Pharmacokinetic of linezolid dose adjustment for creatinine clearance in critically ill patients: a multicenter, prospective, open-label, observational study

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Research

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Abstract

Background

Linezolid (LNZ) is a common antibiotic used to treat bacterial infections. But there is a lack of evaluation of pharmacokinetics (PK) of LNZ dose adjustment for creatinine clearance (CrCL) in highly heterogeneous critically ill patients. By using a population PK approach, we aimed to determine the optimal dosing strategy for LNZ in critically ill patients, especially those along with renal dysfunction.

Methods

This multicenter, prospective, open-label, observational study was conducted in intensive care units of 4 tertiary hospitals. Of the 152 eligible patients, 117 were included for establishing the PK model. Besides internal validation, external validation was conducted using another 35 patients as a validation group. The area under curve from 0 to 24h at steady-state divided by the minimum inhibitory concentration (AUC\textsubscript{24}/MIC) >80 and trough concentration of LNZ <10 mg/L was used as the target pharmacodynamic index. Dosing regimens for MIC of 0.5 to 4 mg/L were evaluated based on low, normal, and high creatinine clearance using Monte Carlo simulation.

Results

A one-compartment model was chosen as the base model. The PK parameter estimates were clearance of 5.60 L/h and the volume of the central compartment of 43.4 L. CrCL had a significant influence on clearance of LNZ, with an adjusting factor of 0.386. The standard dosing regimen [600 mg every 12 hour (q12h)] achieved adequate exposure in patients with severe renal impairment (CrCL, 40 mL/min). A daily dose of 1200 mg could provide sufficient exposure for MIC less than 2 mg/L in patients with normal renal functions (CrCL, 80 mL/min). For augmented renal clearance (ARC), a daily dose of 1200 mg could provide sufficient exposure for MIC less than 2 mg/L. Continuous infusion obtained a similar clinical response.

Conclusions

For critically ill patients, the standard dose of 600 mg LNZ q12h was adequate for MIC<1 mg/L. With ARC, a 1200 or 1800 mg/day 24h continuous infusion was recommended.

Introduction

Linezolid (LNZ), an oxazolidinone antibiotic [1], is an important therapeutic option for infections caused by methicillin-resistant \textit{Staphylococcus aureus} (MRSA) [2, 3], and \textit{Enterococcus}-induced complicated intra-abdominal infections [4, 5], especially in critically ill patients. For its property of low protein binding (~ 27%) and wide distribution, it achieved high concentrations in infected organs, such as the lungs, brain, and skin [5, 6]. As a time-dependent antibiotic, the area under curve from 0 to 24 h at steady-state divided by the minimum inhibitory concentration (AUC\textsubscript{24}/MIC) >80 and the percentage of time that plasma concentrations exceed the MIC (%T\textsubscript{> MIC}>85%) were often used the pharmacodynamic (PD) indexes [7–10]. The trough concentrations (C\textsubscript{min}) of LNZ in the range of 2–10 mg/L were also associated with clinical response and adverse effects. The occurrence of thrombopenia increased by 50% if the C\textsubscript{min} was higher than 10 mg/L [11]. However, previous studies had revealed that low target achievement and high interindividual variability at a standard dose [600 mg every 12 hour (q12h)], with 30.7–50% of critically ill patients exposed in the subtherapeutic levels (C\textsubscript{min} < 2 mg/L) [12, 13].
For dose optimization, the population pharmacokinetic (PK) approach had been used to simulate the dosing regimens in Caucasian patients with acute respiratory distress syndrome (ARDS) [14], renal impairment [15], augmented renal clearance (ARC) [16], or on continuous renal replacement therapy (CRRT) [17]. Based on a population PK model of LNZ in healthy Chinese volunteers, Yang et al. simulated different dosing regimens for a range of MICs [18]. As the MICs tested in China were around 1 mg/L, without consideration of the renal functions, the standard LNZ dosing regimen (600 mg q12h) achieved enough exposure for most gram-positive bacterial infections in China. Nevertheless, with complex and severe pathophysiological conditions, critically ill patients are more potential to alter PK and PD variables [18]. Previous studies using a population PK model were performed mostly on critically ill Caucasian patients. A better knowledge of the PK/PD of LNZ dose adjustment for creatinine clearance (CrCL) might help develop efficacious intervention of infections [19]. But there is a lack of evaluation of PK/PD of LNZ dose adjustment for CrCL in highly heterogeneous critically ill patients, especially in the Chinese. To explore the PK/PD of LNZ dose adjustment for CrCL, and to clarify the optimal dosing strategy for LNZ in critically ill patients, especially those Chinese patients along with renal dysfunction, this multicenter, prospective, open-label, observational study was taken in the adult intensive care units (ICUs) of 4 tertiary hospitals in China.

Materials And Methods

Study design and patients

This multicenter, prospective, open-label, observational study was conducted in ICUs of Guangdong Provincial People’s Hospital, Nanfang Hospital, Guangzhou First People’s Hospital, and Guangzhou 999 Brain Hospital (Guangdong, China). The inclusion criteria were as follows: patients aged more than 18 years and patients who received LNZ intravenously (often 600 mg q12h). The exclusion criteria were as follows: incomplete information and oral administration. Patients enrolled before October 30, 2018, were included in the model establishment group, and those enrolled after were included in the external validation group. The study protocol was designed according to the SPIRIT guideline [20]. All experiments were performed under the approved protocols, guidelines, and regulations, and all patients (or appropriate surrogates for patients unable to consent) provided written informed consent simultaneously. This study was approved by the Ethics Committee of the Guangdong Provincial People’s Hospital, Nanfang Hospital, Guangzhou First People’s Hospital, and Guangzhou 999 Brain Hospital (Guangdong, China) and carried out in accordance with the Declaration of Helsinki.

The demographic data, including age, weight, height, and sex, were collected. Renal and hepatic functions, including the levels of alanine aminotransferase, aspartate aminotransferase, total bilirubin, direct bilirubin, and serum creatinine (sCr), and the platelet count were evaluated. CrCL was estimated using the Cockcroft-Gault formula [21]. Other potential covariates (COV) included the CRRT status, baseline sequential organ failure assessment (SOFA) scores, and acute physiology and chronic health evaluation (APACHE) II scores. The components of the SOFA, APACHE II scores were collected from the historical medical records.

Sample collection

Venous blood samples were collected in EDTA-K$_2$ tubes at the end of the infusion (2.5 h after the start of infusion) and before the next dose in patients administered at least one dose. The plasma samples were separated by centrifuging the blood samples at 2000g for 10 min at room temperature and stored at −80°C before analysis.
Analytical procedures

All plasma samples were quantified at the Department of Medical Sciences within Guangdong Provincial People's Hospital using a validated high-performance liquid chromatography-tandem mass spectrometry method. The method was fully validated according to the guidelines of the US Food and Drug Administration for bioanalysis [22]. As the protein binding of LNZ is <15% in critically ill patients [23], the total LNZ concentration was measured. The linear range of the method was 0.05–20 mg/L. The inter-day and intra-day precisions were 1.7%–5.8%, and the relative error (accuracy) was -3.3% to -1.3%. The matrix effect and recovery were 88.4%–92.5% and 89.5%–91.4%, respectively.

PK modeling

A one-compartment model with first-order elimination was used as the base model. The potential covariates, including demographic characteristics, renal and liver functions were evaluated. Covariate models were chosen based on the types of variables used. Discrete covariates (such as sex) were modeled as follows. COV_{gender} is a binary variable, which is 1 for male and 0 for female patients.

\[ P_{ij} = P_{tv,j} \cdot (1 + \theta_j \cdot COV_{gender}) \cdot e^{\eta_i} \]

For continuous covariates (such as age and CrCL), an exponential model was chosen with average covariate values (COV_{ave}) and an adjusting factor (\theta_j),

\[ P_{ij} = P_{tv,j} \cdot \left(\frac{COV}{COV_{ave}}\right)^{\theta_j} \cdot e^{\eta_i} \]

The change in the objective function value (OFV) was asymptotically distributed as $\chi^2$. The covariate evaluation was followed by a stepwise univariate forward at least a 3.84 reduction in the objective function value (OFV) ($\alpha=0.05$, 1 degree of freedom) and backward elimination analysis of the covariates ($\alpha=0.001$) with an OFV increase at least 10.82.

Residual variability (RV) was modeled using a mixture of additive and proportional error model.

The adequacy of the final model was assessed using goodness-of-fit (GOF) plots, normalized prediction distribution error (NPDE), and external validation. One thousand times of bootstrap for the 95% confidence intervals (CIs) of the parameters were conducted on Pearl-speaks-NONMEM version 4.8.0 (Uppsala University, Sweden). The GOF plots and NPDE statistics were conducted using R and the add-on package NPDE version 2.0 [24]. The mean prediction error (MPE) and the root mean square error (RMSE) were calculated as follows to assess the accuracy and precision of the final model:
Analytical procedures

All plasma samples were quantified at the Department of Medical Sciences within Guangdong Provincial People’s Hospital using a validated high-performance liquid chromatography-tandem mass spectrometry method. The method was fully validated according to the guidelines of the US Food and Drug Administration for bioanalysis [22]. As the protein binding of LNZ is <15% in critically ill patients [1], the total LNZ concentration was measured. The linear range of the method was 0.05–20 mg/L. The inter-day and intra-day precisions were 1.7%–5.8%, and the relative error (accuracy) was -3.3% to -1.3%. The matrix effect and recovery were 88.4%–92.5% and 89.5%–91.4%, respectively.

Simulations and target attainment

The PK profiles of different infusion dosing regimens were obtained using Monte Carlo simulations using NONMEM: daily dose of 1200, 1800, and 2400 mg, given by every 12 h, 8 h, 6 h, and 24-h continuous infusion, respectively. The virtual patients (n=10000) stratified three CrCL levels were simulated as follows: (1) patients with a renal-impaired CrCL value of 40 mL/min, besides the above dose regimens, 800 mg q12h was also simulated; (2) patients with a normal CrCL value of 80 mL/min/1.73m²; and (3) virtual patients with augmented renal clearance, a 3-fold CL value than the normal one (CrCL=80 mL/min/1.73m²) were set. The probability of target attainment (PTA) was calculated using $\frac{AUC_{24}}{MIC} \geq 80$ meanwhile $C_{min}$ at steady-state <10 mg/L for the MIC range from 0.5 to 4 mg/L. $AUC_{24}$ was calculated by the daily dose divided by the individual CL. A priori, a dosing regimen was considered optimal if the PTA was higher than 90%, whereas a PTA between 70% and 90% was considered to indicate a moderate probability of success.

Statistical analysis

All baseline data (demographic and characteristics) were summarized with median and range and compared using R version 3.5 (Team R, 2018). Population PK analyses were performed using the software NONMEM (version 7.3, ICON plc, NY, USA), implementing the first-order conditional estimation method with interaction. A Fortran compiler was used, and the runs were executed on Pirana (version 2.9.0) [25].

Results

Patient characteristics
Of the 160 patients enrolled in the model establishment group, 7 were excluded for incomplete information and 1 for oral administration (Fig. 1). The patients had normal to severely impaired renal function (CrCL, 7.5–222.4 mL/min per 1.73 m²); of these, five had ARC. Further, 83 male and 34 female patients (117 in total) with a median age of 62 years, BMI 21.2 kg/m² were included for establishing the population PK model (Table 1), with 241 observations in total. With a high inter-subject variability of $C_{\text{min}}$ values, the maximum was more than 330-fold higher compared with the minimum (range, 0.1–33.6 mg/L). Only 43.6% of the patients achieved the optimal $C_{\text{min}}$ range (2–10 mg/L). In total, 22 (27.0%) $C_{\text{min}}$ values were less than the common MIC (2 mg/L), whereas 35 (26.2%) $C_{\text{min}}$ values were more than the reported upper arm concentration (10 mg/L).
Table 1
Demographic characteristics of the critically ill patients

| Descriptive data                  | Model establishment n or median (range) | Model Validation n or median (range) | P value |
|-----------------------------------|----------------------------------------|-------------------------------------|---------|
| **Demographic variables**         |                                         |                                     |         |
| Male                              | 117 (34/83)                            | 35 (9/26)                           | 0.783   |
| Age (years)                       | 62 (19–90)                             | 55 (28–85)                          | 0.343   |
| Weight (kg)                       | 63.0 (43.8–115.0)                     | 65.8 (40.0–91.0)                    | 0.386   |
| Height (m)                        | 168 (150–183)                         | 169 (150–179)                       | 0.257   |
| BMI (kg/m²)                       | 21.2 (19.5–35.5)                      | 23.0 (17.7–31.5)                    | 0.344   |
| **Coexisting illness/comorbidities** |                                       |                                     |         |
| Diabetes mellitus                 | 29 (25%)                              | 7 (20%)                             | 0.596   |
| Hypertension                      | 46 (39%)                              | 17 (49%)                            | 0.359   |
| Hyperlipidemia                    | 3 (3%)                                | 0 (0%)                              | 0.234   |
| Acute renal failure               | 7 (6%)                                | 4 (11%)                             | 0.424   |
| Chronic renal failure             | 3 (3%)                                | 2 (6%)                              | 0.221   |
| Charlson Comorbidity Index        | 2 (0–10)                              | 2 (0–9)                             | 0.638   |
| **Main reason for linezolid treatment** |                                     |                                     |         |
| Pneumonia                         | 89 (76%)                              | 23 (66%)                            | 0.511   |
| Skin and soft tissue infections   | 3 (3%)                                | 1 (3%)                              | 0.832   |
| Bone and joint infections         | 1 (1%)                                | 0 (0%)                              | 0.799   |
| Intra-abdominal infections        | 7 (6%)                                | 3 (9%)                              | 0.653   |
| CNS infection                     | 5 (4%)                                | 1 (3%)                              | 0.233   |
| Bloodstream infections            | 2 (2%)                                | 5 (14%)                             | 0.093   |
| **Microbiological isolate**       |                                         |                                     |         |
| S. aureus                         | 5 (4%)                                | 5 (14%)                             | 0.102   |
| Enterococcus spp.                 | 3 (3%)                                | 1 (3%)                              | 0.846   |
| Streptococcus spp.                | 2 (2%)                                | 2 (6%)                              | 0.231   |
| MRSA                              | 23 (20%)                              | 9 (26%)                             | 0.098   |

BMI: body mass index; CNS: central nervous system; MRSA: methicillin-resistant Staphylococcus aureus; \( C_{\text{max}} \): the peak concentration post dose; \( C_{\text{min}} \): the trough concentration; APACHE II: acute physiology and chronic health evaluation; SOFA: sequential organ failure assessment; CRRT: continuous renal replacement therapy.
| Descriptive data | Model establishment n or median (range) | Model Validation n or median (range) | \( P \) value |
|------------------|----------------------------------------|--------------------------------------|--------------|
| Other gram-positive bacteria | 3 (3%) | 3 (9%) | 0.155 |
| Unknown | 18 (15%) | 8 (23%) | 0.632 |

**Additional antibiotics**

| Antibiotics | Model establishment n or median (range) | Model Validation n or median (range) | \( P \) value |
|-------------|----------------------------------------|--------------------------------------|--------------|
| Glycopeptides | 20 (17%) | 12 (34%) | 0.315 |
| Penicillins | 21 (18%) | 11 (31%) | 0.122 |
| Cephalosporins | 32 (27%) | 8 (23%) | 0.511 |
| Carbapenem | 58 (50%) | 18 (51%) | 0.648 |
| Macrolides | 1 (1%) | 1 (3%) | 0.833 |
| Fluoroquinolones | 18 (15%) | 5 (14%) | 0.230 |
| Aminoglycosides | 2 (2%) | 2 (6%) | 0.387 |
| Others | 10 (9%) | 2 (6%) | 0.465 |

**Linezolid therapy**

| Therapy | Model establishment | Model Validation | \( P \) value |
|---------|---------------------|------------------|--------------|
| Dose of linezolid | 600 mg q12h | 600 mg q12h | 0.943 |
| Duration of linezolid treatment | 8 (1–27) | 9 (1–27) | 0.843 |
| Plasma \( C_{\text{max}} \) of linezolid (mg/L) | 16.3 (1.4–104.0) | 17.7 (5.56–36.8) | 0.954 |
| Plasma \( C_{\text{min}} \) of linezolid (mg/L) | 5.05 (0.1–33.6) | 6.44 (0.1–29.6) | 0.843 |

**Others**

| Test | Model establishment (µmol/L) | Model Validation (µmol/L) | \( P \) value |
|------|-------------------------------|----------------------------|--------------|
| Serum creatine concentration | 125.9 (24.9-520.6) | 117.1 (21.8-619.1) | 0.427 |
| Creatinine clearance (mL/min) | 47.4 (8.75–222.4) | 48.8 (7.5–196.0) | 0.539 |
| Alanine aminotransferase, (ALT, U/L) | 24 (2-953) | 27 (5-3314) | 0.075 |
| Aspartate aminotransferase, (AST, U/L) | 36 (3.8–4134) | 48 (11-1849) | 0.406 |
| Total bilirubin, (TBIL, µmol/L) | 19.5 (2.7–336) | 19.2 (2.7-500.3) | 0.844 |
| Direct Bilirubin, (DBIL, µmol/L) | 5.7 (0.8–187) | 6.3 (0.8-253.2) | 0.745 |
| Platelet count (PLT, \( \times 10^9 \)/L) baseline | 190.0 (15.0-1204) | 179 (66–415) | 0.729 |

BMI: body mass index; CNS: central nervous system; MRSA: methicillin-resistant *Staphylococcus aureus*; \( C_{\text{max}} \): the peak concentration post dose; \( C_{\text{min}} \): the trough concentration; APACHE II: acute physiology and chronic health evaluation; SOFA: sequential organ failure assessment; CRRT: continuous renal replacement therapy.
Another 35 patients with 72 observations were used in external validation with demographic characteristics similar to those in the model building group (Table 1). Similarly, more than 31% of the patients did not achieve the target $C_{\text{min}}$ range.

**Population PK model**

LNZ plasma concentrations were adequately fitted using the one-compartment model with a proportional error of 36.2% and an additive residual error of 0.055 mg/L. The population PK parameter estimates with 95% CI based on bootstraps are listed in Table 2. The estimate of elimination clearance (CL/F) and volume of distribution (V/F) was 5.60 L/h (95% CI, 4.50–6.41 L/h) and 43.4 L (95% CI, 38.4–49.1 L), respectively, with intersubject variability of 63.9% for CL/F and 17.6% for V/F. Only CrCL had a significant influence on the clearance with an adjusting factor ($\theta_{\text{CrCL}}$) of 0.386. Other potential covariates such as age, weight, liver function, and CRRT were not found to have a significant influence on the PK parameters. However, CrCL was a comprehensive index including age, weight, sex, and renal function of sCr.
Table 2
Population pharmacokinetic parameter estimates of linezolid in the critically ill patients.

| Parameters       | Estimates | %CV | 95%CI by 1000 bootstraps |
|------------------|-----------|-----|--------------------------|
| CL/F, L/h        | 5.60      | 7.1 | 4.50–6.41                |
| V/F, L           | 43.4      | 5.9 | 38.4–49.1                |
| $\theta_{\text{CrCL-CL}}$ a,b | 0.386     | 20.3 | 0.26–0.61               |
| CL_{\text{INTER VAR}}, % | 63.9    | 8.9 | 48.6–69.1               |
| V_{\text{INTER VAR}}, % | 17.6 | 44.5 | 11.1–25.6                |
| Additive error, mg/L | 0.055 | 56.1 | 0.01–1.27              |
| Proportional error, % | 36.2 | 8.8 | 20.6–42.8               |

Cl: confidence interval; CL: clearance of the central compartment; CL_{\text{INTER VAR}}: the inter-individual variability of CL; F: the bioavailability; V: the distribution volume of the central compartment; V_{\text{INTER VAR}}: the inter-individual variability of V.

a, CL = CL_{\text{TV}} (\text{CrCL/61})^{\theta_{\text{CrCL-CL}}}, \text{CrCL is the creatinine clearance.} \theta_{\text{CrCL-CL}} \text{ is the adjusting factor of the CrCL on the CL.}

b, Cockcroft and Gault formula for CrCL. CrCL = (140-AGE)*WT/0.818/sCr (µM) [× 0.85 if Female], AGE is the age of the patient in years; WT is the body weight in kg; sCr (µM) is the serum creatinine concentration in µM.

Model evaluation
The GOF plots showed an adequate fitness of the final model to the LNZ observations (Fig. 2A and 2B). With 1000 simulations, the distribution histogram (Fig. 2C) of NPDE, with a mean of 0.0484 and a variance of 0.923 ($P = 0.0888$), showed a good prediction of the final model. No trends were found between NPDE and the predictions (Fig. 2D). These results of the internal evaluation indicated good accuracy and reliability of the final PK model.

The bias (MPE) was 0.866 mg/L and the RMSE was 9.93 mg/L based on external validation. For the target range of 2–10 mg/L, the prediction was found to agree well with observed concentrations without any significant bias. No obvious patterns were seen in the distribution of prediction errors.

Simulations
The PTA values based on different dosing regimens are shown in Fig. 3 and the full table of PTA in each dose regimens (Table 3). For patients with severe renal dysfunction with CrCL as low as 40 mL/min/1.73 m², both 400 mg q12h and 600 mg q12h regimens were enough to achieve the target AUC_{24}/MIC > 80 with $C_{\text{min}} < 10$ mg/L for MIC ≤ 2 mg/L (Fig. 3A). A decrease in daily dose (400 mg q12h) or each dose (400 mg q8h or 300 mg q6h) seemed unnecessary. In addition, 24-h continuous infusion was not recommended for half occurrence of $C_{\text{min}} > 10$ mg/L (56%). For patients with normal renal function, with CrCL of 80–120 mL/min/1.73 m², a daily dose of 1200 mg could provide sufficient exposure for MIC less than 2 mg/L but 24-h continuous infusion was still not recommended (Fig. 3B). For MIC equals 2 mg/L, 900 mg q12h obtained adequate AUC_{24}/MIC without $C_{\text{min}} > 8$ mg/L. Continuous infusion of 1200 mg or 1800 mg per day had the risk of adverse effects. The virtual patients with 3-fold normal clearance mimicked the ARC in critically ill patients. A daily dose of 1200 mg was
insufficient for MIC above 0.5 mg/L, no matter what the dose frequency was (Fig. 3C). An increased daily dose could increase the PTA for MIC = 1 mg/L, whereas 24-h continuous infusion showed similar PTA but a more stable PK profile, compared with other dose regimens. Daily dose up to 2400 mg could achieve a higher PTA for MIC = 1 mg/L. However, for higher MIC, no successful dose regimens were obtained in the patients with ARC.
Table 3
Probabilities of target attainment (PTA) and percentages of patients with concentrations constantly below minimum inhibitory concentrations (MICs) of 0.5 to 4 mg/L for all dosages in the patient group and stratified by the creatinine clearance (CrCL).

| GROUP | MIC(mg/L) | PTA (%) | AUC$_{24}$/MIC $< 80$ | $C_{\text{min}}$ $>10$ mg/L |
|-------|-----------|---------|-----------------------|-----------------------------|
|       | 0.25      | 0.5     | 1                     | 2 | 3 | 4 | 0.25 | 0.5 | 1 | 2 | 3 | 4 |
| 400 q12h | 100 | 100 | 100 | 58 | 10 | 0 | 0 | 0 | 0 | 42 | 90 | 100 | 0 |
| 600 q12h | 94 | 94 | 94 | 94 | 52 | 16 | 0 | 0 | 0 | 0 | 43 | 78 | 6 |
| 400 q8h | 80 | 80 | 80 | 80 | 38 | 4 | 0 | 0 | 0 | 0 | 43 | 78 | 20 |
| 300 q6h | 73 | 73 | 73 | 73 | 29 | 0 | 0 | 0 | 0 | 0 | 43 | 78 | 27 |
| 1200 24 h inf | 44 | 44 | 44 | 44 | 0 | 0 | 0 | 0 | 0 | 0 | 44 | 80 | 56 |
| 900 q12h | 67 | 67 | 67 | 67 | 36 | 0 | 0 | 0 | 0 | 0 | 31 | 33 |
| 600 q8h | 45 | 45 | 45 | 45 | 16 | 0 | 0 | 0 | 0 | 0 | 29 | 55 |
| 450 q6h | 35 | 35 | 35 | 35 | 6 | 0 | 0 | 0 | 0 | 0 | 29 | 65 |
| 1800 24 h inf | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 29 | 100 |
| 1200 q12h | 44 | 44 | 44 | 44 | 44 | 0 | 0 | 0 | 0 | 0 | 0 | 56 |
| 800 q8h | 24 | 24 | 24 | 24 | 24 | 0 | 0 | 0 | 0 | 0 | 0 | 76 |
| 600 q6h | 10 | 10 | 10 | 10 | 10 | 0 | 0 | 0 | 0 | 0 | 0 | 90 |
| 2400 24 h inf | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 100 |
| 600 q12h | 100 | 100 | 100 | 75 | 26 | 0 | 0 | 0 | 0 | 25 | 74 | 100 | 0 |
| 400 q8h | 100 | 100 | 100 | 75 | 24 | 0 | 0 | 0 | 0 | 25 | 76 | 100 | 0 |
| 300 q6h | 100 | 100 | 100 | 73 | 24 | 0 | 0 | 0 | 0 | 26 | 76 | 100 | 0 |
| 1200 24 h inf | 75 | 75 | 75 | 50 | 0 | 0 | 0 | 0 | 0 | 25 | 75 | 100 | 25 |
| 900 q12h | 96 | 96 | 96 | 96 | 69 | 33 | 0 | 0 | 0 | 0 | 27 | 63 | 4 |
| 600 q8h | 80 | 80 | 80 | 80 | 54 | 18 | 0 | 0 | 0 | 0 | 26 | 62 | 20 |
| 450 q6h | 68 | 68 | 68 | 68 | 41 | 6 | 0 | 0 | 0 | 0 | 27 | 63 | 32 |
| 1800 24 h inf | 26 | 26 | 26 | 26 | 0 | 0 | 0 | 0 | 0 | 0 | 26 | 61 | 74 |
| 1200 q12h | 78 | 78 | 78 | 78 | 78 | 52 | 0 | 0 | 0 | 0 | 0 | 26 | 22 |
| 800 q8h | 55 | 55 | 55 | 55 | 55 | 28 | 0 | 0 | 0 | 0 | 0 | 27 | 45 |

AUC$_{24}$/MIC: the area under curve from 0 to 24 h at steady-state divided by the minimum inhibitory concentration; Cmin: the trough concentration.
AUC<sub>24</sub>/MIC: the area under curve from 0 to 24 h at steady-state divided by the minimum inhibitory concentration; C<sub>min</sub>: the trough concentration.

**Discussion**

The present study showed that the standard dosing of LNZ (600 mg q12h) for all patients led to subtherapeutic LNZ exposure in critically ill Chinese patients. The high variability and outside-the-target ranges of LNZ levels were in line with those in other studies on Caucasian patients [8, 20–23]. In this study, CrCL was identified as the most important covariate on the LNZ clearance, which is a comprehensive indicator including body weight, age, serum creatinine, and sex. For the bacterial MICs < 2 mg/L, the standard dosing regimen could be enough in most cases except for the ARC. However, for MICs > 2 mg/L, the findings of this PK/PD analysis suggested that 1800 mg or higher dose were needed but the adverse effects caused by the high C<sub>min</sub> should be paid close attention.

The final model in the present study included a single covariate CrCL, which was a comprehensive index including weight, sex, age, and Scr. Age and weight were also investigated alone during the covariate screening, but the decrease in the OFV was not similar to that in CrCL. A series of covariates, including body weight, CrCL, fibrinogen, antithrombin concentration, lactate concentration, SOFA score, and ARDS, were found to significantly influence the clearance and distribution volume of LNZ in patients [13, 14, 26]. LNZ clearance increased in patients with ARDS.
and those with elevated fibrinogen or decreased lactate concentration [24]. Independent covariates, which were related to significant decreases in the LNZ concentration, included higher weight, CrCL, and fibrinogen and antithrombin concentrations; lower lactate concentration; and the presence of ARDS [22]. Based on a rich plasma (n = 1598) concentration data pooled from 3 clinical trials with 51 individuals receiving 600 mg of intravenous and oral LNZ, a full covariate model was established comprising the covariates CrCL and sepsis on CL [27]. Patients with sepsis had a higher clearance, leading to a lower LNZ concentration. The CrCL and total body weight further impacted LNZ exposure. Increased patient weight and a decreased SOFA score were associated with increased LNZ clearance. Suboptimal achievement of therapeutic targets occurred at the EUCAST breakpoint MIC of 2 mg/L using 600 mg iv every 12 h [13]. However, for obese patients, a longer % \( T_{>MIC} \) was achieved under a continuous infusion compared with an intermittent infusion, whereas MIC > 4 mg/L had no advantage [28]. Further, 18.7–48.9% of LNZ could be eliminated by CRRT [29].

The \( T_{>MIC} \) and AUC\(_{24}/\)MIC ratios are often defined as the PD effect indices [30]. The \( C_{\text{min}} \) is a good predictor for the AUC\(_{24}\) because the trough concentration of LNZ (\( C_{\text{min}} \)) has a good linear relationship with AUC\(_{24}\). A study conducted on seriously ill adult patients demonstrated that higher success rates were achieved when \( T_{>MIC} \) exceeded 85% and the AUC\(_{24}/\)MIC value was in the range of 80–120 [30]. However, when AUC\(_{24}/\)MIC was increased from 80 to 120, the corresponding probability of target attainment decreased from 99.91–18.97%, revealing a relatively lower efficacy with the recommended LNZ dosing [31].

The standard dose ensured a relatively high probability of treatment success in patients with MIC ≤ 1 mg/L [16, 31]. However, in patients with normal or residual renal function, the standard dose was insufficient, and 900 mg q8h provided a higher probability of treatment success without compromising the safety [16]. In the present study, 1800 mg/day (600 mg q8h) or 1200 mg/day continuous infusion resulted in \( C_{\text{min}} \) within MIC of 10 mg/L. The continuous infusion helped achieve a faster and stable steady state. These results were similar to previous findings on Caucasian patients, showing that the best target attainment according to \( T_{>MIC} \) was observed for continuous infusions of 1200 mg/day [5]. Another population PK study proposed a decreased regimen (600 mg q24h) in patients with sepsis having CrCL < 50 mL/min [15]. In patients with sepsis with a preserved renal function, 800 mg q12h was proposed [15]. In the present study, a 24 h continuous infusion (1200 mg/day) was not recommended for patients with normal CrCL because nearly 25% of the simulated \( C_{\text{min}} \) was higher than 10 mg/L. This was different from the previous studies on Caucasian patients, for the upper limits of the concentrations were not included in their PK/PD indexes. The patients with ARC were common in the ICU, a 24 h continuous infusion of a daily dose of 1200 mg or 1800 mg LNZ was recommended in a previous study [16]. In our study, 900 mg q12h could also achieve a similar clinical response.

An increase in the volume of distribution and metabolism interference [e.g., drug-drug interactions such as P-glycoprotein (P-gp) inhibitors or inducers] are responsible for high interindividual variability of LNZ plasma concentrations [18, 27, 32, 33]. In critically ill obese patients affected by ventilator-associated pneumonia, LNZ CL may overcome the limits of standard administration [28]. However, in the present study, no P-gp inducer was co-administered with LNZ.

This study had some limitations. The limited number of participants clearly could not represent all relevant patient groups and, in conjunction with the high observed variability, led to some statistical limitations. Therefore, all relevant cofactors probably could not be identified.
Conclusions

Standard dosing of LNZ (600 mg q12h) is often potentially insufficient in critically ill patients. In this study, based on the simulation of the final model, the standard dosing regimen was found to be enough in patients with bacterial MICs < 2 mg/L and CrCL < 80 mL/min per 1.73 m². For patients with polyuria (CrCL > 160 mL/min), a loading dose (300 mg) plus a continuous infusion (1200 mg/day) might help achieve sufficient efficacy. For a higher MIC > 2 mg/L, the standard dosing of LNZ was adequate for patients with severe renal dysfunction. For patients with normal renal function, a dose of 600 mg q8h or a 1200-mg/day continuous infusion was recommended.

Abbreviations

AGE, age of the patient in years; ALT, alanine aminotransferase; APACHE, Acute physiology and chronic health evaluation; ARC, augmented renal clearance; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; AUC, area under the receiver operating characteristic curve; BMI, body mass index; CI, confidence interval; Cl, clearance of the central compartment; ClINTER VAR, the inter-individual variability of CL; Cmax, the peak concentration post dose; Cmin, the trough concentration; CNS, central nervous system; COV, covariates; COVave, average covariate values; CrCL, creatinine clearance; CRRT, continuous renal replacement therapy; DBIL, direct bilirubin; F, the bioavailability; GOF, goodness-of-fit; ICU, intensive care unit; IPRED, individual predicted concentrations; LNZ, linezolid; MIC, minimum inhibitory concentration; MPE, mean prediction error; MRSA, methicillin-resistant Staphylococcus aureus; NPDE, normalized prediction distribution error; OFV, objective function value; PD, pharmacodynamic; P-gp, P-glycoprotein; PK, pharmacokinetic; PLT, platelet count; PRED, population predicted concentration; PTA, probability of target attainment; q12h, every 12 hour; RMSE, root mean square error; RV, residual variability; sCr (µM), serum creatinine concentration in µM; SOFA, sequential organ failure assessment; TBIL, total bilirubin; V, the distribution volume of the central compartment; VINTER VAR, the inter-individual variability of V; WT, weight; θCrCL-CL, the adjusting factor of the CrCL on the CL.

Declarations

Ethics approval and consent to participate

The ethics committee of the Guangdong Provincial People's Hospital, Nanfang Hospital, Guangzhou First People's Hospital, and Guangzhou 999 Brain Hospital approved the protocol. Written informed consent was obtained from each patient or from appropriate surrogates for patients unable to consent.

Consent for publication

Not applicable. No individual personal data are included in the study. All patients provided the necessary consent to participate in the present study.

Availability of data and materials

The datasets generated and/or analyzed during this study are not publicly available, owing to currently ongoing research studies, but the data are available from the corresponding author on reasonable request.
Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

XPW, FY, YFW, and CBC contributed to the conception/design of the research and interpretation of the data and critically revised the manuscript. FY, YFW, SLC, YRW, ZW, and JHL performed the research and collected data. ZJZ, JBL, BHQ, and ZFL experimented. XPW and SLC analyzed the data. All authors contributed to the acquisition and analysis of the data, drafted the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work. All authors read and approved the final manuscript.

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