The risk factors for linezolid-induced lactic acidosis in patients older than 85 years

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Abstract

Background

Lactate is considered a prognostic indicator in critically ill patients; however, studies on linezolid-induced lactic acidosis (LILA) are limited, and data from patients older than 85 are even more scarce, therefore we evaluated the risk factors for LILA in patients older than 85 years and established a risk prediction model.

Methods

In a retrospective cohort study, patients older than 85 years who were monitored for blood gas analysis and arterial lactate levels during the use of teicoplanin or linezolid were enrolled. After using propensity score-matched analyses we compared the incidence of lactic acidosis between teicoplanin or linezolid therapy and identified the risk factors of LILA.

Results

After propensity score-matched analyses, the incidence of lactic acidosis with teicoplanin therapy was significantly lower than that with linezolid therapy (0% vs 35.7%; p<0.0001). Duration of linezolid therapy ≥9 days (OR, 3.541; 95% CI, 1.161-10.793; p=0.026), arterial blood glucose level ≥8 mmol/L (OR, 4.548; 95% CI, 1.507-13.725; p=0.007) and high sequential organ failure assessment (SOFA) score (OR, 1.429; 95% CI, 1.213-1.685; p<0.0001) were risk factors for LILA. A risk model is predictive of LILA (area under the curve, 0.849; specificity, 65.1%; sensitivity, 91.4%, with a negative predictive value of 93.2% and a positive predictive value of 59.3%) with high stability.

Conclusions

LILA can occur in patients older than 85 years with a relatively shorter duration of linezolid; hence, the close monitoring of blood gas and arterial lactate levels during the use of linezolid in the super-elderly population is necessary.
Introduction

Lactate is produced by anaerobic glycolysis, mainly in the skeletal muscles, skin, erythrocytes and central nervous system\(^1\). Clinically, elevated lactate levels often represent hypoxia in tissues, so lactate is commonly used to evaluate tissue perfusion and the prognosis for critically ill patients\(^2, 3\). It has been reported that a slight increase in lactate levels leads to a higher mortality rate\(^4, 5\).

However, elevated lactate levels caused by drugs do not necessarily indicate hypoxia, and the lactate levels gradually decrease back to the normal range after drug withdrawal.

Among the different types of drug-induced lactic acidosis, little is known about linezolid-induced lactic acidosis. Linezolid is the first clinically available oxazolidinone antibacterial agent against infections caused by sensitive and multidrug-resistant gram-positive pathogens and multidrug-resistant tuberculosis (MDR-TB)\(^6-8\). The most common adverse reaction to linezolid is reversible myelosuppression (anaemia, thrombocytopenia, leukopenia)\(^9\), and some rare adverse reactions are toxic optic neuropathy\(^10, 11\), irreversible peripheral neuropathy\(^12-14\) and lactic acidosis\(^15, 16\). The incidence of linezolid-induced lactic acidosis (LILA) has been reported to be between 5 and 33%, and it affects the survival of patients\(^17-20\).

However, there have been no large-sample studies on the risk factors for LILA and no relevant data exist pertaining to the extremely elderly population. Hence, we analysed the risk factors for LILA and established a risk prediction model.

Methods

Study Design and Population

This was a retrospective cohort study using a case-control study conducted at the Second
Medical Centre of Chinese PLA General Hospital. The hospital is a 500-bed tertiary and teaching hospital located in Beijing, China.

We included patients older than 85 years who were monitored for blood gas analysis and arterial lactate levels during the use of teicoplanin or linezolid from October 2016 to April 2019 in our hospital. To compare the incidence of lactic acidosis between teicoplanin and linezolid therapy, the baseline characteristics of patients were adjusted using the propensity score matching. Patients with linezolid therapy were invided into lactic acidosis group and non-lactic acidosis group, and then we evaluated the risk factors of LILA. Patients with shock; those who used drugs that affect lactate levels, such as metformin, salicylates, and nucleotide reverse transcriptase inhibitors; patients with respiratory failure or liver failure (Child-Pugh classification C); and those receiving renal replacement therapy were excluded.

Lactic acidosis was defined as a serum pH < 7.35 and arterial lactate ≥ 3.5 mmol/L in our study. The baseline and the end-point lactate levels were obtained in blood gas analyses performed when teicoplanin or linezolid therapy was started and stopped.

Data Collection

The following baseline clinical and laboratory variables were collected retrospectively from the electronic medical record system: sex; age; duration of linezolid therapy; infection site; the use of invasive ventilation; comorbid diseases such as chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, coronary heart disease, hypertension, atrial fibrillation (AF), diabetes mellitus (DM), chronic kidney disease (CKD), neurological disease, malignant tumour, and thyroid hypofunction; laboratory indexes including the levels of serum creatinine, albumin, haemoglobin, creatine kinase and lactate dehydrogenase, alanine dehydrogenase (ALT), aspartate transaminase (AST), troponin I (TNI), pro-brain natriuretic peptide (pro-BNP), D-dimer, and arterial blood sugar
and the estimated glomerular filtration rate (eGFR); the sequential organ failure assessment (SOFA) score; and arterial lactate levels at baseline and the end-point.

Statistical Analysis

Quantitative datas with normal distribution were expressed as mean and standard deviation and analysed by t tests. Quantitative datas with abnormal distribution were expressed as medians and interquartile range (IQR) assessing by Mann-Whitney U tests. Categorical variables were described as frequency, and comparison was performed by the Chi-square test. To adjust for the significant differences in baseline characteristics of patients, we used propensity score matching by implementing nearest neighbor matching in a 1:1 ratio. Factors with significant differences in the univariate analysis were entered into a multivariate binary logistic regression model (forward: LR) to determine their independent effects. The results of the binary logistic regression model are presented as odds ratios (ORs) and the associated 95% confidence intervals (CIs). The sensitivity and specificity of the risk prediction model were tested by receiver operating characteristic (ROC) curve analysis. Variables with p-values less than 0.05 were considered statistically significant. All analyses were performed using the IBM SPSS statistical software package version 23.0 (SPSS, Chicago, IL, USA).

Results

2.1 Patient characteristics and clinical factors

In this retrospective cohort study, 199 and 108 patients were administered teicoplanin or linezolid therapy, and the patient characteristics and clinical factors were shown in Table 1. Infection site, underlying disease (coronary heart disease, atrial fibrillation and neurological disease) and sequential organ failure assessment (SOFA) were significant different between the two groups(p<0.05, Table 1). we used propensity score matching to
adjust the significant differences in baseline characteristics of the two groups. As a result, 98 patients each in the teicoplanin or linezolid therapy groups were matched. The balance in baseline characteristics between two groups was improved considerably (Table 2).

2.2 Arterial lactate at baseline and the end-point of patients in teicoplanin and linezolid therapy groups

In the matched pairs, the incidence of lactic acidosis between teicoplanin and linezolid therapy groups were 0%(0/98) vs 35.7%(35/98) with significantly difference (p<0.0001, Table 3). No significant difference was found at baseline arterial lactate between the two groups, while the arterial lactate at end-point in linezolid therapy groups were significantly higher than that in teicoplanin therapy groups (p<0.0001, Table 3, Figure 1).

2.3 Univariate analysis of risk factors of linezolid-induced lactic acidosis

In linezolid therapy group, 35 and 63 patients were included in the lactic acidosis group and non-lactic acidosis group, respectively. The characteristics of the patients are described in Table 4. No significant differences were observed between the two groups in terms of sex, age, infection site, use of invasive ventilation and prevalence of comorbid diseases (COPD, pulmonary fibrosis, coronary heart disease, coronary heart disease, atrial fibrillation, diabetes mellitus, neurological disease, malignant tumour, thyroid hypofunction). The median duration of linezolid therapy was 10 [7,12] days in the lactic acidosis group and 8 [5,11] days in the non-lactic acidosis group (p=0.053, Table 4). The numbers of patients with CKD in the lactic acidosis group and the non-lactic acidosis group were 24 (68.6%) and 31 (49.2%) (p=0.064, Table 4), respectively. Arterial lactate levels at the end-point were significantly different in the two groups (4.6 [3.7,5.5] vs 2.1 [1.6,2.6], p<0.0001, Table 4). The clinical parameters such as serum creatinine,
haemoglobin, TNI, pro-BNP, D-dimer, and arterial blood glucose levels and the eGFR were significantly different between the two groups (p<0.05, Table 4). The SOFA scores of the two groups were 10 [9,15] and 6 [5,9] (p<0.0001, Table 4), respectively. The 30-day mortality rates were 48.6% and 28.6%, respectively, which were significantly different (p=0.015, Table 4, Figure 2).

2.4 Risk factors associated with linezolid-induced lactic acidosis according to multivariate binary logistic regression

Factors (p<0.1) in the univariate analysis were entered into a multivariate binary logistic regression model to determine their independent effects. No associations were observed between LILA and CKD, serum creatinine levels, haemoglobin levels, TNI levels, pro-BNP levels, D-dimer levels or the eGFR. A duration of linezolid therapy ≥9 days (OR, 3.541; 95%CI, 1.161-10.793; p=0.026,Table 5), an arterial blood glucose level ≥8 mmol/L (OR, 4.548; 95% CI, 1.507-13.725; p=0.007,Table 5) and a high sequential organ failure assessment (SOFA) score (OR, 1.429; 95% CI, 1.213-1.685; p<0.0001,Table 5) were associated with linezolid-induced lactic acidosis.

2.5 Establishment of the risk prediction model

The risk of LILA can be predicted by three factors: the duration of linezolid therapy, the arterial blood glucose level and the SOFA score.

\[
\text{Logit}(P) = -5.263 + 1.264 \times \text{Duration of linezolid} (\geq 9 = 1, < 9 = 0) + 1.515 \times \text{Arterial blood glucose level} (\geq 8 = 1, < 8 = 0) + 0.357 \times \text{SOFA score}.
\]

The probability of LILA in each patient: \(P = e^{\text{Logit}(P)}/(1+e^{\text{Logit}(P)})\)

Receiver operating characteristic (ROC) curve analysis was used to evaluate the accuracy of the risk prediction model. Area Under the Curve (AUC) was 0.849 with 95% CI (0.772-0.926) (p<0.0001). Cutoff was 0.2825 with a sensitivity of 91.4%, a specificity of 65.1%,
negative predictive value of 93.2%, and a positive predictive value of 59.3%.

2.6 The stability of the model was validated in 32 other patients

Thirty-two patients older than 85 years, who were monitored for blood gas analysis and arterial lactate levels during the use of linezolid, were included from the First Medical Centre of Chinese PLA General Hospital from January to October 2019 to verify the stability of the risk prediction model. The gold standard for the diagnosis of LILA was the combination of blood gas analysis and arterial lactate measurements.

According to the fourfold table (Table 6), the sensitivity of the risk prediction model was 100%, the specificity was 80%, the negative predictive value was 100%, and the positive predictive value was 58.3%.

Discussion

Lactate is an important product of cell metabolism during anaerobic glycolysis. Clinically, lactic acidosis can occur due to either excessive production or impaired metabolism. In addition to type A lactic acidosis caused by tissue hypoxia, common drugs such as nucleotide reverse transcriptase inhibitors, salicylates, and metformin cause type B lactic acidosis by interfering with oxidative phosphorylation when there is no obvious tissue hypoxia[1].

Linezolid is a major tool in the treatment of MDR gram-positive pathogens and MDR-TB and can also cause type B lactic acidosis. We found that all patients showed different degrees of elevated lactate levels after using linezolid (1.2 [0.9,1.4] vs. 2.6 [1.8,3.7], p < 0.0001), and 35.7% had lactic acidosis; this percentage was higher than those in previous reports[17-20]. This may be because patients with mild disease were excluded due to the absence of blood gas monitoring, while the included patients had relatively severe disease, with multiple comorbid diseases in our study. In addition, patients who were not
monitored for lactate in some previous studies were included in the non-lactic acidosis group, which led to the underestimation of LILA\cite{20}.

The 30-day mortality rate was 48.6% in the lactic acidosis group, which was significantly higher than that in the control group (p < 0.05). In a systematic review and meta-analysis of 47 cases of LILA retrieved from PubMed, 25.5% of the patients died, indicating a high risk of death with LILA\cite{21}.

Previous reports have shown that LILA is associated with a longer duration of medication\cite{15, 16, 22-24}. In a retrospective study, a duration of linezolid therapy > 6 weeks was a risk factor for LILA\cite{19}, but LILA has been reported to occur after a shorter duration of linezolid therapy (4 hours-7 days)\cite{21, 25-28} and to occur even earlier in children, with a median time of 2 (1,13) days\cite{29}. Del Pozo showed that the median duration of the administration of linezolid in lactic acidosis patients was 8 days\cite{20}. We found that a duration of linezolid therapy ≥ 9 days was a risk factor for LILA in the super-elderly population, which suggested that LILA in the super-elderly population could occur after a short course of medication; therefore, the early and routine monitoring of lactate levels and blood gas is necessary.

We found that when the arterial blood glucose level was ≥ 8 mmol/L, the risk of lactic acidosis was increased. A high SOFA score is also a risk factor for LILA, and the risk of lactic acidosis increased 0.429 times for every 1 point increase in the SOFA score, suggesting that super-elderly patients with high blood glucose or sequential organ failure are more prone to lactic acidosis. One study of 10 cases of LILA found that a SOFA score ≥ 11 and duration of linezolid therapy ≥ 7 days were not risk factors for LILA\cite{20}. This was inconsistent with our results, which may be related to the univariate analysis employed in the other study.
Del Pozo also found that an eGFR ≤ 30 mL/min (OR, 7.4; 95% CI, 1.0-84.4, p = 0.02) was a risk factor for LILA; however, we did not find that the eGFR was associated with LILA\(^{[20]}\). This difference may have occurred because 30% of lactate metabolism occurs in the kidney, and only when lactate is above 6–10 mmol/L can it be excreted by the kidney\(^{[1]}\). Therefore, the eGFR may only be associated with severe hyperlactic acidaemia. In our study, the lactate levels were mostly mildly to moderately elevated, so no correlation was found between LILA and the eGFR.

Based on the multivariate logistic regression analyses, we established a risk prediction model with high sensitivity and specificity (91.4% and 65.1%, respectively) for the occurrence of LILA, and the cut-off value was 0.2825. After verifying the model in 32 patients from another medical centre, it showed high stability. Therefore, the risk prediction model can be applied in the super-elderly population.

The mechanism of LILA is unclear. Linezolid inhibits 23 s rRNA from the 50S subunit of the bacterial ribosome, which is similar to human mitochondrial 16S rRNA. Hence, linezolid may produce toxic mitochondrial effects by binding to human mitochondrial 16S rRNA and inhibiting mitochondrial protein synthesis\(^{[24]}\). Human mitochondrial DNA polymorphisms (A2706G and G3010A) have been reported to be associated with LILA\(^{[30, 31]}\), although this finding is controversial due to the high frequency (up to 80%) of these polymorphisms and the relatively rare occurrence of LILA\(^{[32]}\).

To the best of our knowledge, we are the first to analyse the occurrence of LILA in patients older than 85 years with a large sample size. Moreover, we established a risk prediction model to predict the occurrence of LILA. There are some limitations. First, the sample size was relatively small. Second, the incidence of and mortality from LILA may have been overestimated due to the relatively severe illness of the included patients.
Third, linezolid plasma concentrations was not tested. The mechanism underlying LILA remains to be further studied.

Conclusion

This study identified the risk factors for LILA and established a stable risk prediction model. LILA can occur in super-elderly patients after a relatively shorter duration of linezolid, so the close monitoring of blood gas and arterial lactate levels during the use of linezolid is necessary.

Abbreviations

LILA, linezolid-induced lactic acidosis
SOFA, Sequential organ failure assessment
IQR, interquartile range
COPD, Chronic obstructive pulmonary disease;
CK, Creatine kinase
LDH, Lactate dehydrogenase
ALT, Alanine dehydrogenase
AST, Aspartate transaminase
TNI, Troponin I
pro-BNP, Pro-brain natriuretic peptide
eGFR, estimate glomerular filtration rate

Declarations

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Authors’ contributions

LHX and LTT contributed to the study design. WJ contributed to the collection of clinical data. LHX and FXQ contributed to the data analysis. LTT and LM drafted the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

As retrospective analysis of the study, no manual interventions were applied and all indicators were observational. Hence, informed consent was waived, and the study protocol was approved by the ethics committee of Chinese People's Liberation Army (PLA) General Hospital.

Consent for publication

Not applicable.

Competing interests

The authors have no conflicts of interest to declare.

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References

1 Seheult J, Fitzpatrick G, Boran G: Lactic acidosis: an update. Clin Chem Lab Med 2017;55:322-333.

2 Vincent JL, Quintairos E Silva A, Couto L Jr, Taccone FS:
The value of blood lactate kinetics in critically ill patients: a systematic review. Crit Care 2016;20:257.

3 Jansen TC, van Bommel J, Schoonderbeek FJ, Sleeswijk Visser SJ, van der Klooster JM, Lima AP, Willemsen SP, Bakker J; LACTATE study group: Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. Am J Respir Crit Care Med 2010;182:752-761.

4 Nichol AD, Egi M, Pettila V, Bellomo R, French C, Hart G, Davies A, Stachowski E, Reade MC, Bailey M, Cooper DJ: Relative hyperlactatemia and hospital mortality in critically ill patients: a retrospective multi-centre study. Crit Care 2010;14:R25.

5 Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC: The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801–810.

6 Brickner SJ, Barbachyn MR, Hutchinson DK, Manninen PR: Linezolid (ZYVOX), the first member of a completely new class of antibacterial agents for treatment of serious gram-positive infections. J Med Chem 2008;51:1981-1990.

7 Zahedi Bialvaei A, Rahbar M, Yousefi M, Asgharzadeh M, Samadi Kafil H: Linezolid: a promising option in the treatment of Gram-positives. J Antimicrob Chemother 2017;72:354-364.
8 Tang S, Yao L, Hao X, Zhang X, Liu G, Liu X, Wu M, Zen L, Sun H, Liu Y, Gu J, Lin F, Wang X, Zhang Z: Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China. Eur Respir J 2015;45:161-170.

9 Vinh DC, Rubinstein E: Linezolid: a review of safety and tolerability. J Infect 2009;59:S59-74.

10 Kreps EO, Brown L, Rennie IG: Clinical recovery in linezolid-induced optic nerve toxicity. Acta Ophthalmol 2017;95:e341-e342.

11 Narita M, Tsuji BT, Yu VL: Linezolid-associated peripheral and optic neuropathy, lactic acidosis, and serotonin syndrome. Pharmacotherapy 2007;27:1189-1197.

12 Bobylev I, Maru H, Joshi AR, Lehmann HC: Toxicity to sensory neurons and Schwann cells in experimental linezolid-induced peripheral neuropathy. J Antimicrob Chemother 2016;71:685-691.

13 Bressler AM, Zimmer SM, Gilmore JL, Somani J: Peripheral neuropathy associated with prolonged use of linezolid. Lancet Infect Dis 2004;4:528-531.

14 Ferry T, Ponceau B, Simon M, Issartel B, Petiot P, Boibieux A, Biron F, Chidiac C, Peyramond D: Possibly linezolid-induced peripheral and central neurotoxicity: report of four cases. Infection 2005;33:151-154.

15 Hanson BL, Sztern B: Cough and bronchial responsiveness in firefighters at the World Trade Center site. N Engl J Med 2003;348:76-77.

16 Boutoille D, Grossi O, Depatureaux A, Tattevin P: Fatal lactic acidosis after prolonged linezolid exposure for treatment of multidrug-resistant tuberculosis. Eur J Intern Med 2009;20:e134-135.

17 Beekmann SE, Gilbert DN, Polgreen PM: Toxicity of extended courses of linezolid: results of an Infectious Diseases Society of America Emerging Infections Network survey.
Diagn Microbiol Infect Dis 2008;62:407–410.

18 Garrabou G, Soriano A, López S, Guallar JP, Giralt M, Villarroya F, Martínez JA, Casademont Reversible inhibition of mitochondrial protein synthesis during linezolid-related hyperlactatemia. Antimicrob Agents Chemother 2007;51:962-967.

19 Im JH, Baek JH, Kwon HY, Lee JS: Incidence and risk factors of linezolid-induced lactic acidosis. Int J Infect Dis 2015;31:47-52.

20 Mori N, Kamimura Y, Kimura Y, Hirose S, Aoki Y, Bito S: Comparative analysis of lactic acidosis induced by linezolid and vancomycin therapy using cohort control studies of incidence and associated risk factors. Eur J Clin Pharmacol 2018;74:405-411.

21 Mao Y, Dai D, Jin H, Wang Y: The risk factors of linezolid-induced lactic acidosis: A case report and review. Medicine (Baltimore) 2018;97:e12114.

22 De Vriese AS, Coster RV, Smet J, Seneca S, Lovering A, Van Haute LL, Vanopdenbosch Lj, Martin JJ, Groote CC, Vandecasteele S, Boelaert JR: Linezolid-induced inhibition of mitochondrial protein synthesis. Clin Infect Dis 2006;42:1111-1117.

23 Sawyer AJ, Haley HL, Baty SR, McGuffey GE, Eiland EH: Linezolid-induced lactic acidosis corrected with sustained low-efficiency dialysis: a case report. Am J Kidney Dis 2014;64:457-459.

24 Velez JC, Janech MG: A case of lactic acidosis induced by linezolid. Nat Rev Nephrol 2010;6:236-242.

25 Contou D, Fichet J, Grimaldi D, Cariou A: Early life-threatening lactic acidosis following a single infusion of linezolid. Int J Antimicrob Agents 2011;38:84-85.

26 Pea F, Scudeller L, Lugano M, Baccarani U, Pavan F, Tavio M, Furlanut M, Rocca GD, Bresadola F, Viale P: Hyperlactacidemia potentially due to linezolid overexposure in
a liver transplant recipient. Clin Infect Dis 2006;42:434-435.

27 Su E, Crowley K, Carcillo JA, Michaels MG: Linezolid and lactic acidosis: a role for lactate monitoring with long-term linezolid use in children. Pediatr Infect Dis J 2011;30:804-806.

28 Protti A, Ronchi D, Bassi G, Fortunato F, Bordoni A, Rizzuti T, Fumagalli R: Changes in Whole-Body Oxygen Consumption and Skeletal Muscle Mitochondria During Linezolid-Induced Lactic Acidosis. Crit Care Med 2016;44:e579-582.

29 Ozkaya-Parlakay A, Kara A, Celik M, Ozsurekci Y, Karadag Oncel E, Ceyhan M, Cengiz AB: Early lactic acidosis associated with linezolid therapy in paediatric patients. Int J Antimicrob Agents 2014;44:334-336.

30 Del Pozo JL, Fernández-Ros N, Sáez E, Herrero JL, Yuste JR, Banales JM: Linezolid-induced lactic acidosis in two liver transplant patients with the mitochondrial DNA A2706G polymorphism. Antimicrob Agents Chemother 2014;58:4227-4229.

31 Palenzuela L, Hahn NM, Nelson RP Jr, Arno JN, Schobert C, Bethel R, Ostrowski LA, Sharma MR, Datta PP, Agrawal RK, Schwartz JE, Hirano M: Does linezolid cause lactic acidosis by inhibiting mitochondrial proteinsynthesis? Clin Infect Dis 2005;40:e113-116.

32 Santini A, Ronchi D, Garbellini M, Piga D, Protti A: Linezolid-induced lactic acidosis: the thin line between bacterial and mitochondrial ribosomes. Expert Opin Drug Saf 2017;16:833-843.

Tables
Table 1 Patient characteristics and clinical factors
|                                | Teicoplanin (n=199) | Linezolid (n=108) | P      |
|--------------------------------|---------------------|-------------------|--------|
| Male sex, N (%)                | 171 (85.9%)         | 99 (91.7%)        | 0.140* |
| Age, years, median (IQR)       | 94[92,97]           | 94.5[91,97]       | 0.677# |
| Duration of antibiotics, days, median (IQR) | 9[6,13]          | 9[6,12]           | 0.527# |
| Infection site, N (%)          | 144 (72.4%)         | 93 (86.1%)        | 0.006* |
| Pulmonary infection            | 149 (74.9%)         | 85 (78.7%)        | 0.452* |
| Non-pulmonary infection        | 26 (13.1%)          | 12 (11.1%)        | 0.620* |
| Invasive ventilation, N (%)    | 78 (39.2%)          | 34 (31.5%)        | 0.180* |
| Underlying disease             |                     |                   |        |
| COPD, N (%)                    | 119 (60.8%)         | 58 (53.8%)        |        |
| Pulmonary fibrosis, N (%)      | 26 (13.1%)          | 12 (11.1%)        |        |
| Coronary heart disease, N (%)  |                     |                   |        |
| stable                         | 181 (91.0%)         | 87 (80.6%)        |        |
| coronary ischemia              | 18 (9.0%)           | 21 (19.4%)        |        |
| Hypertension, N (%)            | 157 (78.9%)         | 86 (79.6%)        | 0.880* |
| Atrial fibrillation, N (%)     | 120 (60.3%)         | 51 (47.2%)        | 0.028* |
| Diabetes mellitus, N (%)       | 83 (41.7%)          | 52 (48.1%)        | 0.278* |
| Chronic kidney disease, N (%)  | 106 (53.3%)         | 55 (50.9%)        | 0.695* |
| Neurological disease, N (%)    | 32 (16.1%)          | 33 (30.6%)        | 0.003* |
| Malignant tumor, N (%)         | 14 (7.0%)           | 14 (13.0%)        | 0.085* |
| Thyroid hypofunction, N (%)    | 4 (2.0%)            | 6 (5.6%)          | 0.182* |
| Serum creatinine, mg/dl, median (IQR) | 101.0[75.0,143.0] | 120.5[74.5,197.5] | 0.081# |
| SOFA, median (IQR)             | 8[5,11]             | 9[6,13]           | 0.013# |

IQR, interquartile range; COPD, Chronic obstructive pulmonary disease; SOFA, Sequential organ failure assessment

*Chi-square test

#Mann-Whitney U test

Table 2 Patient demographic and clinical characteristics after propensity score matching (nearest neighbor matching)
|                          | Teicoplanin (n = 98) | Linezolid (n = 98) | P     |
|--------------------------|----------------------|--------------------|-------|
| Male sex, N (%)          | 88(89.8%)            | 89(90.8%)          | 0.809*|
| Age, years, median (IQR) | 94[91,96.25]         | 94[91,97]          | 0.739#|
| Duration of linezolid, days, median (IQR) | 8.5[6.75,12.00] | 9[6,11.25] | 0.937#|
| Infection site, N (%)    |                      |                    | 0.400*|
| Pulmonary infection      | 87(88.8%)            | 83(84.7%)          |       |
| Non-pulmonary infection  | 11(11.2%)            | 15(15.3%)          |       |
| Invasive ventilation, N (%) | 38(38.8%)    | 34(34.7%)          | 0.553*|
| Underlying disease       |                      |                    |       |
| COPD, N (%)              | 80(81.6%)            | 78(79.6%)          | 0.718*|
| Pulmonary fibrosis, N (%)| 13(13.3%)            | 11(11.2%)          | 0.663*|
| Coronary heart disease, N (%) |            |                    | 0.817*|
| stable                   | 88(89.8%)            | 87(88.8%)          |       |
| coronary ischemia        | 10(10.2%)            | 11(11.2%)          |       |
| Hypertension, N (%)      | 79(80.6%)            | 78(79.6%)          | 0.858*|
| Atrial fibrillation, N (%)| 53(54.1%)            | 44(44.9%)          | 0.199*|
| Diabetes mellitus, N (%) | 45(45.9%)            | 43(43.9%)          | 0.774*|
| Chronic kidney disease, N (%) | 46(46.9%)    | 49(50.0%)          | 0.668*|
| Neurological disease, N (%) | 30(30.6%)            | 29(29.6%)          | 0.876*|
| Malignant tumor, N (%)   | 11(11.2%)            | 12(12.2%)          | 0.824*|
| Thyroid hypofunction, N (%) | 3(3.1%)              | 5(5.1%)            | 0.718*|
| Serum creatinine, mg/dl, median (IQR) | 124.0[78.0,160.0] | 110.50[72.75,160.0] | 0.257#|
| SOFA, median (IQR)       | 9[6,13]              | 9[6,12]            | 0.233#|
| Lactic acidosis, N (%)   | 0                    | 35(35.7%)          | <0.0001*|

IQR, interquartile range; COPD, Chronic obstructive pulmonary disease; SOFA, Sequential organ failure assessment

*Chi-square test

#Mann-Whitney U test

Table 3 Arterial lactate at baseline and the end-point of patients
|                               | Teicoplanin (n=98) | Linezolid (n =98) | P     |
|-------------------------------|-------------------|-------------------|-------|
| Arterial lactate,(mmol/L)     |                   |                   |       |
| At baseline                   | 1.2 [0.9,1.525]   | 1.2 [0.9,1.4]     | 0.450#|
|                               |                   |                   |       |
| At end-point                  | 1.1[0.9,1.425]    | 2.6 [1.875,3.7]   | <0.0001#|
| P                             | 0.312#            | <0.0001#          |       |
| Lactic acidosis, N (%)        | 0                 | 35(35.7%)         | <0.0001#|

# Mann-Whitney U test

Table 4 Univariate analysis of risk factors of linezolid-induced lactic acidosis

|                               | Lactic acidosis (n= 35) | Non-lactic acidosis (n= 63) | P    |
|-------------------------------|-------------------------|-------------------------------|------|
| Male sex, N (%)               | 32(91.4%)               | 57(90.5%)                     | 1.000*|
| Age, years, median (IQR)      | 94[90,96]               | 94[91,97]                     | 0.471#|
| Duration of linezolid,days,median (IQR) | 10[7,12] | 8[5,11] | 0.053#|
| Infection site,N (%)          |                         |                               | 0.707*|
| Pulmonary infection           | 29(82.9%)               | 54(85.7%)                     |      |
| Non-pulmonary infection       | 6(17.1%)                | 9(14.3%)                      |      |
| Invasive ventilation,N (%)    | 15(42.9%)               | 19(30.2%)                     | 0.206*|
| Underlying disease            |                         |                               |      |
| COPD, N (%)                   | 27(77.1%)               | 51(81.0%)                     | 0.654*|
| Pulmonary fibrosis, N (%)     | 5(14.3%)                | 6(9.5%)                       |      |
| Condition                                      | Stable (N=34)   | Unstable (N=61)    |
|-----------------------------------------------|----------------|-------------------|
| Coronary heart disease, N (%)                 | 24(68.6%)      | 47(74.6%)         |
| Coronary ischemia                             | 5(14.3%)       | 6(9.5%)           |
| Hypertension, N (%)                           | 29(82.9%)      | 49(77.8%)         |
| Atrial fibrillation, N (%)                    | 16(45.7%)      | 28(44.4%)         |
| Diabetes mellitus, N (%)                      | 19(54.3%)      | 24(38.1%)         |
| Chronic kidney disease, N (%)                 | 24(68.6%)      | 31(49.2%)         |
| Neurological disease, N (%)                   | 9(25.7%)       | 22(34.9%)         |
| Malignant tumor, N (%)                        | 5(14.3%)       | 7(11.1%)          |

| Lactate in baseline, mmol/L, median (IQR)     | 1.2[0.9,1.5]   | 1.2[0.9,1.4]      |
| Lactate in end-point, mmol/L, median (IQR)    | 4.6[3.7,5.5]   | 2.1[1.6,2.6]      |
| Serum creatinine, mg/dl, median (IQR)         | 1.5[0.89,2.68] | 1.12[0.79,1.56]   |
| Albumin, g/L, median (IQR)                    | 31.4±5.3973    | 32.3±6.3950       |
| Hemoglobin, g/dl, median (IQR)                | 8.9[8.0,10.1]  | 10.0[8.8,11.8]    |
| CK, U/L, median (IQR)                         | 29.3[21,56]    | 36[19,49.9]       |
| LDH, U/L, median (IQR)                        | 301[188,510]   | 241[172,345]      |
| ALT, U/L, median (IQR)                        | 10[6,23]       | 16[10,30]         |
| AST, U/L, median (IQR)                        | 29[16,81]      | 26[18,41]         |
| TNI, ng/ml, median (IQR)                      | 0.17[0.055,0.304] | 0.044[0.017,0.107] |
| pro-BNP, pg/ml, median (IQR)                  | 4675[2336,9387] | 2205[640.3,5853]  |
| D-dimer, μg/ml, median (IQR)                  | 3.14[1.87,5.11] | 1.71[1.24,3.09]   |
| Arterial blood glucose, mmol/L, median (IQR)  | 8.7[6.5,11.1]  | 6.8[5.6,8.5]      |
| eGFR, ml/min/1.73 m2, median (IQR)            | 32.0[19.0,56.0] | 45.0[32.0,63.0]   |
| SOFA, median (IQR)                            | 10[9,15]       | 6[5,9]            |
| 30-day mortality, N (%)                       | 17(48.6%)      | 18(28.6%)         |

**IQR**, interquartile range; **COPD**, Chronic obstructive pulmonary disease; **CK**, Creatine kinase; **LDH**, Lactate dehydrogenase; **ALT**, Alanine dehydrogenase; **AST**, Aspartate transaminase; **TNI**, Troponin I; **pro-BNP**, Pro-brain natriuretic peptide; **eGFR**, estimate glomerular filtration rate; **SOFA**, Sequential organ failure assessment
Table 5 Multivariate analyses of risk factors for lactic acidosis

| Risk prediction factor                        | OR (95% CI)    | P    |
|-----------------------------------------------|----------------|------|
| Duration of linezolid, ≥9 days                | 3.541 (1.161-10.793) | 0.026 |
| Arterial blood glucose, ≥8mmol/L             | 4.548 (1.507-13.725) | 0.007 |
| SOFA                                          | 1.429 (1.213-1.685) | 0.0001 |

Table 6 Fourfold table of 32 patients older than 85 years verifying the stability of the risk prediction model.

| Risk prediction mode          | Gold Standard | Total |
|-------------------------------|---------------|-------|
|                               | Lactate acidosis | Non-lactate acidosis |
| Lactate acidosis              | 7             | 5     | 12    |
| Non-lactate acidosis          | 0             | 20    | 20    |
| Total                         | 7             | 25    | 32    |

Figures
Figure 1

Lactic acidosis at baseline and the end-point
Figure 2

Kaplan-Meier plot showing 30-day survival rate between lactic acidosis group and non-lactic acidosis group
Diagonal segments are produced by ties.

Figure 3

ROC curve analysis of the risk prediction model
Figure 4 screening of patients using linezolid during the study period