**Hospital Pharmacometrics for Optimal Individual Administration of Antimicrobial Agents for Anti-methicillin-resistant *Staphylococcus aureus* Infected Patients**

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Therapeutic drug monitoring and target concentration intervention based on population pharmacokinetic and pharmacodynamic models has been strongly recommended for anti-methicillin-resistant *Staphylococcus aureus* (MRSA) agents in order to provide appropriate antimicrobial chemotherapy to each individual patient, and pharmacokinetic and pharmacodynamic analyses in hospitalized patients have been actively conducted, as evidenced with vancomycin. Teicoplanin, daptomycin, and linezolid have been the most studied antibiotics, using population pharmacokinetics of patients with MRSA. Infections caused by MRSA have higher severity and fatality rates than other antimicrobial-susceptible infections. Therefore, many medical facilities have been implementing infection control programs based on antimicrobial stewardship to prevent nosocomial infections and drug-resistant strains. Studies detailing pharmacometrics for these antibiotics have been reported to elucidate the pharmacokinetic and pharmacodynamic properties, to determine significant factors influencing variabilities between individuals, and to develop target concentration interventions and dosing regimens for adults, the elderly, patients with renal insufficiency including those on continuous renal replacement therapies, patients with low body weight, obese patients, and pediatric patients. This review presents the details of our recent research on the optimal dosing design of antimicrobial agents for the treatment of MRSA infection based on hospital pharmacometrics. In addition, the prospect of using modeling and simulation has shown major advantages in supporting dosing regimen selection.

**Key words** therapeutic drug monitoring; target concentration intervention; pharmacometrics; hospital pharmacometrics; methicillin resistant *Staphylococcus aureus*

1. INTRODUCTION

Pharmacokinetics (PK) is essential for predicting drug efficacy and side effects by quantifying the time course of drug concentrations. The field developed methods link PK to steady-state pharmacologic responses (PD). The various methods for PKPD model development have been discussed for decades. The collection of all essential data by frequent blood sampling is ethically difficult, and thus, a population PK approach has been used for PK modeling in clinical studies. The population PK approach enables the development of a PK model, even if the available observations in each patient are limited. However, a large-scale population and the availability of complete data are necessary to build a model with high predictability and robustness. Modeling in special populations, such as patients with orphan diseases or pediatric patients, is often difficult. To overcome some problems for PKPD model building based on actual patient medication in clinical practice, the pharmacometrics approach has been applied to clinical PKPD analysis in patients. Holford and Karlsson described pharmacometrics as the “concept of integrating multiple time courses–physiology, disease, drug intake, absorption, disposition, and action– and thus characterizing (patho) physiological and pharmacological systems.” The number of studies focusing on pharmacometrics has increased, and the first academic conference to discuss pharmacometrics research (called the American Conference of Pharmacometrics; ACoP) was instigated in 2008.

Severe infections caused by antimicrobial-resistant strains have higher morbidity and fatality rates than other drug-susceptible infections. Therefore, many medical facilities have been implementing infection control programs based on antimicrobial stewardship to prevent nosocomial infections and drug-resistant strains. In addition, infection with highly antimicrobial-resistant pathogens may lead to excessive administration of antimicrobial agents. Methicillin-resistant *Staphylococcus aureus* (MRSA) causes severe infections, has a high mortality rate, and leads to prolonged hospitalization; therefore, the control and treatment of this infection is one of the most major problems for medical workers. Nosocomial infections and community-acquired MRSA infections are growing public health concerns. Six antimicrobial agents have been clinically approved for the treatment of MRSA in Japan as of December 2020. These include glycopeptide vancomycin (VCM), teicoplanin (TEIC), aminoglycoside arbekacin (ABK), oxazolidinones linezolid (LZD), tedizolid (Tzd), and the cyclic lipopeptide, daptomycin (DAP). The measurement of drug concentration in the blood is a routine practice for monitoring VCM, TEIC, and ABK. However, this is generally not performed with other anti-MRSA agents.

The therapeutic window used for therapeutic drug monitoring (TDM) refers to the “range” of doses that can achieve sufficient efficacy while avoiding the occurrence of toxic effects. Target concentration intervention (TCI) incorporates...
the concept of PKPD to determine a “single target” dose for each individual patient rather than a “range.”\textsuperscript{10,11} The population PKPD analysis uses a nonlinear mixed effect model that evaluates the average in the population (fixed effect) and inter- or intra-variability (random effects) for each PKPD parameter. In this paper, the author reviews the recent research on the optimal dosing design of antimicrobial agents for the treatment of MRSA infection based on hospital pharmacometrics. The study was conducted in accordance with the principles of the Declaration of Helsinki and its amendments, and the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan.\textsuperscript{12} The Ethics Committee of the School of Pharmacy of Nihon University (and the author’s former affiliation) approved the study protocol.

2. NOVEL CLINICAL INDEX FOR PHARMACOKINETICS OF VANCOMYCIN

VCM is a glycopeptide antimicrobial agent, and this drug is the most frequently used for the treatment of MRSA. In clinical practice, the area under the concentration–curve ($AUC$) is evaluated as vancomycin exposure, and the minimum (trough) concentration ($C_{min}$) of VCM is measured to predict the $AUC$.\textsuperscript{13} A 24 h $AUC$ ($AUC_{24}$)/minimum inhibitory concentration (MIC) ratio of $\geq 400$ is recommended as the target exposure of VCM according to an American consensus review because the clinical benefits of VCM are increased when the exposure achieves this target value.\textsuperscript{13,14} However, adequate efficacy of VCM treatment is not always obtained even when the $AUC_{24}$/MIC ratio is maintained $\geq 400$.\textsuperscript{13,14} We defined novel PK parameters for predicting the exposure and efficacy of VCM, and evaluated and compared the usefulness of these parameters.\textsuperscript{15}

Two novel PK parameters were defined by dividing the $AUC$ into the area above and under $C_{min}$, and these parameters were named AATL and AUTL (Fig. 1). The analysis was conducted on 81 hospitalized patients treated with VCM. The individual PK parameters for each patient were estimated by an empirical Bayesian method using published population PK parameters.\textsuperscript{16} The $AUC_{24}$ value for each patient was calculated by dividing the dose of VCM by the estimated individual clearance (CL). AUTL was calculated as the product of $C_{min}$ and 24 h, and then AATL was obtained by subtracting AUTL from $AUC_{24}$. The results of logistic regression analysis showed that AUTL was a significantly better predictor of the efficacy of VCM than $AUC_{24}$ and AATL. The cutoff value of AUTL was 331 mg·h/L, and this value can be converted to a $C_{min}$ of

![Diagram showing Vancomycin Concentration–Time Curve Model for the Estimation of AATL and AULT for Pharmacokinetic Parameters](image)

**Fig. 1.** Vancomycin Concentration–Time Curve Model for the Estimation of AATL and AULT for Pharmacokinetic Parameters

$AUC$, area under the time–concentration curve; AATL, area above the trough level; AUTL, area under the trough level. Takeuchi et al. reported that $AUC$ is more significantly associated with AATL for cyclosporine, and $AUC$ is more significantly associated with AUTL for Tacrolimus.\textsuperscript{9}

**Biography**

Dr. Yasuhiro Tsuji was born in Nagasaki in 1973. After graduating from the School of Pharmacy at Nihon University in 1997, he worked as a hospital-pharmacist at the Sasebo Chuo Hospital. Subsequently, he transferred to the Graduate School of Medicine and Pharmaceutical Sciences for Research, University of Toyama as Associate Professor in 2012. Dr. Tsuji studied clinical pharmacometrics under the guidance of Professor Nick Holford at the University of Auckland, New Zealand, for one year from 2015. Dr. Tsuji currently works as a Professor at the School of Pharmacy at Nihon University. He is a certified senior pharmacist and senior pharmacotherapy specialist of the Japanese Society of Pharmaceutical Health Care and Sciences (JSPHCS), and a certified infection control doctor at the Japanese College of Infection Control Doctors. Dr. Tsuji obtained his Ph.D. degree in Pharmaceutical Sciences from Fukuoka University in 2008. He was awarded the JSPHCS Award for Young Scientists in 2011 and the Sato Memorial Domestic Award in 2020. His research focus involves target concentration intervention for dose individualization based on patient features and responses to treatment. He is particularly interested in the application of artificial intelligence. His research interests also include the application of artificial intelligence to dose individualization design.
13.8 mg/L. TCI, using AUTL (which is a novel PK parameter), will contribute to providing effective VCM treatment in patients infected with MRSA.

Although the dosage regimen for VCM based on PK parameters has been provided, there are still large, unexplained PK variabilities even in patients who had similar parameters, including age, sex, renal function (RF), and total body weight (TBW).17) VCM is mainly excreted via the renal route; hence, VCM concentrations tend to be higher in patients with renal dysfunction.18,19) Nevertheless, there were some patients in whom VCM concentration did not increase, although they were receiving high-dose VCM. This indicates that the PK of VCM varies among patients due to unidentified factors.20)

VCM has six dissociation constants (pKₐ) (Fig. 2), which are associated with different functional groups: pKₐ 1 = 2.9 (carboxyl group); pKₐ 2 = 7.2, pKₐ 3 = 8.6 (amino groups), pKₐ 4 = 9.6, pKₐ 5 = 10.5, and pKₐ 6 = 11.7 (phenolic groups). We investigated the factors that increase the clearance of VCM in 48 MRSA infectious patients treated with VCM.20) Urinary pH (p = 0.029) was identified by multivariate analysis as an independent factor associated with a decrease in VCM concentration. There were no significant differences in estimated PK parameters among the different pH groups, indicating that the statistical background of patients used for the estimates (i.e., Ccr and TBW) could be considered equivalent in all pH groups (Table 1). Nevertheless, VCM concentrations in patients with a urine pH of 8 were lower (p = 0.028) than those in patients with urinary pH of 5. As the urinary excretion rate of VCM increases with increasing urine alkalinity, leading to a lower blood concentration of VCM than predicted. This finding suggests that urinary pH influences the disposition kinetics of VCM by affecting the ratio of ionized to unionized forms of the major functional groups of VCM. For the treatment of MRSA infections in patients, the rapid establishment of a serum VCM concentration within the effective therapeutic range is a major factor influencing treatment outcome. Thus, urinary pH should be considered as a factor associated with VCM elimination when determining individual dosing of VCM in the clinical setting.

3. POPULATION PHARMACOKINETICS AND PHARMACODYNAMICS OF TEICOPLANIN

The clinical efficacy of TEIC is associated with AUC₂₄/MIC, and thus maintenance Cₘ₉₅ of 15–30 mg/L has been recommended as the therapeutic window.21–23) A previous study suggested...
a target TDM for TEIC at an AUC_{24}/MIC ratio of ≥ 900.21) TEIC has a long elimination half-life (>30h), and it takes a long time to reach steady-state.24–27 Therefore, a loading dose is recommended to achieve the target concentration promptly in the initial administration.28–31 but it has been reported that the standard loading dose (i.e., 400mg of TEIC twice a day) is insufficient.28,32 We simulated the probability of achieving the target concentration range at steady-state using a Monte Carlo simulation to investigate the optimal loading and maintenance dose.30) The result of the simulation suggested that a 1200mg/d loading dose and 600mg mg maintenance dose might be necessary to maintain >15mg/L of C_{min} (at a probability of >80%). In patients with severe infection, a loading dose of 1600mg/d and a maintenance dose of 800mg might be necessary to maintain >20mg/L of C_{min} (at a probability of 80%).

Accurate estimation of the glomerular filtration rate (GFR) is important for evaluating the pharmacokinetics of drugs that are mainly excreted by the kidneys, such as TEIC and VCM. In clinical practice, creatinine clearance (CLcr), estimated using the Cockcroft–Gault equation, is frequently used as the estimated GFR value because of its simplicity.33) Cystatin C (Cys-C) is a low molecular mass protein. Several studies using serum Cys-C levels to estimate the GFR have been reported recently.34–39)

We conducted a population PK analysis of TEIC to evaluate the usefulness of Cys-C as a predictor of renal clearance in 36 patients who were treated with TEIC.40) A preliminary PK analysis was conducted to estimate the parameters of the basic model without any covariates. Cys-C and TBW were then included in the CL of the basic model (Table 2). The model incorporating Cys-C and TBW into the CL showed the best predictability, and Cys-C was a better predictor of renal clearance than CLcr35) or other six eGFR equations.34–39) The final PK model parameters are shown in Eq. 1.

\[
\begin{align*}
\text{CL} \ (L/h) &= 0.510 \times \left( \frac{\text{Cys-C}}{1.4} \right)^{-0.68} \times \left( \frac{\text{TBW}}{60} \right)^{0.81} \\
\text{VC} \ (L) &= 78.1
\end{align*}
\]

These results indicate the benefit of Cys-C for accurately predicting the pharmacokinetics of drugs that are primarily excreted by the kidneys. Estimating GFR using Cys-C will help clinicians understand the management of TEIC dosing in patients with MRSA.

C-Reactive protein (CRP) concentrations in serum are usually monitored when clinicians assess the clinical efficacy in the treatment of infectious diseases.41,42) We evaluated variations in CRP concentrations in patients receiving TEIC treatment using population PKPD approaches.33) The number of the patients was 181, and 710 observations of serum CRP concentration from these patients were used for the population PD model building. The median (95% observation interval) of baseline CRP concentrations was 8.60mg/dL (0.44–26.85mg/dL). The time-series variations in CRP concentrations were explained by the basic turnover model, and the effect of TEIC was assumed to indirectly inhibit CRP production by exhibiting antibacterial activities in the infected tissues (Eq. 2, Fig. 3).

\[
\text{OFV} = \text{OFV}_{\text{Basic model}} + \text{OFV}_{\text{Cys-C on CL}} = \text{OFV}_{\text{Basic model}} + \text{OFV}_{\text{Cys-C on CL}}
\]

**Table 2. Summary of Covariate Model Building of Teicoplanin with Forward Addition**

| Model | OFV |
|-------|-----|
| Basic model | 707.16 |
| Basic model + Cys-C on CL | 702.80 |
| Basic model + TBW on CL | 697.70 |
| Basic model + eGFR Filler on CL | 692.66 |
| Basic model + eGFR Hoek on CL | 692.84 |
| Basic model + eGFR Larsson on CL | 697.70 |
| Basic model + eGFR Grubb on CL | 694.27 |
| Basic model + eGFR Sjostrom on CL | 694.93 |
| Basic model + eGFR Grubb 2 on CL | 697.60 |
| Basic model + CLcr on CL | 690.82 |
| Basic model + Cys-C + TBW on CL | 687.93 |

OFV, minimum value of the objective function (~2 log likelihood) in each NONMEM® run; CL, total clearance; VC, volume of the central compartment; Cys C, cystatin C; TBW, total body weight; eGFR, estimated glomerular filtration rate; CLcr, creatinine clearance.

Fig. 3. Structural Pharmacokinetic Model for Teicoplanin and Pharmacodynamic Model for C-Reactive Protein (CRP) Concentrations

\(K_{in}\) is the zero-order production rate of CRP (mg/dL/h), and \(K_{out}\) is the elimination rate constant (h⁻¹) of CRP. The half-life of CRP \(T_{1/2CRP}\) (h) was estimated instead of \(K_{out}\), which is the ratio of natural logarithm 2 (ln 2), and \(T_{1/2CRP} K_{out}\) was calculated from \(K_{in} \times \text{initial CRP serum concentration (BASE}_{\text{CRP}} \) (mg/dL), with the assumption of a steady state before teicoplanin administration. The observed CRP value for each patient was used for the BASE_{CRP} \(J_{max}\) and IC_{50} in the formula of the drug effect represent the maximum extent of inhibition and the teicoplanin concentration (mg/L), producing 50% of the maximum inhibition of the effect, respectively.
The first line in Eq. 2 is the differential equation representing the variation in CRP concentration ($C_{\text{CRP}}$). $K_{\text{in}}$, PDI_{TEIC}, and $K_{\text{out}}$ represent the production rate of CRP, the drug effect, and the elimination rate constant of CRP, respectively. The second line of the equation represents the PDI_{TEIC} change with TEIC concentration ($C_{\text{TEIC}}$). $I_{\text{max}}$ and IC$_{50}$ represent the maximum extent of the inhibition effect, and the TEIC concentration producing 50% of the maximum inhibition of effect, respectively. The final estimated values of the half-life of CRP ($T_{1/2 \text{CRP}}$), $I_{\text{max}}$, and IC$_{50}$ were 61.1 h, 1, and 2.66 mg/L, respectively. The between-subject variability of IC$_{50}$ was large (78%). The relationship between TEIC and CRP concentration was evaluated based on the final estimated parameters. The probabilities of reaching the target $C_{\text{min}}$ (15–30 mg/L) and CRP concentration were simulated simultaneously using the final model. When it was assumed that the target $C_{\text{min}}$ was reached (15–30 mg/L) on day 7, CRP concentrations were predicted to decrease by more than 65% over 168 h (7 d) (Fig. 4). The PKPD simulation using population mean values is useful for considering the initial dosing regimen. When one or more observations are obtained, the individual PKPD parameters can be estimated using the empirical Bayesian method. The individual value (Bayesian estimation) of IC$_{50}$ provides important information about the susceptibility of TEIC. The present population PKPD model will provide clinicians with time-series predictions of TEIC and CRP concentrations in various patients with different clinical backgrounds and contributes to the consideration of optimal dosing strategies for TEIC.

4. PHARMACOKINETICS OF DAPTOMYCIN

The recommended dose of DAP according to the package insert is 4–6 mg/kg/d.$^{44}$ In recent years, some studies have suggested the benefits of administering a higher dose (≥8 mg/kg/d) for severe infections, such as infective endocarditis.$^{45,46}$ The relationship between $C_{\text{min}}$ (≥24.3 mg/L) and the probability of creatine phosphokinase elevation is well known.$^{47}$ These studies suggest that monitoring DAP concentrations and modifying the dose based on the measurements may be useful for safer and more beneficial treatment.

DAP is hydrolyzed and inactivated by general proteases, which indicates that hydrolysis by proteases in the human body or serum may influence the PK of DAP and its stability in the corrected serum samples of patients.$^{48}$ The activities of proteases generally vary with temperature. Therefore, we evaluated the stability of DAP in serum at various temperatures by repeatedly measuring DAP concentration.$^{49}$ The stability of DAP in serum samples stored at −80, −20, and 4 °C when long-term storage was assumed, and 35, 37, and 39 °C when body temperature was assumed. The decrease in DAP concentration in serum samples stored at 4 °C was more than 70% after 168 d (6 months), while the decrease in samples stored at 80 and −20 °C was less than 10%. Furthermore, DAP concentrations in serum samples stored at body temperature range decreased by more than 50% after only 24 h, but the concentrations of DAP in aqueous solution under the same conditions decreased by only 10%. The calculated elimination rate constants and elimination half-life of DAP in serum samples stored at body temperatures (35, 37, and 39 °C) are shown in Table 3. The elimination rate constant of DAP in serum increased and the elimination half-life decreased with an increase in the temperature of the serum sample. Addition of a protease inhibitor cocktail significantly inhibited the decrease in DAP concentration in serum samples stored at body temperature ($p < 0.05$). The results of this study suggest that the DAP concentrations in serum need to be measured rapidly or the serum samples collected from patients should be stored at an adequately low temperature (≤ −20 °C) until

\[
\begin{align*}
\frac{dC_{\text{CRP}}}{dt} &= K_{\text{in}} \times PDI_{\text{TEIC}} - K_{\text{out}} \times C_{\text{CRP}} \\
PDI_{\text{TEIC}} &= 1 - \frac{I_{\text{max}} \times C_{\text{TEIC}}}{\text{IC}_{\text{50}} + C_{\text{TEIC}}} 
\end{align*}
\]
measurement. When stored at temperatures close to body temperatures, DAP was rapidly eliminated from the serum, and its stability varied with temperature.

The antibacterial activity of DAP is concentration-dependent. The relationship between the clinical efficacy of DAP and maximum concentration/MIC or \( \text{AUC/MIC} \) has been reported, and an \( \text{AUC/MIC} \) of \( \geq 666 \) is suggested as the therapeutic target.\(^{50} \)

Although maintenance of an adequately high DAP concentration is necessary for desirable clinical efficacy, increasing the dose of DAP increases the risk of inducing concentration-dependent adverse events. We investigated the achievement rates for a target AUM/MIC of \( \geq 666 \) and the factors that influence the rate in hospitalized patients treated with DAP.\(^{51} \)

The target \( \text{AUC/MIC} \) was obtained in six patients (35.3\%) at a 4–6 mg/kg dose (Group 4–6 mg/kg), and in four patients (18.2\%) at a dose of \( >6 \) mg/kg (Group \( >6 \) mg/kg).

There were significant differences in the CL of DAP between these groups, but no differences were observed in patient characteristics. Multiple linear regression analysis was performed to evaluate the influence of patient characteristics on the \( \text{AUC/MIC} \)

Serum creatinine (SCR) was incorporated into the final model as a significant predictor, but this parameter provided a partial explanation (13\%) of the variance in the achievement rate of the target \( \text{AUC} \).

A receiver operating characteristic curve suggested \( \geq 0.450 \) L/h of daptomycin clearance as the optimal cut-off value to achieve an \( \text{AUC/MIC} \) ratio of 666. The measurement of DAP concentration is difficult in many hospitals. The efficacy of DAP should be monitored carefully to avoid treatment failure in any dosing regimen.

5. POPULATION PHARMACOKINETICS AND PHARMACODYNAMICS OF LINEZOLID

Conventional dose regimens of LZD are 600 mg twice daily for patients aged 12 years, and 10 mg/kg three times daily for pediatric patients. The package insert of LZD indicates that dose adjustments based on age, sex, and RF are unnecessary.\(^{22,53} \)

LZD taken into the body is metabolized non-enzymatically, without being affected by liver metabolism or renal excretion.\(^{24} \)

However, Pea et al. reported that there was a large variability in LZD concentration between patients, and suggested that TDM could be a useful tool to optimize the exposure of LZD in each individual patient.\(^{54} \)

Our group has characterized the pharmacokinetics and pharmacodynamics of linezolid to determine significant factors influencing variability between individuals, and to develop optimal dosing regimens for adults, the elderly, patients with renal insufficiency including those on continuous renal replacement therapies, patients with low body weight, those who are obese, and pediatric patients.\(^{56-62} \)

Thrombocytopenia, one of the most important adverse effects of LZD treatment, has been observed in 7.4\% and 11.8\% of Caucasian patients.\(^{63,64} \)

A much higher incidence (38.6–69.1\%) of LZD-induced thrombocytopenia has been reported in Japanese patients.\(^{65-72} \)

Interestingly, these different studies reported a significant relationship between thrombocytopenia and LZD overexposure in patients with renal dysfunction. Although the incidence of LZD-induced thrombocytopenia varies among studies, impairment of renal function has been suggested as a risk factor. Two published myelosuppression models (assuming that linezolid induced a decrease in platelet production by non-immune mediation), suggest that the platelet count reached a nadir 15–20 d after the initiation of LZD treatment.\(^{73,74} \)

Meanwhile, several case reports propose that the elimination of platelets is stimulated by LZD-induced, immune-mediated destruction.\(^{75,76} \)

Considering that the mechanism for the development of LZD-induced thrombocytopenia is unidentified, we examined the possibility that either non-immune-mediated myelosuppression or immune-mediated destruction of platelets was important for thrombocytopenia in each individual, hospitalized patient.\(^{77} \)

The PK of LZD was described using a two-compartment distribution model with first-order absorption and elimination. Overall clearance was assumed to be the sum of non-renal clearance and renal clearance, and renal clearance was the product of the population mean value and RF (representing the renal function in each patient). RF was the ratio of CLcr (L/h/70 kg) in each patient to a standard CLcr (6 L/h/70 kg), and CLcr was calculated using the Cockcroft–Gault formula.\(^{33} \)

The decrease in platelets due to LZD exposure was assumed to occur in one of two ways in every patient. These mechanisms include the inhibition of platelet formation (PDI LZD), or stimulation of the elimination (PDS\(_{LZD}\)) of platelets. Platelet counts were assumed to change only after exposure to LZD in both the PDI\(_{LZD}\) and PDS\(_{LZD}\) models. The PD model is composed of a compartment representing proliferating platelet precursor cells in the bone marrow, a compartment of systemic circulating platelets, and a link between two compartments and three transit compartments, reflecting platelet maturation (Fig. 5). A mixture model was used to identify the proportion of the study population assigned to PDI\(_{LZD}\) or PDS\(_{LZD}\). The final PK model parameters are shown in Eq. 3.

\[
\text{CL} (\text{L/h}) = (1.86 \times e^{-0.0205 \times (\text{AGE} - 69)} + 1.44 \times \text{RF}) \times \left( \frac{\text{TBW}}{70} \right)^{3/4}
\]

\[
V_F (\text{L}) = 22.9 \times \left( \frac{\text{TBW}}{70} \right)
\]

\[
V_P (\text{L}) = 24.7 \times \left( \frac{\text{TBW}}{70} \right)
\]

\[
Q (\text{L}) = 10.9 \times \left( \frac{\text{TBW}}{70} \right)^{3/4}
\]

Renal function was identified as a significant covariate of the CL (i.e., exposure) of LZD, as in previous studies. The non-renal CL decreased slightly with age. The final estimated population mean value of the plasma protein binding ratio was 18\%, and no significant differences were observed between the
patients. Ninety-seven percent of patients in the study population were assigned to the PDI LZD group, and 3% were assigned to the PDS LZD group.

A comparison of the PD parameters in this study with those of previous studies is shown in Table 4. Sasaki et al. used a platelet proliferation cell model to predict platelet inhibition. Boak et al. reported the use of a platelet stem cell model. Both models underwent preliminary testing and were accepted as platelet proliferation cell models. In the current study, the estimated mean transit time (MTT), feedback parameter \(\gamma\), and LZD potency (SLOPE) were similar to those reported by Sasaki et al. while Boak et al. reported an MTT that was about 50% longer, \(\gamma\) that was 5-fold larger, and a SLOPE that was 10-fold larger.

Variations in platelet count were simulated using the final PDI LZD and PDS LZD models with conventional LZD dosages. When PDI LZD was assumed, the predicted platelet count reached the nadir 14 d after initial LZD administration. When PDS LZD was assumed, the platelet count dropped sharply and reached the nadir only two days after the initiation of LZD treatment. We identified (using the population PKPD modeling approach) that the most common mechanism for the development of LZD-induced thrombocytopenia was the inhibition of platelet formation in the bone marrow. Performing TCI based on the population PKPD model built in this study is expected to reduce the risk of LZD-induced thrombocytopenia.

### Table 4. Comparison of Linezolid Pharmacodynamic Parameters

| Study          | Platelet inhibition models | MTT (h) | \(\gamma\) | PLTZERO \((10^3/\mu L)\) | SLOPE \(1/(mg/L)\) | SMAX | SC50 (mg/L) |
|----------------|---------------------------|---------|------------|--------------------------|---------------------|------|-------------|
| Tsuji et al.\(^{77}\) | Proliferation cell        | 104 (20) | -0.164 (23) | 204 (57)               | 0.0051 (48)         | 2.3  | 0.33        |
| Sasaki et al.\(^{73}\)   | Proliferation cell        | 110 (33.9) | -0.203      | 253 (45.9)               | 0.0042 (93.8)       |      |             |
| Boak et al.\(^{74}\)     | Stem cell                 | 163 (20.3) | -1.02       | 252 (65.1)               | 0.055 (at 10 mg/L)  |      |             |

Between-subject variability (BSV\%) was calculated from \(100 \times \sqrt{\text{NONMEM® OMEGA}}\); MTT, mean transit time; \(\gamma\), feedback parameter; PLTZERO, baseline platelet count; SLOPE, slope of inhibition effect; SMAX, maximal extent of stimulation effect; SC50, linezolid total concentration producing 50% of the maximum stimulation effect.

### Fig. 5. Schematic Representation of the Structural Pharmacokinetic and Pharmacodynamic Model for Representing Progenitor Cells in the Bone Marrow

\(CL\), clearance; \(FBACK\), empirical feedback mode; \(K_a\), absorption rate constant; \(K_{prol}\), proliferation rate constant of progenitor cells; \(K_{circ}\) (\(K_{out}\)), rate constant of PLTCIRC; \(K_{TR}\) (\(K_{out}\)), intercompartment transit rate constant; MTT, mean transit time; PLTCIRC, circulating platelets; PLTFORM, initial rate of platelet formation; PLTZERO, baseline platelet count; \(Q\), inter-compartment clearance; T half, elimination half-life; VC, volume of the central compartment; VP, volume of the peripheral compartment; \(\gamma\), feedback parameter; Smax, maximal extent of stimulation effect; SC50, LZD total concentration producing 50% of the maximum stimulation effect.

### 6. DEVELOPMENT OF PKPD SIMULATION SOFTWARE FOR ANTI-MRSA AGENTS

A “good” simulation model is a model which shows good predictive performance using novel data, and such a model is a very important tool for predicting the time-series variations in drug pharmacokinetics and pharmacodynamic responses. However, the process of predicting dependent variables from population models is very time-consuming because of the conventional use of general-purpose spreadsheet software, which limits the scope of application. The current study introduced a Bayesian dose forecasting software using TDM and TCI, “Pycsim.”\(^{78}\) Pycsim is interactive with pharmacokinetic and pharmacodynamic models via a web-browser interface on R Shiny\(^{79}\) that can be viewed on the local host (user’s own computer) or on another computer accessed by means of the Internet. This software is designed to work in an environment even if R is not installed. The population and individual predictions are returned after performing the dosing simulation. One or more observations are required to calculate the individual patient values. Simulations were performed based on dosing and observation records. Pycsim incorporated PKPD models of VCM, TEIC, ABK, DAP, and LZD.
7. CONCLUSION

Modeling and simulation have major advantages in dosing regimen selection. We have attempted to identify the variability in efficacy and side effects using a population PKPD analysis with anti-MRSA agents. The results of the present review suggest that pharmacokinetic analysis should be applied to ensure the proper use of anti-MRSA agents, with emphasis placed on safety and efficacy.

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Conflict of Interest The author declares no conflict of interest.

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