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Optimization of linezolid therapy in the critically ill: the effect of adjusted infusion regimens

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Objectives: Insufficient linezolid levels, which are associated with a poorer outcome, are often observed in ICU patients who receive standard dosing. Although strategies to overcome these insufficient levels have been discussed, appropriate alternative dosing regimens remain to be identified.

Methods: Various infusion regimens (1200–3600 mg/day; q6h, q8h, q12h and continuous) were simulated in 67 000 ICU patients. The probability of attaining pharmacodynamic targets ($T_{>MIC} \geq 85\%$, AUC/MIC ≥ 100, cumulative fraction of response for *Staphylococcus aureus* and *Enterococcus* spp., PTA for an MIC of 0.5–4 mg/L) as well as the avoidance of toxic concentrations and concentrations constantly below the MIC (lack of antibiotic effect) or inside a mutant selection window (resistance development) were evaluated.

Results: Best target attainment according to $T_{>MIC}$ was observed for continuous infusions, followed by q6h, q8h and q12h. A substantially reduced target attainment was observed in patients with acute respiratory distress syndrome (ARDS). In patients without ARDS, 1200 mg/day was insufficient irrespective of the regimen, while a dose of 1400 mg/day administered q6h or by continuous infusions provided an acceptable target attainment (e.g. cumulative fraction of response with regards to $T_{>MIC} \geq 93\%$). Higher rates of potentially toxic trough concentrations (28% versus 12%) and concentrations constantly inside the mutant selection window (15% versus <0.1%) were observed with continuous infusions compared with q6h infusions (1400 mg/day, patients without ARDS).

Conclusions: Irrespective of the regimen, 1200 mg/day linezolid might be insufficient for the treatment of ICU patients. Patients without ARDS might particularly benefit from q6h infusions with increased daily doses (e.g. 1400 mg/day).

Introduction

Adequate concentrations of the antibacterial drug linezolid have been shown to strongly correlate with treatment efficacy in seriously ill patients.[1] In a recent study, we showed that target attainment in such patients was distinctly low when applying a standard dosing regimen of 1200 mg/day.[2,3] Although several strategies for therapeutic adjustment in critically ill patients, including therapeutic drug monitoring (TDM),[4] continuous infusions[5] and increased daily doses,[6] have been discussed, no single proper dosing regimen has been identified. First studies indicated an advantage of continuous over short-time infusions,[5,7,8] but the patient numbers were low and the effect of continuous infusions on several important pharmacokinetic/pharmacodynamic parameters was not evaluated thoroughly. Therefore, it remains unclear whether linezolid therapy in seriously ill patients could be adjusted sufficiently by prospective approaches or whether TDM is indispensable. In the present evaluation, we systemically investigated the effect of continuous infusions, shortened infusion intervals and/or increased doses of linezolid to reach concentration ranges that were expected to reflect (lack of) efficacy, mutant selection and toxicity. The effects of the therapeutic adjustments were simulated in a large heterogeneous group of patients as well as in subgroups stratified by previously identified covariates, such as the presence of acute respiratory distress syndrome (ARDS).

Methods

Data

The population pharmacokinetic model was based on a heterogeneous group of 52 critically ill patients with a clinically suspected or confirmed infection (e.g. septic pneumonia, septic peritonitis) who received linezolid in three ICUs within the Department of Anesthesiology, Hospital of the Ludwig-Maximilians-University of Munich, as described recently[2] (https://clinicaltrials.gov/ct2/show/NCT01793012). Simulations using this pharmacokinetic model were performed using covariate characteristics and their combinations as observed in a similar but larger, independent group of 134 patients (28 with ARDS). For clinical and demographic data on the patients, please refer to the respective publication.[2]

Criteria for adequate antibiotic treatment

The attainment of a sufficient cumulative fraction of response (CFR)[9] for clinically relevant pathogens and the avoidance of concentrations that are either potentially toxic or constantly below the MIC_{90} were defined as primary therapeutic targets. Additionally, the avoidance of concentrations that are constantly inside a mutant selection window (MSW) was defined as a secondary target. As optimum (minimum) targets, we defined that sufficient linezolid concentrations should be attained in ≥90% (≥80%) and that toxicity thresholds should not be exceeded in ≥10% (≥20%) of all patients; we also defined that ≤2% (≤5%) of all patients should have concentrations that are constantly below the MIC and that ≤20% (≤50%) of the patients should have concentrations that are constantly inside the MSW. Minimum targets were considered in case optimum targets could not be reached.

For quantification of sufficient linezolid exposure, the ratio of the AUC to the MIC (AUC/MIC) and the fraction of time over 24 h that the drug concentration exceeded the MIC ($\%T_{>MIC}$) were used. Respective targets were an AUC/MIC of ≥100[1] and a $T_{>MIC}$ of ≥85%.[4] The MIC_{90} was defined as the concentration that inhibits the growth of 90% of clinically relevant pathogens, particularly *Staphylococcus aureus* and *Enterococcus* spp. Based on the ZAAPS programme,[10] an MIC_{90} of 1 mg/L was defined. CFR values for *Enterococcus* spp. and *S. aureus* were calculated using MIC distributions from the ZAAPS programme[10] ($CFR_{AUC/MIC}$ and $CFR_{T>MIC}$). As CFR calculations are based on MIC distributions, they do not represent pathogens with less frequently observed MIC values appropriately. Therefore, PTA[9] values were calculated for a typical range of MIC values (0.5–4 mg/L) and evaluations were extended to elevated MICs of 2–4 mg/L, which might be linked to a decreased target attainment. Toxicity was assessed in terms of trough values (C_{min}), which should not exceed 10 mg/L,[4] and the AUC, which should not exceed 400 mg·h/L.[4,11,12]

We calculated the fractions of patients that had concentrations constantly below the MIC, who are likely prone to therapy failure, or are constantly inside the MSW, which might promote the selection of resistant mutant clones.[13] Both evaluations might be of special importance in continuous infusions because of the lack of peak concentrations. For these calculations, we defined an MSW from 1 mg/L to the mutant prevention concentration (MPC) of 4 mg/L. The MSW definition was based on a study that showed that the MSW ranged from the MIC to four times the MIC for different relevant strains.[14] For the MSW, the following additional pharmacodynamic parameters were defined: the mean fraction of time that the concentration stayed inside the MSW ($\%T_{MSW}$) or exceeded the MPC ($\%T_{>MPC}$). All of the calculations were performed for treatment day 4, at which the steady-state is approximated in most patients.

Population pharmacokinetic model

The simulations were based on a recently published population pharmacokinetic two-compartment model of linezolid in critically ill patients.[2] The covariates were patient weight and the presence/absence of peritonitis on the central volume of distribution as well as the presence/absence of ARDS, fibrinogen and lactate levels on the elimination clearance. For more information on the model, please refer to aforementioned publication.

Simulations

Monte Carlo simulations were conducted to evaluate the influence of dosing regimen alterations on the criteria for adequate antibiotic treatment. To reflect appropriately the variability of the population pharmacokinetic model, the inter-individual variability terms for each patient were sampled 500-fold, giving 67000 virtual patients in total. Resulting pharmacokinetic parameters were verified to reflect appropriately the expected distributions. To prevent parameters sampled from the outer tails of the distributions (i.e. pharmacokinetic parameters that are unlikely to be observed) from driving the results of the study, their influence on target attainment rates was evaluated. No restriction on the range of parameters was imposed if their influence was negligible (change in respective target attainment rates <0.5%). Adjusted dosing regimens with doses from 1200 (standard dose) to 3600 mg/day in steps of 200 mg with short-time infusions (infusion rate of 20 mg/min linezolid with a minimum duration of 30 min) every 6, 8 or 12 h (q6h, q8h and q12h) as well as continuous infusions were simulated in each patient. Individual AUC/MIC and $\%T_{>MIC}$ values were calculated. All pharmacokinetic/pharmacodynamic parameters were calculated both for the whole patient group and for different subgroups stratified by previously identified covariates.[2]

Results

Simulated patients

Summary statistics of pharmacokinetic parameters used in the simulations are presented in Table S1 (available as Supplementary data at *JAC* Online). The influence of parameters sampled from the outer tails of respective distributions on target attainment rates was negligible; therefore, no restrictions on parameter ranges were imposed.

Evaluation of the whole patient group

Target attainment based on $CFR_{AUC/MIC}$

The attained AUC values in the whole population largely varied with increasing variability for higher doses of linezolid (Figure S1). In accordance with the dose–linear pharmacokinetics of linezolid, only marginal (≤1%) differences in the AUC values between different infusion regimens (q6h, q8h, q12h or continuous infusions) were observed. The AUC values depended only on the administered dose. Given a standard dose (1200 mg/day), only 75% (69%) of the patients reached the target $CFR_{AUC/MIC}$ for *S. aureus* (*Enterococcus* spp.) and 1800 (2200) mg/day would have been needed to increase the $CFR_{AUC/MIC}$ to at least 90% (optimum target) (Figures 1 and 2).

Target attainment based on $CFR_{T>MIC}$

The $CFR_{T>MIC}$ clearly differed between q6h, q8h, q12h and continuous infusions (Figure 1). With q12h infusions, the optimum target for $CFR_{T>MIC}$ could not be reached with any dose up to 3600 mg/day. High doses of at least 2200 (2400) mg/day would have been needed with q8h infusions for *S. aureus* (*Enterococcus* spp.) while only slightly increased doses of 1400 (1600) mg/day would have been needed to reach the target with q6h infusions. Switching to continuous infusions had the most distinct effect on

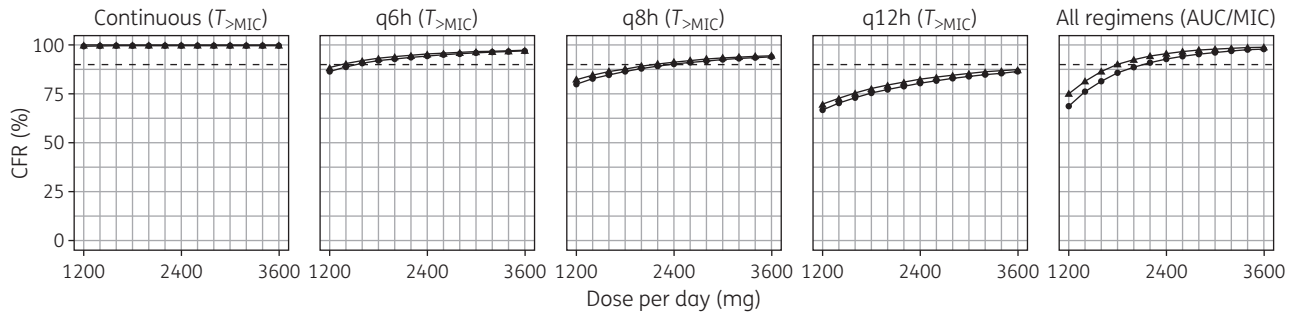

Figure 1. CFRs based on $T_{>MIC}$ and AUC/MIC in different infusion regimens and doses of linezolid for the whole patient group. CFRs for different pathogens (triangles, *S. aureus*; circles, *Enterococcus* spp.), four dosing regimens and linezolid doses from 1200 to 3600 mg/day based on $T_{>MIC}$ and AUC/MIC. CFRs with regards to AUC/MIC are only shown once because AUC is independent of regimens. Broken line indicates the optimum target of 90%.

target attainment; a continuous infusion of 1200 mg/day was sufficient to attain the optimum $CFR_{T>MIC}$ target (Figures 1 and 2).

Toxicity thresholds

A potentially toxic AUC (>400 mg·h/L) was reached in >10% of the patients with a daily dose of ≥1800 mg in all infusion regimens (Figure S1). Clear differences in the number of patients exceeding the trough level toxicity threshold could be observed among different infusion intervals (Table 1). The maximum daily doses at which the C_{min} toxicity threshold was not exceeded in ≥10% of the simulated patients were 1800 mg/day in q12h, 1400 mg/day in q8h, 1200 mg/day in q6h and <1200 mg/day in continuous infusions.

Concentrations constantly below the MIC or inside the MSW

In the whole patient group and for all investigated dosing regimens, <0.5% of the patients had linezolid concentrations that were constantly below the MIC_{90} of 1 mg/L. In q6h, q8h and q12h infusions, nearly no patient (<0.1%) had concentrations that were constantly inside the defined MSW of 1–4 mg/L. For mean times within the MSW, see Table S2. A larger fraction of patients, e.g. 30% at a daily dose of 1200 mg, had concentrations constantly inside the MSW when administering continuous infusions.

Target attainment at elevated MIC values

When assuming an MIC of 2 or 4 mg/L, no increase in dose of up to 3600 mg/day was sufficient to attain an optimal $PTA_{AUC/MIC}$ of ≥90% (Figure 3) in the whole patient group. Even the minimum target $PTA_{AUC/MIC}$ could not be reached given an MIC of 4 mg/L while a dose of 3200 mg/day would have been sufficient for 2 mg/L. Continuous infusions were capable of attaining an optimal $PTA_{T>MIC}$ at doses of 1200 mg/day (MIC 2 mg/L) or 2000 mg/day (MIC 4 mg/L), but they were linked to a relevant fraction of the whole patient group having linezolid concentrations constantly below the MIC (5% for 1200 mg/day and an MIC of 2 mg/L; 9% for 2000 mg/day and an MIC of 4 mg/L) (Figure S2). Given that toxicity parameters must be expected to be exceeded in a relevant fraction of patients when increasing the dose such that an acceptable $PTA_{AUC/MIC}$ is attained, no proper dosing regimen for elevated MICs of 2–4 mg/L could be identified.

Evaluation of patient subgroups

The optimum targets for $CFR_{T>MIC}$, $CFR_{AUC/MIC}$ and toxicity parameters (potentially toxic trough concentrations and AUCs) could not be reached simultaneously in any investigated infusion regimen for any subgroup. Because differences were highest for the subgroups of patients with/without ARDS, these two patient groups were evaluated separately.

Patients with ARDS

In patients with ARDS, substantially lower concentrations were reached for each infusion regimen. In these patients, only continuous infusions of standard doses and q6h infusions of highly increased doses (≥3200 mg/day for *S. aureus*, ≥3600 mg/day for *Enterococcus* spp.) attained the optimum $CFR_{T>MIC}$ target (Figure 2). To reach at least the minimum $CFR_{AUC/MIC}$ target with continuous infusions, a daily dose of ≥2200 (2400) mg would have been needed for *S. aureus* (*Enterococcus* spp.), which was linked to toxic trough concentrations in 22% (26%) of the patients with ARDS. Therefore, no appropriate continuous infusion regimen could be identified. In contrast, administering 2400 mg/day by q6h infusions raised the $CFR_{T>MIC}$ and $CFR_{AUC/MIC}$ for both pathogens at least to the minimum target while toxicity and MSW parameters were in the optimum range (toxic trough concentrations in 7%, toxic AUC in 6%, concentration inside MSW in <0.1%).

Patients without ARDS

In the subgroup of patients without ARDS, the pharmacodynamic target attainment rates were much higher than in patients with ARDS (Figure 2). While no dosing regimen was capable of attaining all of the defined optimum targets simultaneously, q6h and continuous infusions showed clear improvements in target attainment compared with the standard regimen. A $CFR_{T>MIC}$ of 100% was reached with continuous infusions of the standard dose, but further increases in daily doses to ≥1400 mg/day would have been needed to attain at least the minimum $CFR_{AUC/MIC}$ target. As such daily doses were linked to toxic concentrations in 28% of the patients, no appropriate continuous infusion regimen could be identified. In contrast, administering 1400 mg/day by q6h infusions raised the $CFR_{T>MIC}$ to >90% (optimum target) and the $CFR_{AUC/MIC}$ to >80% (minimum target) while toxicity parameters were still acceptable (toxic AUC in 7%, toxic trough concentrations in 12%).

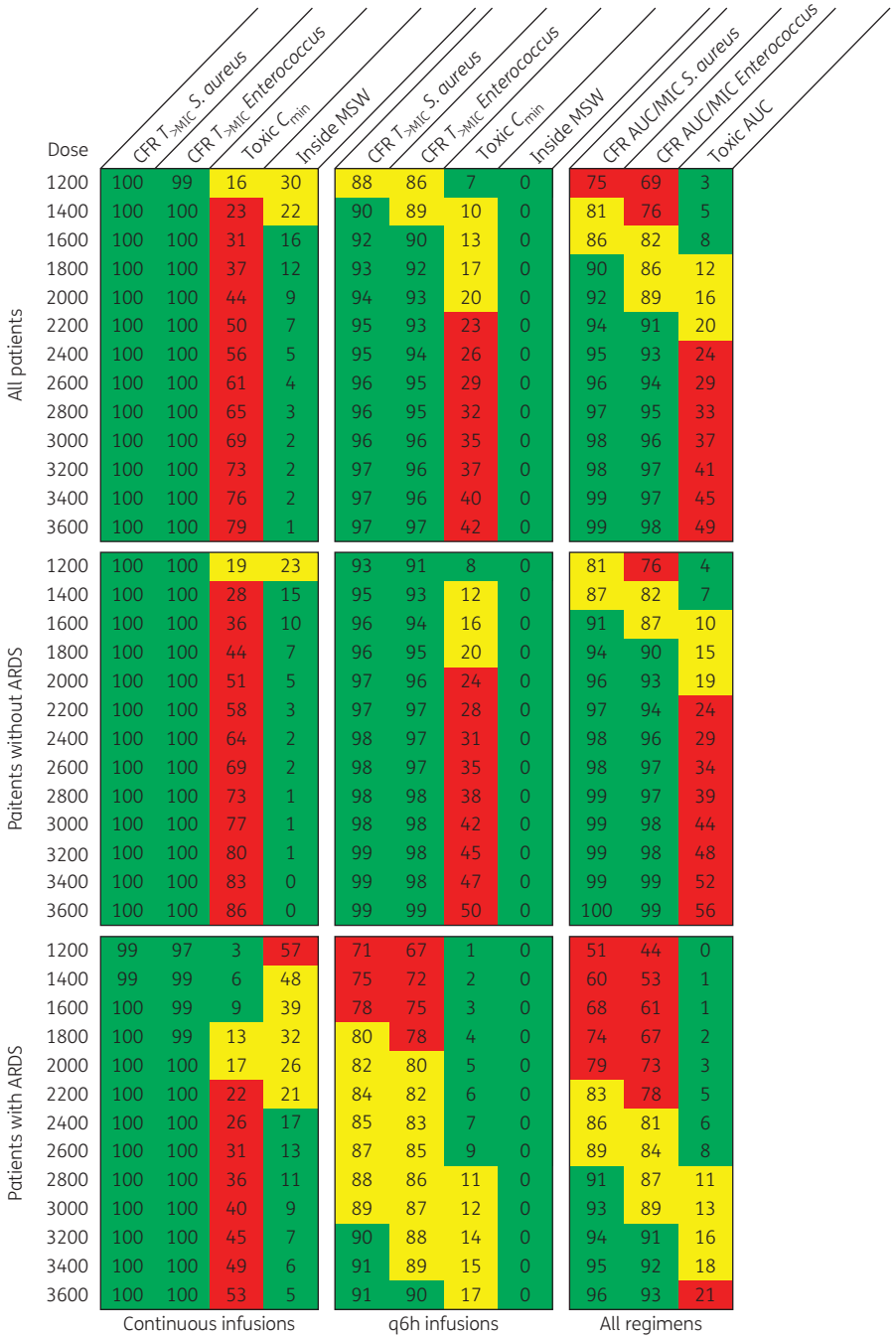

Figure 2. Pharmacokinetic/pharmacodynamic target attainment (%) for continuous and q6h infusions of different doses in the whole patient group as well as stratified by the presence of ARDS. CFRs ($CFR_{T>MIC}$ and $CFR_{AUC/MIC}$) for *S. aureus* and *Enterococcus* spp., the percentage of patients exceeding the toxic trough value (C_{min} ≥10 mg/L) or AUC (≥400 mg·h/L) threshold and the percentage of patients with concentrations constantly inside the MSW (1–4 mg/L). Results are stratified by the infusion regimen (continuous and q6h infusions) and the presence of ARDS (top to bottom). Parameters that depend on AUCs are only shown once (all regimens) because they do not differ between q6h and continuous infusions. Green/yellow boxes indicate reaching the optimum/minimum target. Red boxes indicate missing both targets. Percentage of concentrations constantly below the MIC_{90} is not shown because it was ≤1% for all dosing regimens. For PTAs and concentrations constantly below certain MICs, see Figure S2.

Discussion

In this study, we demonstrated that continuous and q6h infusions show distinct advantages over standard q12h short-time infusions with respect to attaining a proper $T_{>MIC}$ in the investigated collective of critically ill patients. When considering all of the target parameters, higher doses of linezolid were needed in most regimens.

Continuous infusions provided the highest target attainment rates with regards to $T_{>MIC}$, but were linked to some potential drawbacks, such as concentrations that are potentially toxic or constantly inside the MSW. In q6h infusions, these drawbacks could be avoided at the cost of slightly decreased target attainments compared with continuous infusions

Increased doses administered by standard q12h infusions were shown to be inappropriate because very large doses would be needed to attain appropriate $T_{>MIC}$ values, putting patients at a high risk of toxic side-effects. To date, mainly continuous infusions of antibiotics have been evaluated as alternatives to intermittent dosing. Although some trials suggest reduced therapeutic failure rates and mortality for continuous infusions,[15] the overall results are inconclusive.[16] Specifically for linezolid, only very limited data on the effect of continuous infusions are available; in a small trial with critically ill patients, the observed $T_{>MIC}$ was higher, whereas the mean AUC/MIC did not change substantially,[5] which is in line with our results. In a study involving 12 patients with ventilator-associated pneumonia, continuous infusions led to a $T_{>MIC}$ of 100%, but no information on the clinical effect of this finding was provided.[8] Finally, the superiority of continuous over intermittent infusions of linezolid has been reported based on an animal endocarditis model with MRSA.[7] A major drawback of these studies is that neither the effect of increased doses nor of other regimens, such as q6h and q8h, has been evaluated. To the best of our knowledge, only single case reports with increased linezolid doses are described in the literature.[6] Additionally, previous studies did not investigate the effects on resistance emergence thoroughly. Recent data from the USA and global surveillance studies have shown that resistance to linezolid is still a rare event (only 1% of *S. aureus* and only 2% of CoNS are linezolid resistant), but multifocal outbreaks of linezolid-resistant staphylococci have been observed, and both vertical and horizontal transmission of linezolid resistance determinants could occur.[17] Although current knowledge on the mechanisms of resistance development against linezolid is scarce, *in vitro* data suggest that concentrations constantly near the MIC[18] or inside the MSW[19,20] increase the risk of resistance development. We observed such cases solely for continuous infusions, which indicates that the general treatment of linezolid by continuous infusion might aggravate the resistance problem and generate significant challenges to the clinical treatment and hygiene management. A further, clear limitation of continuous infusions is that the simultaneous attainment of AUC/MIC and toxicity target parameters was not feasible in our evaluation. Although $T_{>MIC}$ target parameters for lower doses of continuously infused linezolid were exceptionally high, AUC/MIC target attainment remained to be low and increased doses were consistently linked to potentially toxic concentrations. Therefore, when considering all target parameters, q6h infusions seem to be the better choice in general.

For the whole patient group and in cases in which the presence of ARDS cannot be excluded, administering q6h infusions of 1600 mg/day appears to provide the best balance between all target parameters. For patients without ARDS, q6h infusions with a dose of 1400 mg/day could be a good choice based on our evaluation. With this regimen, the attained $CFR_{T>MIC}$ and the probability of toxic AUC values were optimal while at least the minimum targets for $CFR_{AUC/MIC}$ and toxic trough values could be reached. In patients with ARDS, administering q6h infusions of at least 2400 mg/day led to the attainment of all minimum targets and might therefore be an option.

Special care should be taken with pathogens that have an MIC of 2–4 mg/L. These pathogens are commonly reported to be susceptible (e.g. according to EUCAST), but the PTA is reduced substantially. In such cases, particularly continuous infusions probably come at a high risk of therapeutic failure and facilitated resistance development as a relevant fraction of critically ill patients must be expected to attain linezolid concentrations constantly below the MIC or inside the MSW. Additionally, this emphasizes that reporting actual MIC values to clinicians might be useful when linezolid treatment is an option. More studies should verify whether the results of our study could be transferred to critically ill patients in general.

Table 1. Excess of toxic trough concentration for different dosing regimens in the whole patient group; percentage of patients exceeding a toxic trough concentration (C_{min} ≥10 mg/L) for five exemplary daily doses (1200–3600 mg/day) and four dosing regimens (q12h, q8h, q6h and continuous)

	1200 mg	1800 mg	2400 mg	3000 mg	3600 mg
q12h	4%	9%	15%	21%	26%
q8h	5%	13%	22%	29%	36%
q6h	7%	17%	26%	35%	43%
Continuous	16%	37%	56%	69%	79%

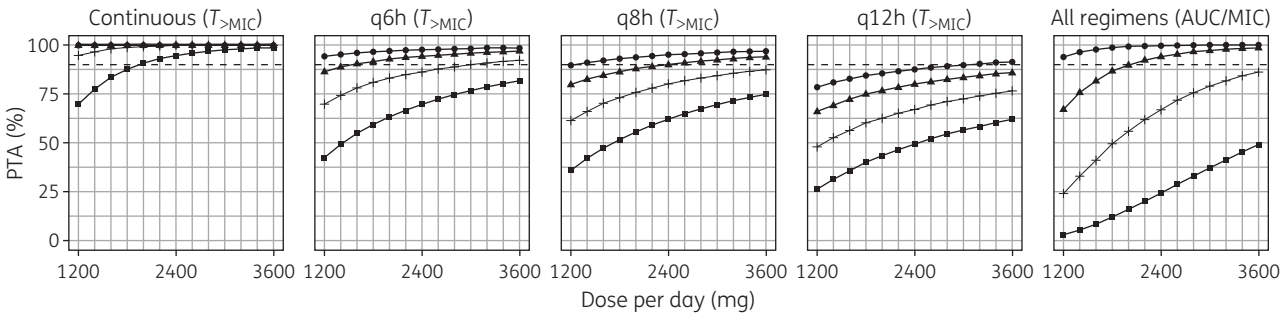

Figure 3. PTAs based on $T_{>MIC}$ and AUC/MIC in different infusion regimens and doses of linezolid for the whole patient group. PTAs for different MIC values (circles, 0.5 mg/L; triangles, 1 mg/L; plus symbols, 2 mg/L; squares, 4 mg/L), four dosing regimens and linezolid doses of 1200–3600 mg/day based on $T_{>MIC}$ and AUC/MIC. PTAs with regards to AUC/MIC are only shown once because AUC is independent of regimens. Broken line indicates the optimum target of 90%.

The fact that no subgroup attained all of the predefined optimum targets simultaneously (CFR ≥90%, probability of potentially toxic trough concentrations ≤10% and probability of concentrations constantly below the MIC ≤2%) supports the conclusions of previous studies that TDM of linezolid might be useful for critically ill patients in general. However, TDM is not available in most situations, the best procedure for TDM of linezolid is still unclear and it seems unlikely that proper TDM schemes for linezolid in critically ill patients will become available in the near future, which highlights the need for improved dosing regimens.

A major obstacle in defining an appropriate dosing regimen for linezolid is the uncertainty of which pharmacodynamic parameter is able to predict best clinical outcomes. While *in vivo* data from animal studies suggest the $T_{>MIC}$ as the main marker of appropriate exposure, studies in humans frequently refer to both the AUC/MIC and the $T_{>MIC}$.[1,21] When only the AUC/MIC would be of interest, adjustments of infusion intervals without adjusting the daily dose would have no influence on target attainment. However, when assuming that both the $T_{>MIC}$ and AUC/MIC are important target parameters, short-time infusions with short infusion intervals (specifically q6h) and slightly increased doses might be favourable. Another difficulty in finding appropriate regimens is caused by the large inter-individual variability and the incapability of the underlying model to reflect all groups of critically ill patients. The term 'critically ill' encompasses patients suffering from a large, heterogeneous group of diseases, which probably prevents the definition of therapy regimens that are best for all patients. Separate investigation of subgroups, such as patients with ARDS, is therefore urgently needed to prevent inappropriate therapy adjustments in special patient groups if no TDM is available. Finally, toxicity thresholds were based on studies with standard infusions.[4,12] The applicability of these thresholds might therefore be questionable when using vastly differing regimens.

Therapeutic adjustments for linezolid in critically ill patients are urgently needed, but the identification of an optimal regimen remains difficult due to the heterogeneity of this patient group. TDM of linezolid would be optimal for all patient subgroups to ensure proper linezolid concentrations in every patient. Standard short-time infusions administered every 12 h are suboptimal and might be replaced by higher doses, such as 1400 mg/day, administered by q6h infusions for critically ill patients without ARDS. Continuous infusions provide best target attainment rates with regards to $T_{>MIC}$, but their use should be evaluated very carefully due to a presumably high risk of toxicity and mutant selection in critically ill patients. Clinicians should be aware that the probability of pharmacodynamic target attainment could be vastly reduced for susceptible pathogens if the MIC is 2–4 mg/L. The effect of the proposed dosing regimens on both the therapeutic outcome and resistance development remains to be evaluated.

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Transparency declarations

None to declare.

Supplementary data

Tables S1 and S2 and Figures S1 and S2 are available as Supplementary data at *JAC* Online.

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