sc*Qef)$ L/h $V_c = 16.1$ L $V_p = 29.1$ L $Q = 72.3$ L/h	BSV CL = 98.7% BSV V_c = 66.6% Add REE = 0.26 mg/L Prop REE = 16%	Age, sex, WT, HT, BMI, CR, CL_{CR}, GLU, HB, HCT, ALB, TP, TBIL, AST, ALT, Sc, Qef	CL: CL_{CR}, Sc, Qef

Table 4 (continued)

Study	Structural PK model	PK parameters	Model variability	Tested covariates	Retained covariates
Wang et al. [72]	One compartment with linear elimination	$CL = 5.60*\left(\frac{CL_{CR}}{61}\right)^{0.386}$ L/h $V = 43.4$ L	BSV CL = 63.9% BSV V = 17.6% Add REE = 0.055 mg/L Prop REE = 36.2%	Age, sex, WT, HT, AST, ALT, TBIL, DBIL, CR, CL_{CR}, CRRT, SOFA, APACHE II	CL: CL_{CR}
Alghamdi et al. [73]	One compartment with delayed absorption and first-order absorption and elimination	$T_{lag} = 0.341$ h $K_a = 1.65$/h $CL/F = 6.32*\left(\frac{CL_{CR}}{97}\right)^{0.449}$ L/h $V/F = 40.6*\left(\frac{WT}{63}\right)$ L	BSV T_{lag} = 88.2% BSV K_a = 70.7% BSV CL/F = 36.8% BSV V/F = 10.9% Prop REE = 25.9%	Age, sex, WT, BMI, fat-free mass, CL_{CR}, type of disease, site	CL/F: CL_{CR} V/F: WT
Töpper et al. [37]	One compartment with linear elimination	$CL = 5.71$ L/h $V = 41.1$ L	BSV CL = 108.2% BSV V = 53.7% Add REE = 0.589 mg/L Prop REE = 16.5%	Age, WT, eGFR, ALB, TBIL	NA
Swoboda et al. [66]	Two compartments with linear elimination	$CL = (0.159*WT) + (Fdia*Dialysis)*(1 - F_{LS}*LS)$ L/h $V_c = (0.273*WT)$ L $V_p = (0.271*WT)$ L $Q = (0.369*WT)$ L/h Where F_{dia} is the factor of dialysis therapy and Dialysis = 1 or 0, with or without dialysis, respectively. F_{LS} is the factor for liver transplantation/resection and LS = 1 or 0, with or without liver transplantation/resection, respectively	BSV CL = 51% BSV V_c = 21% Add REE = 0.285 mg/L Prop REE = 4.13%	Age, sex, WT, BMI, APACHE II, SOFA, liver transplantation/resection, CR, dialysis	CL: WT, dialysis, liver transplantation/resection V_c: WT V_p: WT Q: WT
Fiaccadori et al. [65]	Two compartments with linear elimination	$CL_{on-dialysis} = 6$ L/h $CL_{off-dialysis} = 4.4$ L/h $V_c = 45.91$ L V_p = NA	BSV $CL_{on-dialysis}$ = 11.0% BSV $CL_{off-dialysis}$ = 12.7% BSV V_c = 14.2%	NA	NA
Wicha et al. [69]	One compartment with first-order elimination	$CL_{non-renal} = 4.41*\left(\frac{WT}{57.9}\right)^{0.75}*\left(\frac{LiMAx}{221.5}\right)^{0.388}$ L/h $CL_{renal} = 0.919*\left[1 + 0.0208*\left(CL_{CR} - 45.6\right)\right]$ L/h $CL_{dialysis} = 1.26$ L/h $V = 33.8*\left(\frac{WT}{57.9}\right)$ L	BSV $CL_{non-renal}$ = 33.6% BSV CL_{renal} = 62.2% IOV $CL_{non-renal}$ = 33.3% IOV CL_{renal} = 56.4% IOV $CL_{dialysis}$ = 64.7% Add REE = 0.1 mg/L Prop REE = 10%	Age, sex, WT, BMI, CL_{CR}, TBIL, INR, AST, ALT, GGT, PCHE, GLDH, LiMAx	$CL_{non-renal}$: WT, LiMAx CL_{renal}: CL_{CR} V: WT
Abe et al. [64]	One compartment with first-order absorption and linear elimination	$K_a = 0.583$/h $CL = 1.28*\left(\frac{WT}{69.5}\right)^{1.91} + 0.0788*(110 - Age)*(1 - AgeC) + 0.078*52*AgeC$ L/h $V = 47*\left(\frac{WT}{69.5}\right)^{0.903}$ L Where AgeC = 1 when subject's age is ≥58 years and 0 otherwise.	BSV K_a = 180.8% BSV CL = 46.6% BSV V = 25.9% Prop REE = 8.14%	Age, sex, WT, ethnicity	CL: WT, age V: WT

Table 4 (continued)

Study	Structural PK model	PK parameters	Model variability	Tested covariates	Retained covariates
Keel et al. [68]	Two compartments with time-dependent clearance inhibition	$F = 0.851$ $K_a = 1.91*[1 + 0.0474*(\text{LBW} - 53.3)]$ /h $\text{CL} = 9.54*[1 + 0.0335*(\text{LBW} - 53.3)]$ L/h $V_c = 26.8$ L $V_p = 17.3$ L $Q = 104$ L/h $\text{K}_{IC} = 0.0005$ L/h RCLF = 32.1 % $\text{IC}_{50} = 0.38$ mg/L	BSV F = 23.0% BSV CL = 36.3% BSV V_p = 85.8% BSV RCLF = 58.3% Prop REE = 22.4%	WT, HT, LBW	K_a: LBW CL: LBW
Whitehouse et al. [62]	Two compartments with linear elimination	$\text{CL} = (0.0487*\text{WT})$ L/h $V_c = (0.634*\text{WT})$ L $V_p = 240$ L $Q = 7.48$ L/h	BSV CL = 48.1% BSV V_c = 22.4% BSV V_p = 146.0% Add REE = 2.34 mg/L Prop REE = 19.0%	Age, sex, WT, HT, CL_{CR}, RRT	CL: WT V_c: WT
Plock et al. [63]	Two compartments with delayed absorption and linear elimination with time-dependent clearance inhibition	$T_{lag} = 1.27$ h $K_a = 1.81$ /h $\text{CL} = 11.1$ L/h $V_c = 20.0$ L $V_p = 28.9$ L $Q = 75.0$ L/h $\text{K}_{IC} = 0.0019$ L/h RCLF = 76.4 % $\text{IC}_{50} = 0.1$ mg/L	BSV K_a = 72.4% BSV CL = 41.7% BSV V_c = 40.1% BSV V_p = 34.8% BSV RCLF = 11.8% Add REE = 0.292 mg/L Prop REE = 8.96%	NA	NA
Boak et al. [18]	One compartment with three absorption lag compartments and linear elimination	$T_{lag} = 1.15$ h $T_{abs1/2} = 0.172$ h $\text{CL} = \left(\frac{\text{WT}}{65}\right)^{0.75} * \left(\text{RF}_i * 2.17 + 4.55\right)$ L/h $V = 44.3 * \left(\frac{\text{WT}}{65}\right)$ L Where $\text{RFi} = \frac{\text{eGFR}}{\text{eGFR}_{STD}}$	BSV T_{lag} = 60% BSV $T_{abs1/2}$ = 14.7% BSV CL = 48.9% BSV V = 3.6% Add REE = 0.309 mg/L Prop REE = 22.5%	NA	CL: CL_{CR}, WT V: WT
Imperial et al. [86]	Two compartments with Michaelis–Menten elimination	$K_a = 1.1$/h $\text{CL}_{int} = 7.9$ L/h $K_m = 16$ mg/L $V_c = 49$ L $V_p = 14$ L $Q = 0.8$ L/h	IOV CL_{int} = 26% BSV K_a = 85% BSV CL_{int} = 18% BSV V_c = 32% Prop REE = 14.1%	Age, sex, WT, BMI, HIV status	NA
Fang et al. [85]	One compartment with linear elimination	$K_a = 0.753$ /h $F = 0.806$ $\text{CL} = 2.93 + 2.33 * \left(\frac{\text{CL}_{CR}}{73}\right) + 0.685 * \left(\frac{\text{WBC}}{9.63}\right)$ L/h $V = 97.5 - 1.42*\text{ALB}$ L	BSV CL = 32.4% BSV V = 33.6% Prop REE = 16.1%	Age, sex, WT, HT, WBC, HB, PLT, TBIL, ALB, ALT, AST, CR, CL_{CR}	CL: CL_{CR} V: ALB

Table 4 (continued)

Study	Structural PK model	PK parameters	Model variability	Tested covariates	Retained covariates
Ide et al. [74]	Two compartments with three different clearance parameters depending on renal function and CRRT	$CL_{preserved} = 6.36$ L/h $CL_{dysfunction} = 2.06$ L/h $CL_{CRRT} = 2.74$ L/h $V_c = 19.6$ L $V_p = 22.4$ L $Q = 26.4$ L/h	BSV $CL_{preserved} = 75.2\%$ BSV $CL_{dysfunction} = 41.8\%$ BSV $CL_{CRRT} = 60.1\%$ BSV $V_c = 61.7\%$ BSV $V_p = 36.2\%$ BSV $Q = 46.3\%$ Prop REE = 5.8%	NA	NA
Tietjen et al. [76]	One compartment with linear elimination	$K_a = 0.679/\text{h}$ $F = 1$ $CL = 7.69*\left(\frac{WT}{61}\right)^{0.75}$ L/h $V = 45.2*\left(\frac{WT}{61}\right)$ L	IOV $K_a = 143.7\%$ BSV CL = 34.1% Add REE = 0.214 mg/L Prop REE = 5.08%	Age, sex, WT, HT, AST, ALT, WBC, RBC, PLT, CL_{CR}, concomitant medications	CL: WT *V*: WT
Tsuji et al. [75]	One compartment with linear elimination	$CL = 0.00327*WT*eGFR^{0.428}*HB^{0.502}*0.283$(if ALT >100 UI/L) L/h $V = 1.31*WT$ L	BSV CL = 31.3% BSV *V* = 33.9% Prop REE = 21.6%	Age, sex, WT, duration of administration, CR, ALT, HB, PLT, eGFR	CL: WT, eGFR, HB, ALT V: WT
Abdelwahab et al. [58]	One compartment with linear absorption with five transit compartments and linear elimination	$K_a = 1.22$ /h $F = 1$ MTT = 0.528 h $CL/F = 3.57*\left(\frac{WT}{56}\right)^{0.75}$ L/h $V = 40.2*\left(\frac{WT}{56}\right)$ L	IOV $K_a = 78.5\%$ IOV MTT = 56.8% IOV $F = 78.5\%$ BSV CL = 37.1% Add REE = 0.651 mg/L Prop REE = 9.53%	Age, sex, WT, $CL_{CR,}$ HIV status	CL: WT *V*: WT
Minichmayr et al. [77]	Two compartments with nonlinear elimination due to with time-dependent clearance inhibition	$K_a = 1.41/\text{h}$ $F = 1$ $F_{CF} = 0.828$ $CL_{healthy} = 7.67*(1 + 0.00835*(CLCR - 80))$ L/h $CL_{septic} = 11.2*(1 + 0.00835*(CLCR - 80))$ L/h $CL_{diabetic} = 6.35*(1 + 0.00835*(CLCR - 80))$ L/h $CL_{CF} = 6.87*(1 + 0.00835*(CLCR - 80))$ L/h $V_c = 22.7$ L $V_p = 19.9*\left(\frac{WT}{69.5}\right)$ L $Q = 57.9*\left(\frac{WT}{69.5}\right)$ L/h $K_{IC} = 0.0017$ L/h RCLF = 51.3 % $IC_{50} = 0.48$ mg/L	BSV $K_a = 118\%$ BSV $F = 4.1\%$ BSV CL = 40.1% BSV $V_c = 36.6\%$ BSV $V_p = 39.4\%$ BSV RCLF = 6.45% Prop REE = 15.7%	Age, sex, patient group, CL_{CR}, AST, ALT, CRP, PLT, BSD	F: patient group CL: patient group, CL_{CR} $V_{p:}$ WT *Q*: WT
Taubert et al. [78]	Two compartments with linear absorption and elimination	$K_a = 1.72/\text{h}$ $CL = 7.92*\left(\frac{\text{fibrinogen}}{13}\right)^{0.04}*\left(\frac{\text{lactate}}{1.91}\right)^{-0.21}*1.82$(if ARDS) $V_c = 15*\left(\frac{WT}{76}\right)^{1.31}*1.53$(if peritonitis) L $V_p = 26.55$ L $Q = 65.59$ L/h	BSV CL = 58% BSV $V_c = 37\%$ Add REE = 0.005 mg/L Prop REE = 33.91%	WT, HT, CL_{CR}, CRP, lactate, ARDS, peritonitis	CL: lactate, fibrinogen, ARDS V_c: WT, peritonitis

Table 4 (continued)

Study	Structural PK model	PK parameters	Model variability	Tested covariates	Retained covariates
Ehmann et al. [79]	Two compartments with parallel linear and non-linear elimination	$CL = \left(8.92 + \frac{C_p * V_{max}}{C_p + K_m}\right) * (1 + 0.00805 * (MAP - 75))$ L/h $V_c = 17 * \left(\frac{LBW}{51.9}\right)$ L $V_p = 33.4 * \left(\frac{LBW}{51.9}\right)$ L $Q = 62.4 * \left(\frac{LBW}{51.9}\right)^{0.75}$ L/h $V_{max} = 45.9$ mg/h $K_m = 2.93$ mg/L	BSV CL = 66.7% BSV V_c = 42.1% BSV V_p = 16.7% BSV Q = 46.8% BSV K_m = 46.8% Prop REE = 4.56%	LBW, FM, MAP, heart rate, anesthesia status	CL: MAP V_c: LBW V_p: LBW Q: LBW
Blackman et al. [80]	One compartment with linear elimination	$CL = \left[\left(5.1 * 0.066^{CIR}\right) + 1.6\right] * \left(\frac{WT}{140}\right)^{1.12}$ L/h $V = 64.3 * \left(\frac{WT}{140}\right)^{1.67}$ L Where CIR = 1 if subject has cirrhosis, otherwise CIR = 0	BSV CL = 25% BSV V = 21% Prop REE = 37.4%	Age, WT, BMI, CR, ALT, AST, TBIL, CIR	CL: WT, CIR V: WT
Yang et al. [84]	Two compartments with linear elimination	$CL = 2.34 * \left(\frac{WT}{15}\right)^{0.8} * \left(\frac{AST}{45.9}\right)^{-0.16}$ L/h $V_c = 5.22$ L $V_p = 28.79$ L $Q = 7.14 * \left(\frac{WT}{15}\right)^{1.09}$ L/h	BSV CL = 52.51% BSV V_c = 55.78% BSV Q = 53.45% Prop REE = 53.85%	Age, sex, WT, BMI, ALB, ALT, AST, CL_{CR}, TBIL, DBIL	CL: WT, AST Q: WT
Thibault et al. [82]	One compartment with linear elimination	$CL = 0.181 * \left(\frac{WT}{1.4}\right)^{0.405} * \left(\frac{PNA}{0.07}\right)^{0.831}$ L/h $V = 1.17 * \left(\frac{WT}{1.4}\right)^{0.801}$ L	BSV CL = 38.3% Add REE = 1.13 mg/L	PMA, PNA, GA, WT, sex, AST, ALT, CR, rifampin treatment	CL: WT, PNA V: WT
Li et al. [81]	One compartment with first-order elimination	$CL = 1.31 * \left(\frac{\ln WT}{2.4}\right)^{0.83} * \left(\frac{\ln eGFR}{4.89}\right)^{0.6}$ L/h $V = 4.24 * \left(\frac{\ln WT}{2.4}\right)^{0.86}$ L	BSV CL = 39.1% BSV V = 28.1% Add REE = 0.02 mg/L Prop REE = 16.48%	Age, WT, HT, BSA, BUN, CR, UA, CYS-C, TBIL, AST, GGT, eGFR	CL: WT, eGFR V: WT
Garcia-Prats et al. [83]	One compartment with linear elimination	$K_a = 0.77$ /h $CL/F = 4.73 * \left(\frac{WT}{70}\right)^{0.75}$ L/h $V/F = 54.8 * \left(\frac{WT}{70}\right)$ L	BSVCL/F = 37.0% BSVV/F = 32.0% AddREE = 0.78mg/L PropREE = 25.0%	Age, sex, WT, HT, ethnicity, HIV status, administration route (oral vs NG tube), formulation, concomitant drugs	CL/F: WT V/F: WT

Table 4 (continued)

ALB albumin, *ALP* alkaline phosphatase, *ALT* alanine aminotransferase, *APACHE II* Acute Physiology and Chronic Health disease Classification System II, *ARDS* acute respiratory distress syndrome, *AST* aspartate aminotransferase, *BMI* body mass index, *BSA* body surface area, *BSD* body size descriptors, *BSV* between-subject variability, *BUN* blood urea nitrogen, *CIR* liver cirrhosis, *CL* creatinine clearance, CL_{int} intrinsic Michaelis–Menten clearance, *CR* serum creatinine, *CRP* C-reactive protein, *CRRT* continuous renal replacement therapies, *CYS-C* serum cystatine C, *DBIL* direct bilirubin, *eGFR* estimated glomerular filtration rate, *F* bioavailability, *FM* fat mass, *GA* gestational age, *GGT* gamma-glutamyl transpeptidase, *GLDH* glutamate dehydrogenase, *GLU* glucose, *HB* hemoglobin, *HCT* hematocrit, *HD* hemodialysis, *HIV* human immunodeficiency virus, *HT* height, IC_{50} inhibition compartment concentration yielding 50% of maximum clearance inhibition, *ICU* intensive care unit, *INR* international normalized ratio, *IOV* inter-occasion variability, K_a absorption rate constant, K_{IC} rate constant intro inhibition compartment, K_m Michaelis–Menten constant, *LBW* lean body weight, *LiMAx* maximum liver function capacity test, *MAP* mean arterial blood pressure, *MTT* mean transit time, *NA* not available, *NG* nasogastric tube, *PA* prothrombin activity, *PCHE* pseudocholinesterase, *PK* pharmacokinetic, *PLT* platelet count, *PMA* post-menstrual age, *PNA* post-natal age, *Q* intercompartmental clearance, *Qef* efluent flow, *RBC* red blood cells, *RCLF* maximum fraction of clearance that cannot be inhibited after infinite doses, *RRT* renal replacement therapy, *Sc* sieving coefficient, *SOFA* Sequential Organ Failure Assessment score, *Tabs1/2* absorption half-life, *TBA* total bile acid, *TBIL* total bilirubin, T_{lag} lag time in absorption, *TP* total protein, *UA* uric acid, V_C central volume of distribution, V_{max} maximum elimination rate, *Vp* peripheral volume of distribution, *WBC* white blood cells, *WT* weight

an approximately two-fold difference. Furthermore, Ide et al. [74] studied patients with sepsis with and without renal impairment and observed great differences between the typical CL values between those populations (2.06 vs 6.36 L/h), and these were very close to those predicted by Matsumoto et al. An even higher influence of renal function was reported in Sasaki et al.'s model, in which the predicted CL ranged between 1 and 8.1 L/h; however, some of the patients also had liver cirrhosis [67]. Nevertheless, other factors such as the lower WT of the Japanese population must be considered, as non-renal CL values could be lower than expected, increasing the influence of renal function in total CL.

Other authors that assessed the influence of renal function were Boak et al., who developed a PK-toxicodynamic model, in which CL_{CR} was a significant covariate on total linezolid CL. Based on the average AUC_{0-24h} of their population, 90%, 50%, and 7% of the patients would have achieved the target of AUC/MIC >100 for MIC values of 1, 2, and 4 mg/L, respectively [18].

Tsuji et al. further developed a PK-toxicodynamic model, measuring both total and unbound linezolid concentrations. Renal function, age, and total body WT were significant covariates of linezolid CL. The authors concluded that renal function significantly affected linezolid renal CL and age slightly affected nonrenal CL. Inhibition of platelet formation was proposed as the main thrombocytopenia mechanism. Mean values of renal and non-renal CL were 1.44 L/h and 1.86 L/h; therefore, endorsing the possibility of the higher influence of renal function in total linezolid CL in Japanese patients [33]. Alternatively, Crass et al. developed a popPK analysis to identify an alternate dosing strategy in renal impairment. With standard dosing, only 33% of patients with eGFR < 60 mL/min would achieve therapeutic trough concentrations (2–8 mg/L), mainly owing to the increased probability of supratherapeutic concentrations. Therefore, the authors suggested reducing the dose in this group of patients to 300 mg every 12 h to increase the PTA up to 65%. Furthermore, they also suggested increasing the dose to 450–600 mg every 8 h in patients with an eGFR ≥ 90 mL/min to ensure a ≥ 90% PTA [19]. It is important to note that the differences between the mean values of non-renal and renal linezolid CL were higher (3.43 L/h/1.89m^2 vs 1.77 L/h/1.89m^2, respectively) compared with the aforementioned studies.

In the same vein, Wang et al., also developed a model proposing dose adjustments based on their CL_{CR}. The exponent of CL_{CR} on the total CL was 0.36, indicating the considerable influence of renal function, the same value as reported by Zhang et al. [70]. They proposed the need for higher doses of linezolid in normal renal function and continuous infusion of 2400 mg every 24 h in the case of augmented

renal CL. None of the regimens was found to be optimal for MIC = 4 mg/L [72].

Another important point to note is that the majority of the popPK models tested renal function as a potential covariate, as creatinine level, CL_{CR}, or eGFR, nonetheless, less than half (12 out of 29) ended up including it as a significant covariate in the model. Most were performed in Japanese patients or in populations with other significant comorbidities, such as hepatic impairment.

In conclusion, renal function appears to be a relevant factor influencing linezolid exposure, as CL_{CR} and eGFR have been identified as covariates of linezolid CL in several published popPK models. In patients with diminished renal CL, higher concentrations of linezolid would be expected, resulting in overexposure. To the contrary, lower concentrations of linezolid would be expected in patients with augmented renal CL, resulting in underexposure. The physiological characteristics of the population could also significantly impact the relative impact of renal CL on total linezolid CL. Dose reductions may be necessary in patients with impaired renal function. However, higher doses may be necessary in patients with eGFR of greater than 90 mL/min.

5.2 Renal Replacement Therapies

Because of its low molecular WT, low protein binding, and relatively low V_d, linezolid is likely to be removed by intermittent hemodialysis (IHD) and continuous renal replacement therapies (CRRT). The impact of IHD on linezolid PK parameters was assessed by Brier et al. (not included in results), who described an apparent increase in oral CL from 4.59 L/h on off-dialysis days to 7.8 L/h on on-dialysis days. Despite 30% of the dose being removed in a dialysis session, no dosing recommendations were deemed necessary, but a supplemental dose was recommended during the first hemodyalisis session [8].

Fiaccadori et al. reported substantial linezolid removal during IHD (32.3%) and sustained low-efficiency dialysis (33.9%), while continuous venous-venous hemodialysis removed 17.5% of the dose. Subtherapeutic concentrations of linezolid were noticed, especially with CRRT and sustained low-efficiency dialysis.

The impact of the different CRRT was also assessed. Meyer et al. (not included in results) conducted a multi-dose study in anuric critically ill patients undergoing continuous venovenous hemofiltration (CVVH) with highly permeable polysulfone membranes. The PK parameters were comparable to healthy subjects and patients without renal impairment, supporting the standard dosage of 600 mg twice daily in these patients [90].

Swoboda et al., analyzed the differences in the popPK parameters in patients with sepsis with normal renal function compared to anuric patients with sepsis undergoing extended dialysis (ED). They concluded that linezolid plasma concentrations can be reduced to subtherapeutic values during ED. Patients with sepsis with and without ED may require higher doses. Body WT, history of liver transplantation or resection, and dialysis were significant covariates [66].

Roger et al., analyzed the differences between CVVH and continuous venovenous hemodiafiltration (CVVHDF) [not included in the results]. No statistical differences were found in terms of CL; however, the mean CL_{CVVHDF} was 20.5% higher than CL_{CVVH} (5.9 vs 4.5 L/h). Increasing WT and decreasing sequential organ failure assessment were associated with higher linezolid CL. The sequential organ failure assessment score reflects the level of organ dysfunction of different systems by measuring several physiological parameters. Those related to the cardiovascular system (mean arterial pressure and need of vasoactive agents) and hepatic function (bilirubin level) probably contribute the most to impaired linezolid CL, owing to decreased cardiac output and subsequent renal excretion, and decreased linezolid metabolism. The authors concluded that patients who undergo CVVH and CVVHDF have a low PTA at standard doses, especially with a body WT of > 90 kg and an MIC ≥ 2 mg/L [91].

On the contrary, Ide et al.'s study also considered the differences between patients with sepsis who underwent CRRT (eight with CVVHDF and two with continuous venous-venous hemodialysis). The differences between linezolid CL in patients with renal dysfunction and those who underwent CRRT were not as large as in the previous studies (2.06 L/h vs 2.74 L/h). The authors suggested that the low CRRT dose could have had an impact on the lower CL values observed [74].

In summary, renal replacement therapies including IHD, CVVH, CVVHDF, and sustained low-efficiency dialysis seem to remove significant amounts of linezolid, around 30% of the dose. The parameters and duration of the renal replacement therapy could also play an important role in total linezolid CL and should be considered. Subtherapeutic concentrations of linezolid were observed more frequently than supratherapeutic concentrations in this subgroup of patients, particularly in those with higher body WT and MICs, in which higher doses might be required.

5.3 Hepatic Impairment

According to the summary of product characteristics, the recommended linezolid dose for mild-to-moderate hepatic impairment is 600 mg twice daily. However, this recommendation was based on a single study with only seven patients with mild-to-moderate hepatic impairment. Although no statistical differences were found in terms of the concentrations and PK parameters, it may not be reliable to state that dose adjustments were not warranted for this population given the

limitations of the very small sample size [92]. No dose recommendations for severe hepatic impairment were included.

As was the case in renal impairment, post-commercialization studies observed increased concentrations of linezolid and a higher incidence of adverse reactions in patients with hepatic impairment. Ikuta et al. [93] reported an incidence of 48.8% for thrombocytopenia, with chronic liver disease being the only significant risk factor. Zhang et al. [94] found a 57.1% incidence of thrombocytopenia in patients with acute-on-chronic liver failure. In a case-control study conducted by Luque et al., 76.9% of the subjects had supratherapeutic trough concentrations; however, the upper limit of the target therapeutic range (10 mg/L) was higher than the currently recommended limit (7 mg/L) [24, 57]. The median steady-state C_{min} was 20.6 mg/L and this was similar among different degrees of hepatic impairment. Liver cirrhosis was the only risk factor associated with supratherapeutic levels (odds ratio 11.4). Around half of the patients experienced hematological toxicity (53.8%). Clinically relevant thrombocytopenia ($< 100 \times 10^3$ platelets/μL) was significantly associated with high trough concentrations (23.6 vs 4 mg/L) and hyperlactatemia (19.9 vs 3.4 mg/L) [95].

As previously mentioned, Sasaki et al. [67] found that the presence of liver cirrhosis leads to a 45.2% reduction in total linezolid CL. Nevertheless, only four patients with liver cirrhosis (Child-Pugh class C) were included in this study. Swoboda et al. [66] also found that liver transplantation or resection was a significant factor affecting linezolid CL, with it dropping by 60%.

Two popPK models were specifically developed in patients with hepatic impairment. Wicha et al., used the maximal liver function capacity (LiMAx) test, which aims to determine liver function by assessing cytochrome P450 1A2 activity measuring the ratio of exhaled ^{13}C and ^{12}C following an intravenous injection of ^{13}C-labeled methacetin [96, 97]. They first separately assessed CL_{renal} and $CL_{non\text{-}renal}$, in which CL_{CR} and LiMAx were significant covariates, respectively. However, when analyzing total linezolid CL, the LiMAx value was the only significant covariate. Patients with LiMAx values < 100 μg/kg/h were at a high risk of linezolid overexposure [69].

Recently, Zhang et al., developed a popPK model to improve dosing in this population. The majority of patients in this study were diagnosed with liver failure or cirrhosis, Child-Pugh class C (66.7%). Creatinine CL and prothrombin activity were significant covariates on CL. In patients with prothrombin activity < 20%, the estimated probability of supratherapeutic trough concentrations was 64.4%. Authors suggested that 300 mg every 12 h would achieve a PK/PD target of AUC/MIC > 80 in 91.9% of patients, even for high MIC values of 4 mg/L [70].

Although the metabolism of linezolid is mediated by non-enzymatic pathways, the liver appears to play a key role in linezolid CL. Observational studies found higher linezolid concentrations and hematological toxicity rates in patients with liver failure. When developing popPK models in this population, one of the main limitations is finding reliable liver function markers. Published models considered the presence of cirrhosis, the prothrombin activity, and the novel LiMax approach as covariates. Decreased linezolid CL values and high rates of overexposure were observed in this population. Dose reductions were proposed to attain the PK/PD target even for high MIC values.

5.4 Elderly Patients

Pivotal studies concluded that age did not alter the PK parameters and that dosage adjustments would not be necessary in this group of patients [9]. Nevertheless, some observational studies observed a significant effect on linezolid PK parameters. In a retrospective observational study by Cattaneo et al., a correlation between age and serum creatinine with C_{min} was observed. Elderly patients, particularly those aged > 80 years, were at a higher risk of overexposure [21]. The authors subsequently reported increasing trough concentrations correlated with age, with a 30% increase per decade from 50 years on. This study had an important limitation that could lead to an overestimation of age effect on linezolid concentrations, which was the absence of information on renal CL [98].

Abe et al. performed a popPK analysis to determine the influence of age and body WT. Clearance diminished as age increased from about 60 years. A 3.5-fold difference in exposure was observed between a patient aged ≥ 80 years with a body WT ≤ 50 kg and another aged <60 years and weighing ≥ 50 kg [64]. Xie et al., also identified an inverse correlation between age and linezolid CL [34] and Tinelli et al., carried out a study specifically on this population. In the first C_{min} measurement, all of them had supratherapeutic trough concentrations. After reducing the dose to 300 mg every 12 h, 85% of subsequent C_{min} was within the therapeutic range [99]. Recently, Cheng et al. also found higher concentrations in elderly patients, correlating this with hematological toxicity [100].

Despite there being no specific dosing recommendations for the elderly population, age appears to be a significant factor that affects linezolid exposure. This might be related to some age-related factors that affect linezolid exposure. Changes in the body composition of elderly patients can decrease the V_d. Furthermore, renal and hepatic functions worsen, decreasing CL. It is important to mention that age was tested as a potential covariate in most of the models; however, it was only significant in a few models. This might be explained by the fact that other covariates such as body WT or renal function could explain the decreasing CL values better than the patient's age.

In summary, increased age, particularly over 60 years, was correlated with higher linezolid concentrations and toxicity. Dose reductions might be needed, especially in patients with a lower body WT and other comorbidities.

5.5 Overweight and Obese Patients

The relationship between linezolid CL and body WT has been documented in several studies, some of them focusing on overweight and obese patients. Cojutti et al. developed a popPK model in which greater CL values and lower AUC were noticed in obese grade III vs overweight patients (not included in results). Estimated glomerular filtration rate was the only significant covariate on CL, while WT was a covariate on both central and peripheral V_d. The authors proposed 450 mg every 8 h when eGFR was ≥ 60 mL/min/1.73m^2. However, when MIC was ≥ 2 mg/L, the majority of the tested regimens would lead to low PTA, except 600 mg every 8 h, which gave an unacceptable high risk of overexposure (> 65%) [47].

In Xie et al.'s popPK model, the simulations concluded that giving standard doses to obese patients would lead to a low PTA, especially in patients aged < 60 years, and this was in line with Cojutti et al.'s findings [34]. In addition, Ehmann et al. performed a study comparing the PTA of non-obese and obese patients eligible for surgical intervention. Lower linezolid exposure was associated with obese patients. Interestingly, the body size descriptor that better related to distribution was the lean body WT, and the mean arterial pressure was found to be correlated with linezolid CL. The authors proposed a dose increase, shorter dosage intervals, and/or prolonging administrations by up to 4 h to maximize the PTA, especially when MIC = 2 mg/L. None of the tested regimens achieved an adequate PTA when MIC = 4 mg/L [79]. In contrast to Ehmann et al.'s results, total body WT was the descriptor that most influenced PK parameters, especially the V_d in Blackman et al.'s model. However, the results of simulations provided similar conclusions, as a low PTA was estimated for MIC ≥ 2 mg/L. In fact, 600 mg every 8 h could achieve an optimal PTA for MIC = 2 mg/L, but not in the case of 4 mg/L [80].

In summary, overweight and obese patients experienced lower exposure to linezolid and seemed to be at a higher risk of treatment failure. Both V_d and linezolid CL could increase in overweight and obese patients. Volume of distribution was allometrically scaled to WT in all models; however, both ideal body WT and total body WT were used as body size descriptors. Higher doses might be required in this population, and the risk of therapeutic failure is greater with decreasing age and when MIC values are ≥ 2 mg/L. The doses needed to attain PK/PD targets could lead to a high risk of overexposure for the higher MIC values.

5.6 Cystic Fibrosis

Keel et al. studied linezolid pharmacokinetics in eight patients diagnosed with cystic fibrosis based on a previously published popPK model that included a theoretical inhibition compartment to explain non-linear CL of linezolid over time [63]. Only lean body WT was a significant covariate for CL in this study. Clearance after the first dose and a 9-day treatment period was calculated, with a mean 38.9% reduction, from 9.7 to 6.1 L/h. The mean parameter values were similar to those recorded in healthy subjects, despite bioavailability (85% vs 100%), possibly owing to characteristic malabsorption of this group of patients [68].

5.7 Critically Ill Patients

Critically ill patients are known to have several clinically relevant PK and physiological alterations that may alter drug concentrations, compromising therapeutic success. Furthermore, the high prevalence of severe infections with high mortality rates still represents a challenge, with linezolid playing a crucial role, given that up to 50% of bloodstream infections in critical care units are caused by Gram-positive bacteria [101, 102]. Therefore, it is a key element to optimize linezolid exposure in this group of patients.

A few studies observed large BSV to linezolid exposure in critically ill patients. Dong et al. remarked that highly variable linezolid PK/PD properties were observed in this group [103]. In the same vein, Zoller et al. reported 100-fold differences in trough concentrations (from < 0.13 to 14.49 mg/L) and $AUC_{0–24}$ (50.1–453.9 mg·h/L). High intra-subject variability was also noted, as only 17% of patients attained trough concentrations within the desired range for the entire study period. Importantly, a large proportion of the patients had linezolid trough concentrations and $AUC_{0–24}$ below the target [104]. To the contrary, most of the patients with out-of-range concentrations fell above the upper limit in the 10-year therapeutic drug monitoring program experience reported by Pea et al. [23]. This could be explained by the differences in the C_{min} target, 2–7 mg/L compared with 2–10 mg/L in the Zoller et al. study. Decreased protein binding in patients with hypoalbuminemia was also observed [35, 105] and non-linearity of CL over time [30].

Töpper et al., developed a popPK model in surgical critically ill patients. Despite no simulations being performed, a high BSV was noted (108.2% in CL and 53.7% in Vd), and the majority of patients experienced underexposure or overexposure to linezolid. The authors proposed the possible role of drug–drug interactions to partially explain the high variability, especially with proton pump inhibitors and levothyroxine [37].

Recently, Soraluce et al. developed a popPK model in critically ill patients, including those subjected to CRRT.

Creatinine CL was the only significant covariate on CL. The extracorporeal CL was calculated by multiplying the effluent flow by the sieving coefficient. The mean sieving coefficient was 0.8 and this did not vary depending on the technique or membrane employed. The PK/PD target was not achieved in many patients, especially for MICs of 2 and 4 mg/L. Authors proposed a continuous infusion of 50 mg/h, given that 85% of patients would achieve the target of Css > MIC for values of 2 mg/L. Nevertheless, for MIC values of 4 mg/L, only 50% of patients achieved the target even with continuous infusion administration [71]. Taubert et al., found interesting significant covariates on linezolid CL, which may reflect the disease and pathophysiological status of critically ill patients: acute respiratory distress syndrome (ARDS), fibrinogen, and lactate. On the one hand, lactate may inversely reflect the organ perfusion and hemodynamic stability, and on the other hand, fibrinogen may indirectly reflect hepatic function. Nonetheless, the most relevant covariate was ARDS, the presence of which would increase linezolid CL by 82%. The authors proposed that the large amount of reactive oxygen species in the lungs of patients with ARDS was a potential underlying mechanism [78]. Wang et al. developed a popPK model to perform dose adjustments according to CL_{CR} values. Mean values of CL and V_d were very similar to those reported by Soraluce et al. Based on simulations, they proposed doses of 600 mg every 12 h for CL_{CR} ~ 40 mL/min, 600–900 mg every 12 h for CL_{CR} ~ 80 mL/min, and a continuous infusion of 2400 mg/day in patients with augmented renal CL.

In summary, critically ill patients appear to be at a high risk of both underexposure and overexposure because of the physiopathological changes experienced by this population, in which the attainment of the PK/PD target is particularly relevant given the high prevalence of severe infections with high mortality rates. Covariates related to the physiopathological status of these patients have been found to be correlated with linezolid CL, such as ARDS diagnosis or lactate and fibrinogen levels; however, further research is needed. Higher-than-standard linezolid doses may be required in patients with augmented renal CL, renal replacement therapy, or when treating high MIC infections. Continuous infusion has also been proposed in order to maximize the PTA when MIC is ≥ 2 mg/L.

5.8 Patients with TB

In addition to Gram-positive infections, linezolid is also widely used for treating TB infections, especially for resistant strains. Lower doses are used but for longer periods of time.

Three popPK models were performed in patients with TB [58, 73, 76], which mainly differed in terms of the PK/PD targets and the PTA results of simulations because of differences in MIC. Large variability in the linezolid CL values was noted. In Abdelwahab et al.'s [58] popPK model developed in South African patients, CL was 3.57 L/h, which was considerably lower than the 6.06 L/h reported by Alghamdi et al. [73] and the 7.69 L/h reported by Tietjen et al. [76]. As the rest of the baseline characteristics were similar, the ethnicity could have a significant influence, as most of the patients in the Abdelwahab model were black or mixed race.

Accordingly, Abdelwahab et al. suggested that a 600-mg daily regimen would be enough to attain the PK/PD target in the South African population, while Tietjen et al., proposed a 600-mg twice-daily regimen. In the same vein, Alghamdi et al., predicted that daily doses of 900–1200 mg would ensure efficacy but potentially with more toxicity.

5.9 Pediatric Patients

A phase I single-dose study including 58 children aged from 3 months to 16 years found significant differences in drug disposition. The mean values of CL and V_d were greater than in adults. As a result, exposure to linezolid measured by dose-normalized AUC was 35% of the mean value in adults (3.72 mg·h/L vs 10.51 mg·h/L per mg/kg of linezolid). A non-linear correlation between CL and age was observed, and children aged < 40 months had the highest values of CL. On the basis of these data, authors suggested 10 mg/kg every 8–12 h in this population [106].

Subsequently, other trials were conducted in different pediatric subpopulations. A study in neonates and young infants, PNA ≤ 3 months, found that linezolid pharmacokinetics varies substantially in the first week of life depending on PNA. Preterm infants aged < 7 days had similar CL values to adults, while infants aged > 7 days had values that were approximately three-fold greater [107]. Pooled data from another three trials that included children also found age-dependent linezolid CL. While adolescents had similar values to adults, young children had higher CL, up to three-fold, and subsequently, a smaller AUC, and shorter half-lives. Finally, a popPK analysis of data from a phase III trial reported that doses of 10 mg/kg every 8 h in children aged under 12 years resulted in similar linezolid exposure to the exposure in adults who received 600 mg every 12 h [108].

A popPK model by Li et al. conducted in pediatric patients aged from 0 to 12 years identified body WT and eGFR as significant covariates on linezolid CL. They also observed risk of underexposure in children treated with 10 mg/kg every 8 h for MIC ≥ 2 mg/L. The authors suggested increasing doses up to 15–20 mg/kg every 8 h in this population [81].

A PK/PD evaluation performed by Cojutti et al., (not included in results) revealed suboptimal values of C_{min} and $AUC_{0–24h}$ with the recommended dosage of 10 mg/kg every

8 h in almost half of the patients. Moreover, a PTA ≥ 90% of AUC/MIC > 100 would only be achieved for MIC ≤ 1 mg/L. Doses of up to 15 mg/kg every 8 h would be necessary for MIC = 2 mg/L, while neither of the dosage regimens tested ensured an acceptable PTA for MIC = 4 mg/L. With regard to significant covariates, none of the demographic characteristics or renal function correlated with C_{min} values, while co-medications (phenobarbital, dexamethasone, proton pump inhibitors, and amiodarone) accounted for two-thirds of the variability [109].

Garcia-Prats et al. developed a popPK analysis to determine optimal dosing for treating multi-drug-resistant TB in children. Weight significantly correlated with linezolid CL. They proposed WT-banded once-daily linezolid dosing, with a range from 80 mg for children weighing 5–7 kg up to 600 mg for those weighing > 44kg. The exposure target was an $AUC_{0-24h,ss}$ = 110 mg·h/L based on adult data [83].

A popPK model in preterm infants was also developed. Thibault et al. found that PNA and WT correlated significantly with linezolid CL. Doses of up to 12 mg/kg every 8 h would be necessary in order to achieve PTA ≥90% for MIC = 2 mg/L. None of the regimens tested attained sufficient PTA for MIC = 4 mg/L [82].

Finally, Yang et al. performed a model in critically ill children in which WT and aspartate transaminase were significant covariates of CL. Higher doses of up to 15 mg/kg every 6 h were estimated to treat pathogens with MIC = 2 mg/L [84].

In summary, linezolid CL seems to vary substantially in the pediatric population. In premature infants, PNA was found to be the main covariate influencing CL, the values of which ranged from those recorded in adults when aged < 7 days to three-fold in premature infants aged > 7 days, possibly owing to organ maturation, mainly the liver. This higher CL appears to be maintained in younger children, but it then seems to decrease in adolescents, reaching values similar to adults. Higher-than-standard doses were suggested in younger children and when treating pathogens with high MIC values.

This comprehensive review had some limitations. First, only parametric non-linear mixed-effect models were included in the results, despite the fact that some non-parametric models have also been published [4, 47, 91, 110, 111] owing to the difficulties in performing a direct comparison. Nonetheless, some information from these studies was included in the discussion when considered necessary.

Apart from that, there were some limitations in the PK/PD targets and MIC values as they only consider the plasma concentration of linezolid. An ideal PK/PD target should include concentrations in the site of infection. Finally, regarding the covariate analysis in each population, we mainly focused on the those in which that covariate was significant and included in the model.

6 Conclusions

This review summarized the most relevant information on population pharmacokinetics of linezolid, highlighting special populations that might be at a higher risk of overexposure and underexposure, leading to toxicity or treatment failure. A dosing simulation analysis also helps to optimize linezolid treatment, as it considers relevant covariates that influence linezolid exposure, such as body WT, renal and hepatic function, and age, as well as the MIC of the target pathogens. Therapeutic drug monitoring may be warranted in a large proportion of patients to maximize the probability of attaining the desired PK/PD target. Further studies focusing on potential covariates, such as renal and hepatic function, drug–drug interactions involving P-glycoprotein, and the influence of gestational age in premature infants, are warranted given that unexplained variability remains high. In addition, the predictive performance of models needs to be assessed in the specific population in which the models are to be used.

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Declarations

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Authors and Affiliations

Enrique Bandín-Vilar[1,2,3] · Laura García-Quintanilla[1,2,3] · Ana Castro-Balado[1,2,3] · Irene Zarra-Ferro[1,2] · Miguel González-Barcia[1,2] · Manuel Campos-Toimil[4] · Víctor Mangas-Sanjuan[5,6] · Cristina Mondelo-García[1,2] · Anxo Fernández-Ferreiro[1,2]

[1] Pharmacy Department, University Clinical Hospital of Santiago de Compostela (SERGAS), Travesía da Choupana, 15706 Santiago de Compostela, Spain

[2] Clinical Pharmacology Group, Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, Spain

[3] Department of Pharmacology, Pharmacy and Pharmaceutical Technology Department, Faculty of Pharmacy, University of Santiago de Compostela (USC), Santiago de Compostela, Spain

[4] Physiology and Pharmacology of Chronic Diseases (FIFAEC), Center for Research in Molecular Medicine and Chronic Diseases (CiMUS), University of Santiago de Compostela, Santiago de Compostela, Spain

[5] Department of Pharmacy and Pharmaceutical Technology and Parasitology, University of Valencia, Valencia, Spain

[6] Interuniversity Research Institute for Molecular Recognition and Technological Development, Polytechnic University of Valencia - University of Valencia, Valencia, Spain