# Quantitative Modeling of Plasma Drug Concentrations and Clinical Surrogate Markers for Vancomycin Optimal Dosage Regimen Design

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Directed by Professor Kyung Soo Park

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연세대학교
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# This certifies that the Doctoral Dissertation of Jinju Guk is approved

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Jinju Guk.

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# ABSTRACT

Quantitative Modeling of Plasma Drug Concentrations and Clinical Surrogate Markers for Vancomycin Optimal Dosage Regimen Design

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(Directed by Professor Kyungsoo Park)

The aim of this thesis is to develop a pharmacokinetic (PK)-pharmacodynamic (PD) model to predict disease progression pattern in patients receiving vancomycin treatment and suggest optimal dose regimen using the developed model.

Routine clinical data for patients who were treated with vancomycin and received therapeutic drug monitoring in Severance hostpital, Seoul, Korea in 2013 were collected from electronic medical records. With serum vancomycin concentration for PK measure and C-reactive protein (CRP), procalcitonin (PCT), and absolute neutrophil count(ANC) for PD measures, information on patients' demographics,

laboratory results, and medical history including comorbidity was obtained as covariates to be tested for potential significance on model parameters. In PK analysis, one- and two- compartment disposition models were tried to describe vancomycin concentration profiles, with allometry scaling incorporated into clearance (CL) and volume of distribution (V). Renal function reduction due to vancomycin-induced nephrotoxicity was also considered. In PD analysis, turn-over model and variations of transduction model were attempted to characterize the dynamics of 3 PD markers or CRP, PCT, and ANC. For bacterial infection severity, which is often latent and not measurable, semi-mechanistic model-based approach was used for its quantification. As for drug effect, linear and Emax models were tested. Latent disease severity, which was modeled to be inhibited by drug exposure, was assumed to stimulate the synthesis of PD markers. In the final stage, an application for predicting PK-PD outcomes was developed. All analyses and development of application were performed using NONMEM 7.3 and visual inspection was carried out using R.3.2.2.

A total of 542 patients data were collected and used in PK analysis and 130 patients out of them were eligible for PD analysis. In a PK model, two-compartment disposition model well described the concentrations over time. For covariates, gender, creatinine clearance, maturation based on postmenstrual age (PMA), BUN, and history of diabetes and renal diseases had significant effect on CL and aging on V. With selected covariates, typical values of CL and V were estimated to be 4.31 L/h and 38.4 L, respectively, for male with body weight of 70 kg and age of 40. Normalized creatinine clearance was the most significant covariate with exponent of 0.65. In a organ maturation function, postmenstrual age where maturation reaches 50% of the adult clearance was 50.6 weeks. Drug-induced nephrotoxicity had also significant influence ($p < 0.0001$) and the rate of decreased creatinine clearance was

0.006 $day^{-1}$. In PD modeling, CRP, PCT, and ANC changes were successfully described by a transduction model with different input function. For latent disease severity, in all of CRP, PCT, and ANC, exponential growth model was selected with drug exposure incorporated as inhibiting growth rate constant. In CRP model, due to the scarcity of data, the elimination rate of CRP was fixed to the literature value of 0.0365 $h^{-1}$ (or 19 h in half-life). The elimination rates of PCT and ANC were estimated to be similar, yielding 0.016 $h^{-1}$ (or 43.3 h in half-life). Estimates of latent disease progression rates were 0.009, 0.05, and 0.004 in CRP, PCT, and ANC, respectively. All parameters were precisely estimated and any significant bias was not observed in goodness of fit plots. Based on developed model, the application was successfully using R shiny and was published on the Internet. In this application, it was designed to simulate vancomycin concentration, CRP, PCT, and ANC when patient's demographics and medical information, are given.

The developed PK-PD model can be used as a supportive tool for designing optimal therapeutic schedule using easily accessible biomarkers.

Key words : vancomycin, pharmacokinetic-pharmacodynamic model, optimal dose regimen, surrogate biomarkers, pharmacometrics

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## I. INTRODUCTION

With improvement of methodology and accessibility of various data from in vitro to clinical stage, pharmacometrics (or quantitative pharmacology), which is a science studying pharmacology in a quantitative manner, has been widely used in various fields from drug development to personalized therapy.[1] Central to pharmacometrics

is pharmacokinetics (PK; relation between drug dose and concentration) and pharmacodynamics (PD; relation between drug concentration and effect) modeling. Infectious disease is a representative disease area to take advantage of PK-PD modeling.[2] For example, it is often not feasible to measure bacterial count at infected site during treatment; however, PK-PD modeling can solve this limitation by integrating PK (drug concentration) and PD (bacterial growth) data.[3] With this approach, exposure-effect relationships between drug kinetics and bacterial growth dynamics can be quantified. Consequently, because PK-PD or exposure-effect relationships obtained can be applied for optimized clinical trial design and personalized therapy in practice, the importance of pharmacometrics approaches has been emphasized in clinical practice as well as drug development.

### A. PK-PD properties of vancomycin

Vancomycin is classified as a glycopeptide antibiotic and is mainly used for the treatment of infections by vancomycin susceptible bacterial species, especially methicillin-resistant *Staphylococcus aureus.*[4] It is also indicated for the treatment of pseudomembranous colitis caused by C.difficile and even for the treatment of infections by Gram-positive bacterial species if patients have an allergy to beta-lactam antibiotics.[5] The mechanism of action of vancomycin is to interrupt the synthesis of bacteria cell wall so that it works effectively to kill Gram positive bacteria; this drug hence can be regarded as bacteriocidal agent. When vancomycin is used to treat Gram negative bacterial infections, it is generally considered as bacteriostatic agent since Gram negative bacteria has a different mechanism to synthesize its cell walls and vancomycin is not considered bacteriocidal in this case.[6] Its pharmacological effect is dependent on drug exposure time in the plasma, not plasma concentration itself, thus this drug is so called a time-dependent antibiotic. Due to poor absorption of vancomycin after oral administration, it is

mostly administered intravenously and given orally only for colitis.[5] According to previous researches, vancomycin can be described by 2- or 3- compartment PK models and the elimination half-life ranges from 6 to 12 h.[7-9] Volume of distribution is 28-70 L for patients who weigh 70 kg, fraction of protein binding ranges from 10 to 50%, and the kidney is the main route of elimination, with 80 to 90% of the dose recovered in urine.[7,10] In the past years, it was known that the toxicity of vancomycin was associated with impurities, not with vancomycin concentration. Ototoxicity and nephrotoxicity had been reported as most frequent side effects.[11,12] Recently, studies have been conducted to determine the concentration-nephrotoxicity relationship and to potentiate the possibility of nephrotoxicity when vancomycin and amoniglycosides antibiotics are given together.[13,14]

**B. Bacterial resistance and MIC**

Bacterial resistance always exists with antibiotics and patients who developed this phenomenon are at a higher risk of worse clinical outcomes. According to "Antibiotic resistance threats in the United States, 2013", published by Centers for Disease Control and Prevention, approximately two million illnesses and twenty thousand deaths are caused by resistance to antibiotics every year and the inappropriate use of antibiotics plays a major role in causing bacterial-resistant infections.[15] Likewise, prevalence of resistance to antibiotics has been steadily increasing in Korea due to heavy consumption of antibiotics.[16,17] Methicillin-resistant staphylococcus aureus and vancomycin-resistance enterococcus faecalis are examples of bacterium that are resistant to antibiotics. In recent years, disastrous impact of bacterial resistance on public health was recognized by government. Subsequently, several strategies to mitigate resistance have been launched but bacterial resistance is still increasing.[18] In order to prevent resistance to vancomycin therapy, the drug is typically administered based on the Minimum Inhibitory

Concentration (MIC), which is defined as lowest concentration capable of blocking the growth of bacteria. The rationale of the use of MIC in vancomycin therapy is that it can be an indicator of the antibiotic potency and the survival of bacterial strains at the same time. Accordingly, guidelines for intravenous administration of vancomycin suggests that dose should be chosen to satisfy AUC/MIC = 400 with AUC denoting area under concentration.[19] However, the adequate dose regimen for relatively high MIC bacteria strains are limited and simply, criteria of AUC/MIC=400 is usually adopted. This empirical dosing system can be inadequate to treating infections and could lead to bacterial resistance.

### C. Surrogate end points related to disease severity

Clinical endpoint is generally defined as clinical outcome that represents the effect of a drug or an intervention in a clinical study. It can be divided into direct endpoint and indirect endpoint such as surrogate or biomarker by its capability to represent the clinical outcome of interest.[20] In the treatment of infectious diseases, bacterial eradiation would be the clinically meaningful endpoint but such endpoint is difficult to be assessed in a clinical situation or practice because often, there is no record of positive culture result at baseline and no specimen available to test the treatment effect. Instead, the use of biomarkers such as C-reactive protein (CRP), procalcitonin (PCT), erythrocyte sedimentation rate, and white blood cell count has been performed as a surrogate endpoint in determining recovery from infection.[21-23]

CRP is a ring-shaped protein in the plasma and the rise of this protein level can be observed when there is inflammation.[24] It is recognized as an acute phase inflammatory protein that is mainly synthesized in the liver by interleukin-6 and interleukin-11 secretion.[24,25] In terms of pathophysiology, CRP is partly responsible for activating the classical complement system by binding to

lysophosphatidylcholine that is expressed on the surface of dying or dead cells.[26,27] CRP level measurements are routinely used as a supportive tool in the diagnosis of bacterial infections since stimulation of CRP production in response to interleukin-6 happens in various types of inflammation as well as bacterial infections. Normally, CRP concentration is maintained between 1 and 10 mg/L and it can rise up to 100-fold within two hours of onset of inflammation and peaks almost within 48 hours.[28] The half-life of CRP is known as 18 hours and its level is controlled by the rate of synthesis which is associated with disease severity.[29]

PCT is a precursor of the calcitonin that plays a major role in calcium homeostasis. In healthy individuals, PCT concentration is negligible to detect in blood stream.[30] When a proinflammatory stimulus originated from bacteria appears, the level of PCT may significantly rise up to 100 mcg/L.[31-33] The mechanism of production of PCT and its role during inflammation has been proposed but it is still not completely understood. At present, PCT is believed to be synthesized by the liver and mononuclear cells and regulated by lipopolysaccharides and sepsis-related cytokines.[34] In many researches evaluating the accuracy of PCT levels for the diagnosis of bacterial infection, PCT level has been used as a marker of severe sepsis induced by bacteria.[33] For differentiating patients with sepsis from those with bacterial infections, PCT shows the highest performance with sensitivity and specificity compared to CRP and ESR.[35-38] Its half-life is 25 to 30 hours[33]and, like CRP, bacteria infection level is determined by the production of PCT.

Neutrophils are a type of granulocytes and comprise 40-75% of white blood cells. In the event of infection, neutrophils are the first line of defense and are responsible for innate immune system. A large number of neutrophils migrate from blood stream to the infected cells to engulf and destroy the invaders.[39] Migrated neutrophils do not reenter the blood, to protect the human from bacteria or virus.

Within 24 hours after onset of bacterial infection, neutrophil count drops below the normal range and the depletion of neutrophils in the blood is a stimulus to release immature cells from bone marrow. As a feedback mechanism, the amount of neutrophils in the bone marrow may be higher than the amount in the circulating pool; this is an indication of controlling bacterial infection well. When a patient is in a healthy state, at least 10 days are needed for the neutrophils to be matured in the bone marrow.[40] In the blood, equilibrium between circulating pool and the marginal pool such as liver and spleen is rapid and it can be regarded as one kinetic pool. On average, the life-span of neutrophils in these pools is only 6h to 8h.[40]

### D. Objectives of the thesis

In this paper, the development of a PK-PD model to predict disease progression pattern in patients receiving vancomycin will be described and optimal dose regimen using modeling and simulation through an application will be demonstrated.

## II. MATERIALS AND METHODS

### A. Data

This was a retrospective study and data were obtained from Electronic Medical Records (EMR) of Severance hospital, Seoul, Republic of Korea. For PK modeling, this study included patients who were treated with vancomycin and were provided with Therapeutic Drug Monitoring service; patients who were infected with *Staphylococcus aureus* were also included in the analysis. Selected patients were excluded from the analysis if dosing history and concentration sampling time were not available. The study was approved by the Institutional Review Board of Severance Hospital.

Demographic information including age (or postmenstrual age), weight, and sex was collected. For the PK model, maximum and minimum vancomycin concentrations were used as dependent variables. Dosing history such as dose, infusion rate and interdose interval was obtained and, if infusion rate was inaccurately recorded, one-hour infusion was assumed based on the guideline for vancomycin use.[41] For PD model, CRP, PCT, and absolute neutrophil count (ANC) were assessed as surrogate endpoints. CRP and PCT concentrations were obtained from EMR but ANC records were calculated as shown in Eq.(1).

$$ANC\left(\text{cells}\times\frac{10^9}{L}\right) = \frac{(\%Neutrophils+\%bands)\times WBC(\text{cells}\times 10^9/L)}{100} \quad \text{Eq.(1)}$$

where %neutrophils and %bands are a proportion that each component account for white blood cells.

The following blood chemistry laboratory results were collected : serum creatinine (mg/dL), serum glucose (mg/dL), albumin (g/dL), and blood urea nitrogen (mg/dL). Information for MIC and co-infection by coagulase negative *Staphylococci* species and *Streptococcus* species were collected from blood cell culture results. Information for comorbidity was also collected as a possible covariate to be analyzed.

## B. Model development

In PK-PD modeling, all dependent variables were analyzed by nonlinear mixed effect modeling (NONMEM), in which the model is composed of fixed and random effects, and dependent variables are nonlinearly related to model parameters. To be specific, fixed effect denotes the effect of typical or mean parameter and individual covariate, and random effect denotes the effect for individual parameter's random deviation from typical parameter value. The size of random effect is represented by inter-individual variability, as compared to intra-individual variability which represents the size of residual error.

## C. PK model

### 1. Basic structural model

One- and two-compartment disposition models were tried since only peak and trough samples were available for each dosing interval as displayed in Figure 1. Weight was incorporated into all PK parameters via allometry scaling as in Eq.(2).

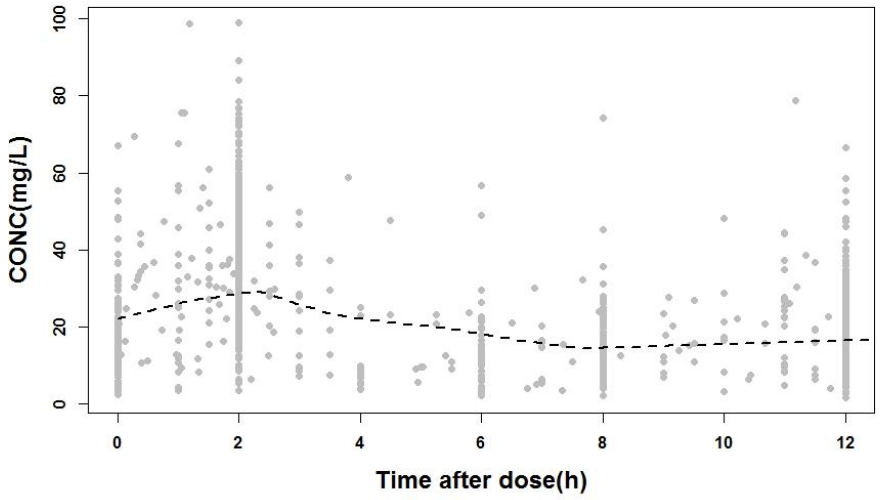



**Figure 1. Vancomycin concentration versus time after last dose.**
Dots are observations and dashed line is a smoother line. In this figure, most of the observations were distributed at specific times such as 0h, 2h, 6h, 8h, and 12h. This is because only peak and trough concentrations were available in a dosing interval

$$\text{SIZE} = \frac{\text{WT}}{70}$$

$$V_{pop} = V_{med} \times \text{SIZE} \qquad \text{Eq.(2)}$$

$$CL_{pop} = CL_{med} \times (\text{SIZE})^{0.75}$$

Where $V_{pop}$ and $CL_{pop}$ denote population or typical values of V and CL, and $V_{med}$ and $CL_{med}$ denote population median values of V and CL.

## 2. Covariate model building

Incorporation of renal function, clearance maturation and nephrotoxicity using prior

knowledge

According to previous studies, creatinine-clearance and organ maturation for clearance were incorporated as below.[8] In Eq.(3), Cr is plasma creatinine concentration, $k_{pro}$ is Cr production rate, and CrCl is creatinine clearance. Here, $k_{pro}$ was assumed to be affected by age, with $k_{pro}$= 58.4 mg/h at 40-year-old.[42]

$$k_{pro}(mg/h) = 58.4(\text{mg/h}) \times e^{(k_{age} \times (AGE-40)}$$

$$\text{CrCl} = \frac{k_{pro}}{Cr} \quad \text{Eq.(3a)}$$

Vancomycin-induced nephrotoxicity has been frequently reported in the literature, which was also observed in the preliminary analysis of our data. Empirically, this reduced creatinine clearance rCrCl was modeled as below

$$\text{rCrCl} = \text{CrCl} \times e^{(-k_{tox} \times \frac{time}{24})} \quad \text{Eq.(3b)}$$

where $k_{tox}$ means a rate constant to describe the reduced creatinine clearance per day.

Renal function factor $F_{REN}$ was then obtained by normalizing rCrCl with median creatinine clearance of 6 0 dL/h as

$$F_{REN} = (\frac{\text{rCrCl}}{60})^{\lambda} \quad \text{Eq.(3c)}$$

,where λ is an exponent parameter describing the relation between $F_{REN}$ and rCrCl.

For clearance maturation factor $F_{MAT}$, sigmoid function was adopted as in Eq.(4).[43]

$$F_{MAT} = \frac{PMA^{\partial}}{PMA50^{\partial} + PMA^{\partial}} \quad \text{for pediatrics under aged 4} \quad \text{Eq.(4)}$$

In the above sigmoid function, PMA50 denotes the postmenstrual age where maturation reaches 50% of the adult clearance and $\partial$ is a steepness of sigmoid

function. Since physiologically maturation of clearance dramatically occurs during the period of afterbirth to infant and slowly reaches the maximum in childhood, maturation function was defined for only ages under 4 to ease parameter estimation.

Vancomycin clearance CL was then obtained by incorporating both $F_{REN}$ and $F_{MAT}$ as

$$CL_{pop} = CL_{med} \times (SIZE)^{0.75} \times F_{REN} \times F_{MAT} \quad \text{Eq.(5)}$$

Additional covariate search using a step-wise approach

With the model in Eq. (2) and (5), additional parameter-covariate relationships were graphically investigated using R and statistically tested using NONMEM. Age, gender, BUN, and history of hypertension, diabetes, renal diseases, neutropenia, cardiovascular disease, neutropenia, hematological diseases, pleural effusion and edema, and sepsis were tested as possible covariates based on pharmacological and physiological plausibility. For continuous variables, unless a specific relationship has been quantified in previous researches, linear, power, and exponential function were attempted as expressed as below where P means model parameters and α is typical value at COV = COVmedian, and β is coefficient of covariates.

$$P = \alpha \times COV$$

Linear: $COV = 1 + \left(\frac{COV - COV_{median}}{COV_{median}}\right)$

Power: $COV = \left(\frac{COV}{COV_{median}}\right)^{\beta}$ Eq.(6)

Exponential: $COV = e^{(\beta \times (COV - COV_{median}))}$

Step-wise covariate modeling building was performed with the criteria of $p < 0.01$ for forward selection and $p < 0.001$ for backward deletion.

Then, the final covariate model was formulated as:

$$V_{pop} = V_{med} \times SIZE \times COV$$
$$CL_{pop} = CL_{med} \times (SIZE)^{0.75} \times F_{REN} \times F_{MAT} \times COV \quad \text{Eq.(7)}$$

and individual values of CL and V were obtained by incorporating inter-individual random differences $\eta_{CL}$ and $\eta_V$ as below.

$$CL = CL_{pop} \times EXP(\eta_{CL})$$
$$V = V_{pop} \times EXP(\eta_V)$$

### 3. Model validation

To check the validity of the constructed PK model, model validation was performed not only internally but also externally. For internal validation, Visual Predictive Check (VPC) was carried out as it is a broadly used diagnostic tool in this field, which checks how well selected percentiles (e.g., 10, 50, and 90$^{th}$ percentiles) of model predictions match with those of observations. For external validation, using additional patients' information collected, root mean squared error (RMSE) between the model predictions and the observation was obtained. Here, RMSE was defined as in Eq.(8)

$$\text{Root mean squared error (RMSE)} = \sqrt{\frac{1}{n}\sum_{i=1}^{n}\left(\frac{C_{pred,1} - C_{obs,i}}{C_{obs,i}}\right)^2} \quad \text{Eq.(8)}$$

## D. Pharmacodynamic model

### 1. Key model components

#### (A) Turnover model

Generally, most biomarkers in our body can be formulated by turnover model. It is assumed that biomarker levels are controlled by production and elimination, and drug effect can affect both processes. CRP and PCT are endogenous compounds and their production is suspected to be substantially stimulated by inflammatory response when there is an infection; such event was modeled with turnover model as shown in Eq.(9) and Eq. (10).

$$\frac{dBio}{dt} = k_{in} - k_{out} \times Bio \quad : \text{ No infection} \quad \text{Eq.(9)}$$

$$\frac{dBio}{dt} = k_{in} \times (1 + f(D)) - k_{out} \times Bio \quad : \text{ CRP in infection}$$

$$\frac{dBio}{dt} = k_{in} \times f(D) - k_{out} \times Bio \quad : \text{ PCT in infection} \quad \text{Eq.(10)}$$

In Eq.(9) and (10), Bio is the amount of CRP or PCT, and $k_{in}$ and $k_{out}$ refer to a zero-order production or synthesis rate and a first order degradation rate constant of biomarkers, respectively, where CRP was assumed to detectable and PCT undetectable under healthy conditions,. f(D) represents a function of D, where D denotes disease severity. In Eq. (10), the initial time was defined to be the time at diagnosis of infection, implying that f(D) is likely to be nonzero at t = 0. It was

assumed that an elevated production rate of biomarkers is directly correlated with disease severity. $k_{in}$, $k_{out}$, and initial levels of biomarkers were estimated in the model. Figure 2(a) shows the schematic of turnover model.

**(B) Cell proliferation model**

In the case of ANC, cell proliferation model had been published and is widely used to predict neutropenia in patients with cancer. The model can be described by Eq.(11).

$$\frac{dProl}{dt} = k_{syn} \times Prol - k_{deg} \times Prol \quad : \text{No infection}$$
$$\frac{dProl}{dt} = k_{syn} \times Prol \times (1 + f(D)) - k_{deg} \times Prol \quad : \text{Infection} \qquad \text{Eq.(11)}$$

In Eq.(11), Prol denotes the amount of immature or progenitor WBC at the proliferation site (i.e., bone marrow), and $k_{syn}$ and $k_{deg}$ refer to first order synthesis and degradation rate constant of progenitor WBC, respectively.

**(C) Transit model**

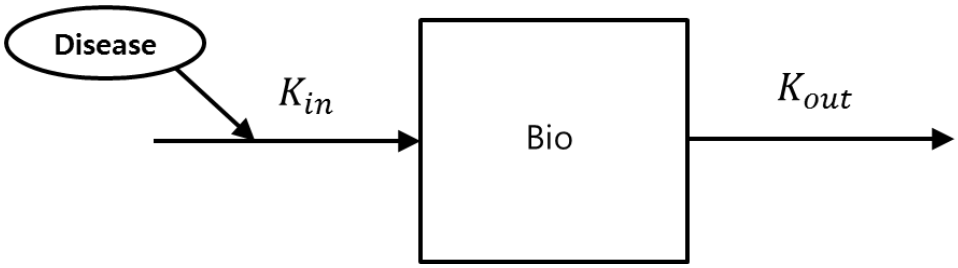
There can be time delay between infection occurrence and biomarker level change in the plasma. In this case, transit model can be used, which involves a series of compartments to describe a cascade of events before the presence of biomarker concentrations in blood stream. Such delay can be more obvious for WBC, which requires maturation in the bone marrow until it appears in the plasma in the matured form.

For example, in the case of ANC, it can be represented as in Eq. (12).

$$\frac{dProl}{dt} = k_{tr} \times Prol \times (\frac{Bio_0}{Bio})^{\gamma} - k_{tr} \times Prol$$
$$\frac{dTran1}{dt} = k_{tr} \times (Prol - Tran1)$$
$$\frac{dTran2}{dt} = k_{tr} \times (Tran1 - Tran2)$$
$$\cdots \qquad \text{Eq.(12)}$$
$$\frac{dTranN}{dt} = k_{tr} \times (Tran(N-1) - TranN)$$
$$\frac{dBio}{dt} = k_{tr} \times TranN - k_{out} \times Bio$$

In Eq. (12), $k_{tr}$ is a transit rate constant, which also represents a simplified version of $k_{syn}$ and $k_{deg}$ (i.e., $k_{syn} = k_{deg} = k_{tr}$), Bio is the amount of matured WBC in bloodstream, with $Bio_0$ being the baseline value, and $k_{out}$ is an elimination rate constant of matured WBC in bloodstream. Note that $(\frac{Bio_0}{Bio})^{\gamma}$ enters the model as negative feedback, indicating that proliferation is dependent not only on the amount of proliferation compartment but also on the circulating compartment via feedback mechanism. This feedback term did not appear in Eq. (11) because transit compartments were not specified there. The mean transit time is estimated as $(N+1)/k_{tr}$. Figure 2(b) shows the schematic of cell proliferation model with transit compartments.

(a)




(b)

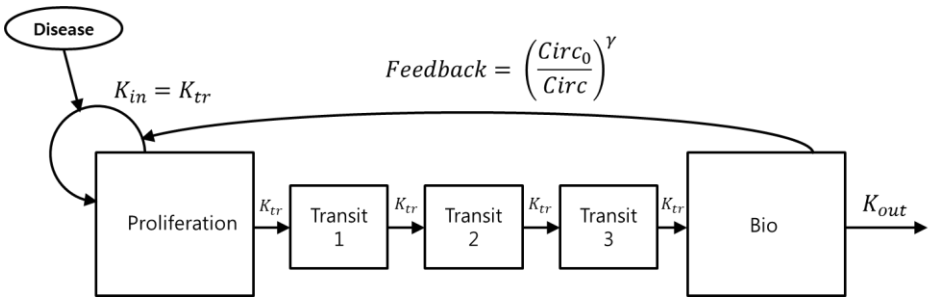



**Figure 2. The base line models for biomarkers describing infection induced changes. (a) turnover model (b) cell proliferation model with transit compartments; BIO denotes level of biomarkers in blood.**

**(D) Disease severity model**

In most cases with infectious diseases, changes in the number of bacterial count at infected site or in bloodstream directly represent prognosis or recovery. However, the number of bacterial count and its alteration are almost always unavailable in real time on practice. Due to lack of bacterial count data, disease severity, which is a hypothetical or latent variable, was generated assuming that it reflects the number of bacterial count in bloodstream. This latent variable was formulated both empirically and semi-mechanistically.

**( D1) Empirical model**

With no information on natural disease progression of infection, empirical models of linear, exponential, and logistic progression model were considered to describe disease severity. Out of these models, exponential model best described the data, which was formulated as in Eq.(13).

$$\frac{dD}{dt} = K_p \times \mathrm{D} \quad : \text{ No drug effect}$$
$$\frac{dD}{dt} = K_p \times \mathrm{D} \times (1 - E_{Drug}) \quad : \text{ Drug effect} \qquad \text{Eq.(13)}$$

In Eq.(13), D is disease severity, Kp is first-order progression rate constant and $E_{Drug}$ is drug effect, where initial disease severity level (D(0)) was arbitrarily set to 1. Exponential model was initially developed to model the growth of bacteria or tumor and it was explained by a growth rate (Kg) and a death rate constant (Kd). However, if data are scarce, it is often difficult to estimate two parameters separately. Accordingly, Kp was defined as a net growth rate constant of disease.

**(E) Drug effect model**

Antimicrobial agents are therapeutically categorized into concentration-dependent and time-dependent agents based on the agent's PK characteristics and its relation to the agent's efficacy to kill bacteria. For instance, certain classes of aminoglycosides and quinolones require high plasma concentrations of the agent for bacterial eradication; thus, an index of Cpeak/MIC, with Cpeak denoting peak concentration, is considered when dosing, which is called as concentration dependent antibiotics. On the other hand, the extensive amount of time when

concentrations exceed MIC plays a key to inhibit the bacterial growth with antimicrobial class such as beta-lactams and macrolides and an index of AUC/MIC is used to determine the optimal therapeutic dose. As for vancomycin, whose effect is time-dependent and is bacteriocidal, using AUC obtained from the established PK model, drug effect was modeled as expressed in Eq.(14).

$$E_{Drug} = \alpha \times \mathrm{AUC} \qquad \text{linear model}$$
$$E_{Drug} = \frac{EMAX \times AUC}{EAUC50 + AUC} \qquad \text{Emax model} \qquad \text{Eq.(14)}$$

## 2. Model for biomarkers

### (A) Model for C-reactive protein

A schematic diagram of CRP model is shown in Figure 3 and model equations are described in Eq.(15) In this model, stimulation of CRP by disease severity was scaled via S_CRP and its effect is proportional to disease severity. One proliferation compartment and two transit compartments were adopted and no feedback mechanism was considered.

$$\frac{dD}{dt} = K_p \times \mathrm{D} \times (1 - E_{Drug})$$
$$E_{Drug} = \alpha \times \mathrm{AUC}$$
$$\frac{dProl}{dt} = k_{tr} \times (1 + S\_CRP \times D(t)) - k_{tr} \times Prol$$
$$\frac{dTran1}{dt} = k_{tr} \times (Prol - Tran1) \qquad \text{Eq.(15)}$$
$$\frac{dTran2}{dt} = k_{tr} \times (Tran1 - Tran2)$$
$$\frac{dCRP}{dt} = k_{tr} \times Tran2 - k_{out} \times CRP$$

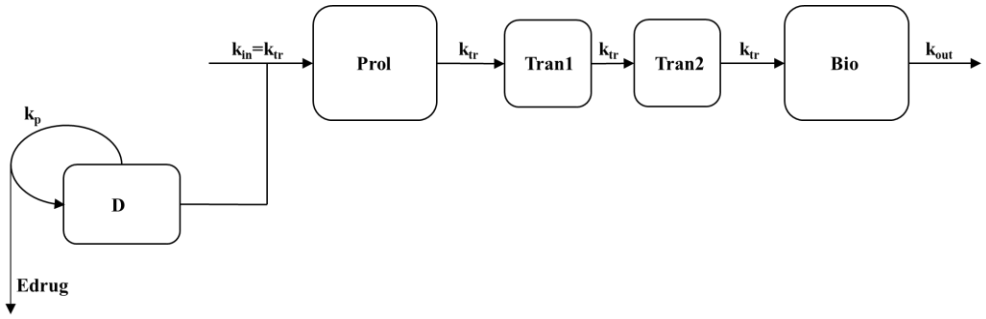



**Figure 3. Schematic diagram of C-reactive protein model.**
The model describing the disease-stimulated CRP synthesis, with disease severity, denoted by D, inhibited by drug and time delay in CRP appearance in blood stream represented by transit compartment; BIO denotes CRP level in blood

**(B) Model for Procalcitonin**

Similarly to the model for CRP, PCT was characterized by one proliferation compartment and two transit compartment model as depicted in Figure 4 and Eq. (16). The only difference from CRP model is that stimulation by disease is directly applied to PCT synthesis rate without being scaled.

$$\frac{dD}{dt} = K_p \times \mathrm{D} \times (1 - E_{Drug})$$

$$E_{Drug} = \alpha \times \mathrm{AUC}$$

$$\frac{dProl}{dt} = k_{tr} \times D(t) - k_{tr} \times Prol$$

$$\frac{dTran1}{dt} = k_{tr} \times (Prol - Tran1) \qquad \text{Eq.(16)}$$

$$\frac{dTran2}{dt} = k_{tr} \times (Tran1 - Tran2)$$

$$\frac{dPCT}{dt} = k_{tr} \times Tran2 - k_{out} \times PCT$$

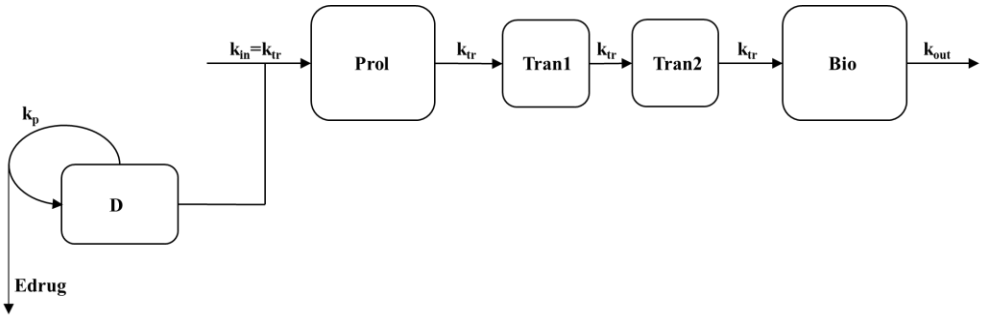



**Figure 4. Schematic diagram of Procalcitonin model.**
The model describing the disease-stimulated PCT synthesis, with disease severity, denoted by D, inhibited by drug and time delay in PCT appearance in blood stream represented by transit compartments; BIO denotes PCT level in blood

**(C) Model for Absolute neutrophil count**

For ANC, one proliferation compartment and three transit compartment model was adopted. In this model as described in Eq.(17), it was assumed that disease severity and feedback mechanism were driving forces, the former stimulating the proliferation of neutrophil in bone marrow and the latter inhibiting it.

$$\frac{dD}{dt} = K_p \times \mathrm{D} \times (1 - E_{Drug})$$

$$E_{Drug} = \alpha \times \mathrm{AUC}$$

$$\frac{dProl}{dt} = k_{tr} \times Prol \times (1 + S\_ANC \times D(t)) \times (\frac{ANC_0}{ANC})^{\gamma} - k_{tr} \times Prol$$

$$\frac{dTran1}{dt} = k_{tr} \times (Prol - Tran1) \qquad \text{Eq.(17)}$$

$$\frac{dTran2}{dt} = k_{tr} \times (Tran1 - Tran2)$$

$$\frac{dTran3}{dt} = k_{tr} \times (Tran2 - Tran3)$$

$$\frac{dANC}{dt} = k_{tr} \times Tran3 - k_{out} \times ANC$$

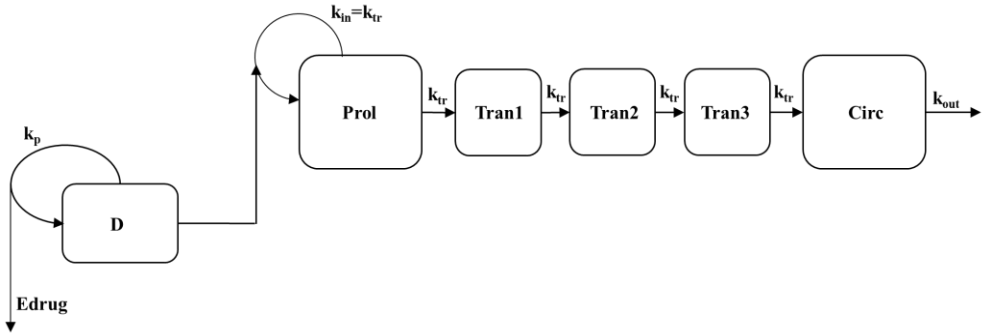



**Figure 5. Schematic diagram of Absolute neutrophil count model.**
The model describing the disease-stimulated neutrophil synthesis with negative feedback, with disease severity, denoted by D, inhibited by drug and time delay neutrophil appearance in blood stream reprented by transit compartments; Cir denotes ANC level in blood

### 3. Covariate model building

Relationships between estimated parameters obtained from the established basic (i.e., no-covariate) models of biomarkers and possible covariates were graphically inspected. With this preliminary analysis, MIC, co-infected species and history of hypertension, diabetes, renal disease, neutropenia, cardiovascular disease, hematological disease, pleural effusion and edema, and sepsis were tested for each biomarker model. A stepwise covariate selection was done with criteria of $P<0.05$ for forward selection and $P<0.01$ for backward deletion. This statistical test was performed based on $\chi^2$-distribution

### 4. Simulation

To establish an application for predicting PK-PD profiles of vancomycin therapy, R shiny packages were utilized. Selected covariates and dosing regimen such as dose,

infusion duration, and inter-dose interval were set as input parameters for the model. The user-interface of this application, a layout that tells Shiny where to show a model, was coded in a ui.R file and R codes were written in a server.R file to build the object, as described in R shiny tutorial. By inspecting PK-PD profiles, optimal dose regimens expected to satisfy the therapeutic range will be proposed.

## III. RESULTS

### A. Patient demographics

A total of 542 patients were eligible for the pharmacokinetic analysis and 130 of 542 patients were included in the pharmacodynamics analysis. Patients' baseline characteristics included in the analysis were summarized in Table 1 and 2. 1526 concentration measurements were obtained, which consisted of peak concentrations of 49.3% (754 samples) and trough concentrations of 50.7% (774 samples). For pharmacodynamics modeling, 845 CRP samples from 128 patients, 153 PCT samples from 69 patients, and 1643 ANC samples from 129 patients were used. Patients ranged from pre-term neonates to elderly; 40 pediatric patients were included in both PK and PD analyses. In Table 2, 69.2% of patients were infected by bacteria showing below 1 MIC μg/ml and 15.4% of patients were co-infected by other species than *Staphylococcus aureus*.

### B. Pharmacokinetic model

Pharmacokinetic data of vancomycin was described better with two-compartment model than one-compartment model and the difference of OFV was 154.838, which was statistically significant ($p<0.0001$). The effect of creatinine clearance, the presence of renal disease, BUN, gender, maturation effect, and the presence of diabetes were chosen as significant covariates on CL and aging effect on V. Also, vancomycin-induced nephrotoxicity during vancomycin therapy significantly improved model prediction ($p<0.0001$). Parameter estimates of the final pharmacokinetic model were summarized in Table 3. Estimated system parameter values of V, CL, V2, and Q were 38.63 L, 4.31 L/h, 66.62 L, and 3.91 L/h, respectively, which were similar to those reported in other vancomycin studies.

**Table 1. Demographics of patients who were included in the pharmacokinetic analysis.**

| N = 542, measurements = 1526 (peak : 754 samples, trough : 774 samples) | | |
|---|---|---|
| | **Mean(SD)** | **Median [Min, Max]** |
| **Age (yr)** | 58.1 (19.6) | 61.0 [0.003, 93] |
| **PMA (month)** | 93.7 (62.7) | 70.0 [39, 232] |
| **Weight (kg)** | 58.9 (16.0) | 59.0[2.6, 106] |
| **Albumin (g/dL)** | 2.87 (0.55) | 2.80 [1, 4.4] |
| **Total protein (g/dL)** | 5.67 (0.93) | 5.60 [3.2, 8.4] |
| **Creatinine (mg/dL)** | 1.35 (1.71) | 0.73 [0.2, 12.9] |
| **BUN (mg/dL)** | 22.4 (18.0) | 16.5 [1.5, 141.5] |
| **Sex** | Male (319, 58.9%) | Female (223, 41.1%) |
| **Hypertension** | No (258, 47.6%) | Yes (284, 52.4%) |
| **Diabetes** | No (388, 71.6%), | Yes (154, 28.4%) |
| **Neutropenia** | No (523, 89.9%), | Yes (19, 3.5%) |
| **Sepsis** | No (447, 82.5%), | Yes (95, 17.5%) |
| **hematological malignancy** | No (420, 77.5%), | Yes (122, 22.5%) |
| **Pleural effusion and edema** | No (493, 91%), | Yes (49, 9.0%) |
| **Cardiovascular diseases** | None<br>One<br>Two<br>Three<br>Four | (286, 52.8%)<br>(6, 1.1%)<br>(178, 32.8%)<br>(14, 2.6%)<br>(58, 10.7%) |
| **Renal diseases** | No disease<br>Acute kidney disease<br>Chronic kidney disease<br>Others | (395, 72.9%)<br>(49, 9.04%)<br>(48, 8.86%)<br>(50, 9.23%) |

**Table 2. Demographics of patients who were included in the pharmacodynamics analysis.**

N = 130
CRP = 845 (128 patients), PCT=153 (69 patients), ANC=1643 (129 patients)

| | Mean(SD) | Median [Min, Max] |
|---|---|---|
| **Age (yr)** | 61.2 (14.7) | 63.0 [9.3, 87.0] |
| **Weight (kg)** | 58.9 (12.3) | 57.2 [31.5, 106.0] |
| **Albumin (g/dL)** | 2.81 (0.54) | 2.8 [1.7, 4.2] |
| **Total protein (g/dL)** | 5.7 (1.0) | 5.6 [3.9, 8.4] |
| **Creatinine (mg/dL)** | 1.58 (1.91) | 0.79 [0.20, 10.34] |
| **BUN (mg/dL)** | 25.1 (19.5) | 19.0 [1.9, 141.5] |
| **Sex** | Male (81, 62.3%) | Female (49, 37.7%) |
| **Pneumonia** | No(89, 68.5 %), | Yes (41, 31.5%) |
| **Hypertension** | No (47, 36.2%) | Yes (83, 63.8%) |
| **Diabetes** | No (77, 59.2%) | Yes (53, 40.8%) |
| **Neutropenia** | No (128, 98.5%) | Yes (2, 1.5%) |
| **Sepsis** | No(103, 79.2%) | Yes(27, 20.8%) |
| **hematological malignancy** | No(116, 89.2%) | Yes(14, 10.8%) |
| **Pleural effusion and edema** | No(119, 91.5%) | Yes(11, 8.5%) |
| **Cardiovascular diseases** | None | (64, 49.2%) |
| | One | (2, 1.5%) |
| | Two | (47, 36.2%) |
| | Three | (8, 6.2%) |
| | Four | (9, 6.9%) |
| **Renal diseases** | No disease | (88, 67.7%) |
| | Acute kidney disease | (14, 10.8%) |
| | Chronic kidney disease | (13, 10.0%) |
| | Others | (15, 11.5%) |
| **MIC (μg/ml)** | NA | (6, 4.6%) |
| | 0.5 | (41, 31.5%) |
| | 1 | (49, 37.7%) |
| | 2 | (23, 17.7%) |
| | 4 | (2, 1.5%) |
| | 6 | (6, 4.6%) |
| | 32 | (3, 2.3%) |
| **Co-infected bacterial species** | None | (110, 84.6%) |
| | Other *Staphylococcus* species | (19, 14.6%) |
| | *Streptococcus* species | (1, 0.8%) |

**Table 3. Parameter estimates of the final pharmacokinetic model.**

| Parameter | | Population estimate (%RSE) |
|---|---|---|
| **Structural parameter** | | |
| **Creatinine clearance** | **CL (L/h)** | 4.31 (4.01) |
| | **V (L)** | 38.63 (3.57) |
| | **Q (L/h)** | 3.91 (11.0) |
| | **V2 (L)** | 66.62 (6.74) |
| | **$K_{age}$ (if age>=40)** ($yr^{-1}$) | -0.014 (15.8) |
| | **$K_{age}$(if age<40)** ($yr^{-1}$) | 0.0074 (84.2) |
| | **λ** | 0.65 (4.39) |
| **Maturation effect** | **PMA50** (weeks) | 50.65 (22.5) |
| | **∂** | 1.55 (62.5) |
| **Nephrotoxicity** | **$K_{tox}$** ($day^{-1}$) | 0.0060 (29.0) |
| **β_age** | | 0.0096 (9.55) |
| **β_ renal disease** | | -0.23 (15.2) |
| **β_BUN** | | -0.0088 (15.7) |
| **β_gender** | | -0.20 (12.7) |
| **β_DM** | | -0.15 (23.5) |
| **Between subject variability** | | |
| **$\omega^2_{CL}$(CV[¶](%))** | | 29.2 (4.93) |
| **$\omega^2_{V2}$(CV (%))** | | 100.4 (8.49) |
| **Residual variability** | | |
| **$\sigma^2_{proportional\_trough\_}$(CV %))** | | 17.8 (6.43) |
| **$\sigma^2_{additive\_trough\_}$(ng/ml)** | | 0.97 (15.9) |
| **$\sigma^2_{proportional\_peak\_}$(CV %))** | | 11.1 (24.7) |
| **$\sigma^2_{additive\_peak\_}$(ng/ml)** | | 4.44 (11.9) |

[¶]CV %: Coefficient of variance

λ in Eq. (3c) was 0.65. Vancomycin clearance slightly increased with BUN level of up to 15 mg/dL but then decreased with BUN level. Under the presence of renal diseases and diabetes, vancomycin clearance was reduced by 23.0% and 15.0%, respectively. Female patients showed 0.80-fold decrease in drug clearance compared to male patients. $k_{tox}$ in Eq.(3b) was 0.0060 $day^{-1}$. For maturation effect, the estimated PMA50 was 50.65 weeks with a hill coefficient ($\partial$) of 1.55. For the elderly, aging effect on volume of distribution was statistically significant. As a result, CL and V were formulated as below, where FEM = 1 for female and 0 for male, DM = 1 for diabetes and 0 for no diabetes, and REN = 1 for renal disease and 0 no renal disease:

$$\mathrm{CL} = 4.31 \times \left(\frac{WT}{70}\right)^{0.75} \times \left(\frac{rCrCl}{60}\right)^{0.65} \times \left(\frac{PMA^{1.55}}{50.65^{1.55}+PMA^{1.55}}\right) \times e^{((BUN-15)\times -0.0088)} \times (1 - 0.2 \times \mathrm{FEM}) \times (1 - 0.15 \times \mathrm{DM}) \times (1 - 0.23 \times \mathrm{REN})$$

$$\mathrm{V} = 38.63 \times \frac{WT}{70} \times e^{((AGE-40)\times 0.0096)}$$

Overall, relative standard error of most parameters seemed good (<30.0%). As displayed in Figure 6, goodness of fit plots showed that there was no significant bias in our model. For internal validation, Figure 7 indicated that observed and predicted median lines almost matched each other. Almost all of the observations were included in 95% confidence interval of 2.5$^{th}$ percentile and 97.5$^{th}$ percentile. Additionally, our model was externally validated as shown in Figure 8. In external validation using the VPC, it was seen that the observed percentile from validation data was roughly in agreement with the predicted percentile from out model. Moreover, it was found that root mean squared error was 37.0%. For comparison of model predictability within each subgroup, goodness of fit plot was drawn in Figure 9, which revealed no serious bias, further supporting the validity of the model.

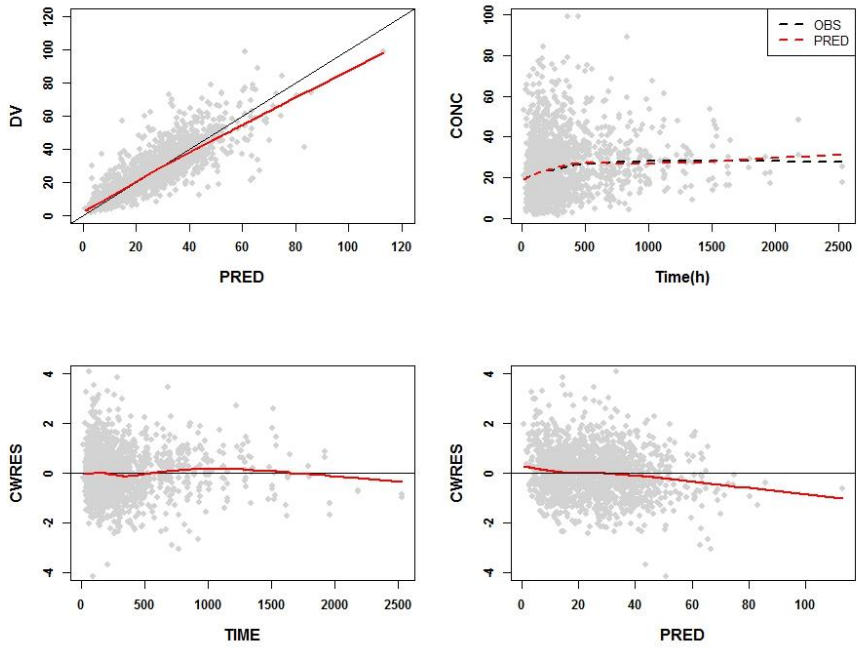



**Figure 6. Goodness of fit plots of the final pharmacokinetic model.**
DV, CONC, CWRES, and PRED denotes dependent variable, concentration, conditional weighted residual errors, and predictions, respectively. Dots are observation and red solid line is a smoother line.

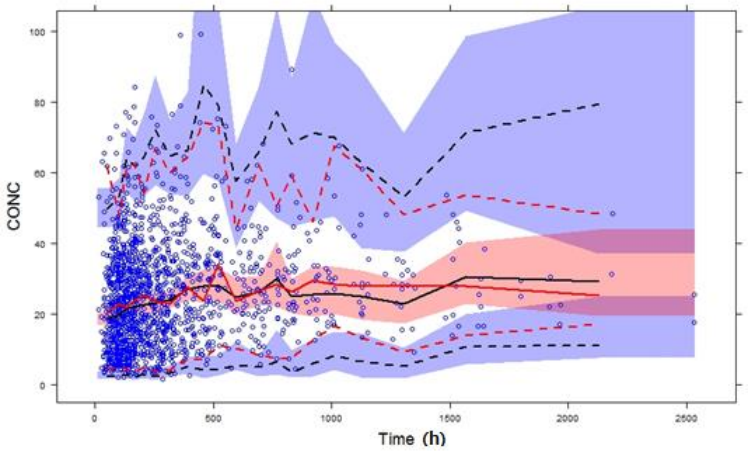



**Figure 7. Visual predictive check of the final pharmacokinetic model (internal validation).**
Open circles are observations and lines are 2.5$^{th}$, median, and 97.5$^{th}$ percentiles of predictions(black) or observations(red). Colored area means confidence interval of each prediction percentile.

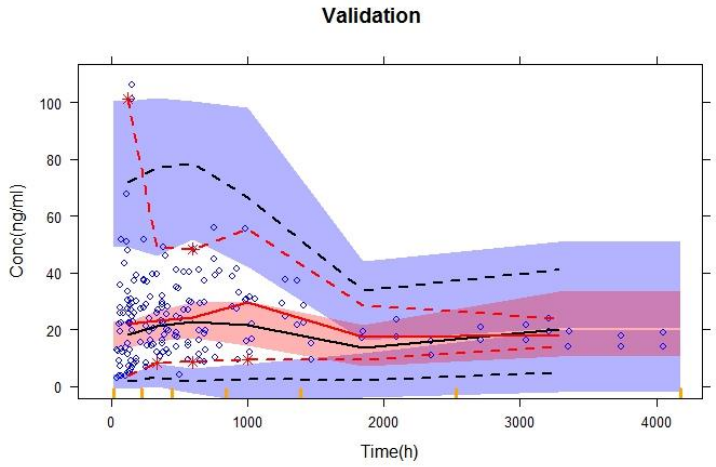



**Figure 8. Visual predictive check of the final pharmacokinetic model (external validation).**
Open circles are observations and lines are 2.5$^{th}$, median, and 97.5$^{th}$ percentiles of predictions(black) or observations(red). Colored area means confidence interval of each prediction percentile.

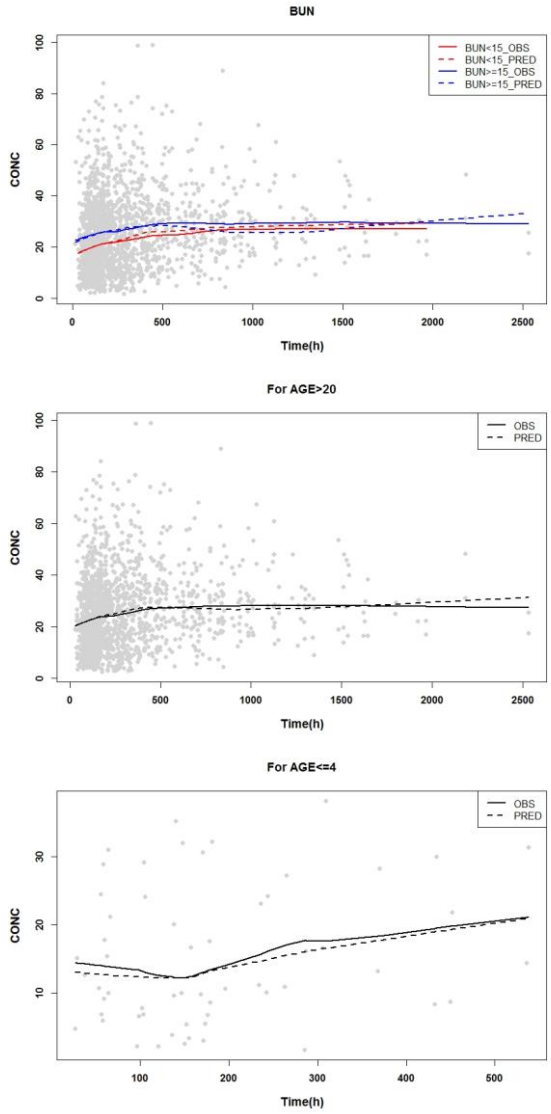



**Figure 9. Goodness of fit for assessing model predictability within each subgroup.** OBS, PRED, and CONC means observations, predictions, and concentration.

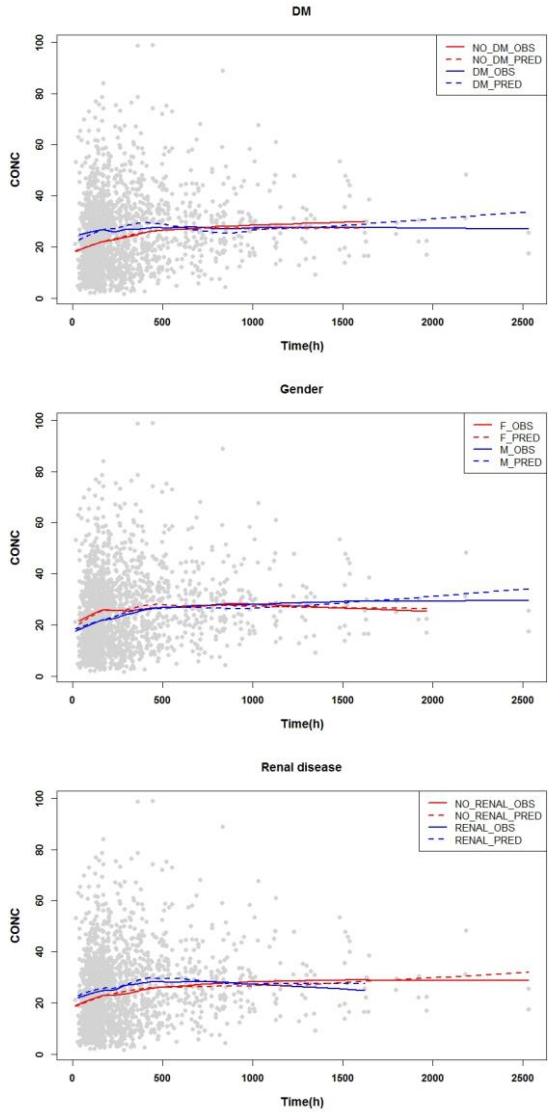



**Figure 10. (Cont'd)**.

## C. Pharmacodynamic model

### 1. C-reactive protein model

With the basic model structure described in Eq.(15), covariate analysis found that pneumonia has a significant effect on the transit rate constant as below, where PNE = for pneumonia and 0 for no pneumonia.

$$k_{tr} = 0.012 + 0.008 \times PNE$$

Parameter estimates of the selected model were listed in Table 4. In the transit model, due to numerical difficulties in estimation, it was assumed that the CRP elimination rate constant was fixed at 0.0364 based on the prior knowledge that CRP's half-life is 19 h. Between-subject variability (BSV) in structural parameters other than Kp and CRP_INI, the initial value of CRP, was also unobtainable due to difficulties in estimation.

Mean transit time was 10.4 days ((no. of transit compartments + 1)/$k_{tr}$ = 3/0.012 = 250 hours = 10.4 days) for non-pneumonia patients and 6.25 days (3/0.02 = 150 hours = 6.25 days) for pneumonia patients. The disease progression rate constant was 0.192 $day^{-1}$ (= $0.008h^{-1} \times 24h/1day$). The estimated drug effect parameter α was 2 per 1000 AUC ng/ml*h**.** As displayed in Figure 10, there was no significant bias in this model. When the PRED vs TIME plot was superimposed on DV, little discrepancy was observed.

### 2. Procalcitonin model

As described in Eq.(16), PCT was described with the same kind of model as CRP, except for no disease scaling factor used for stimulating the production of PCT. In

fact, a stimulating scaling factor was tried to be incorporated into the model but it failed due to identifiability problems. For covariate analysis, no significant covariate was found. Table 5 reported parameter estimates of PCT model. The elimination rate constant in circulating compartment was 0.016 $h^{-1}$, which corresponds to the PCT half-life of 43.3 h. Kp was 0.984 $day^{-1}$ and drug effect was 2.22 per 1000 AUC ng/ml*h. Figure 11 was drawn in order to investigate the bias in the model prediction. In CWRES vs PRED and CWRES vs TIME plots, there was no trends deviating from the y=0 horizontal line. Also, in PRED vs TIME plot, superimposed on DV, overall trends of DV and PRED well matched each other.

**Table 4. Parameter estimates of C-reactive protein model.**

| **Model** | **CRP model** |
|---|---|
| **Parameter** | **Population estimate (%RSE)** |
| **Structural parameter** | |
| $k_{tr\_nonpn}$ **(/h)** | 0.012 (11.4) |
| $k_{tr\_pn}$ **(/h)** | 0.020 (33.9) |
| $k_{out}$ **(/h)** | 0.0365 FIX |
| **CRP_INI (mg/dl)** | 132.6 (11.4) |
| $K_p$ **(/h)** | 0.008 (41.6) |
| **α** | 0.002 (15.4) |
| **S_CRP** | 35.1 (54.1) |
| **Between subject variability** | |
| $\omega^2_{Kp}$**(CV¶(%))** | 66.3 (13.6) |
| $\omega^2_{CRP\_INI}$**(CV (%))** | 118.2 (13.7) |
| **Residual variability** | |
| $\sigma^2_{proportional}$ **(CV %))** | 52.4 (4.27) |

¶CV %: Coefficient of variation

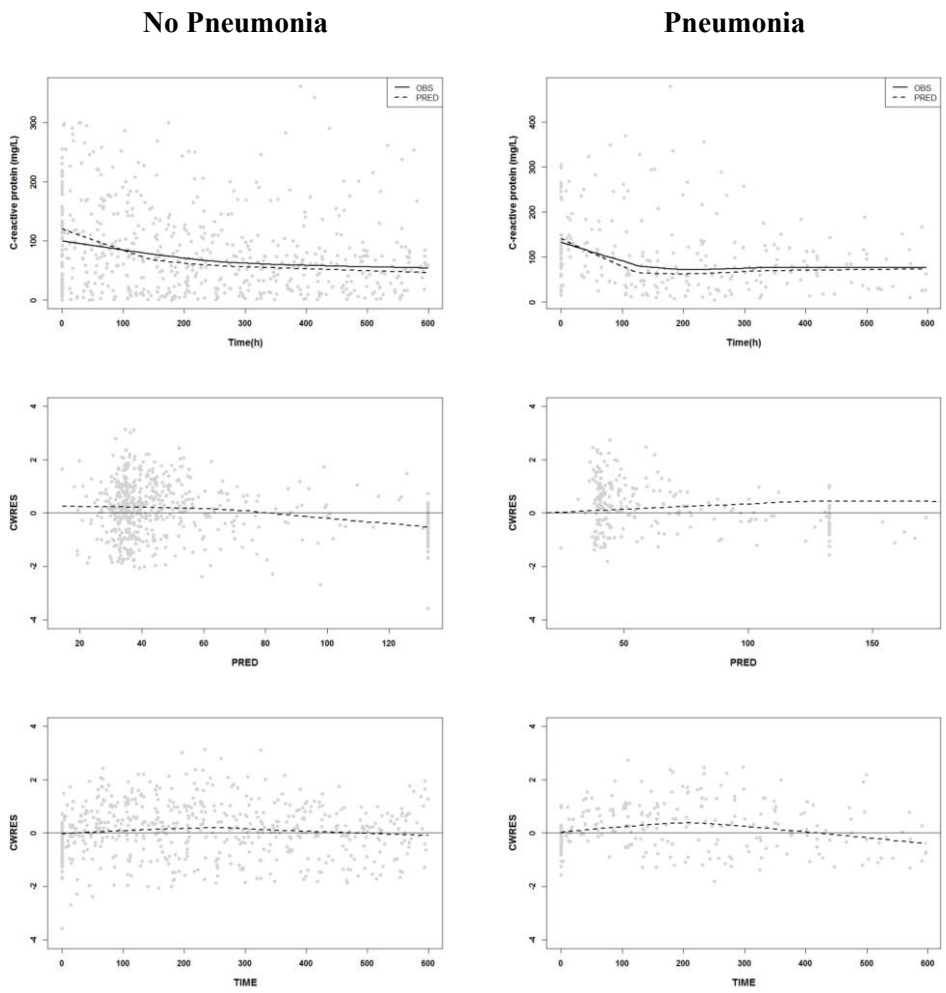



**Figure 11. Goodness of fit plots (CRP model) (Upper : PRED vs TIME, middle : CWRES vs PRED, lower : CWRES vs TIME).**
Dots are observations. In PRED vs TIME plot, solid and dotted line denote a smoother line of observations and predictions, respectively. CWRES and PRED means conditional weighted residual errors and predictions.

### 3. Absolute Neutrophil Count model

ANC was characterized by the model described in Eq. (17). However, due to numerical difficulties with the model, other latent models and drug effect models were tested but minimization was not achieved. As a residual error model, combined error model was more appropriate than a proportional error model. The estimated parameters for the ANC model were presented in Table 6.

Estimated neutrophil half-life in bloodstream was 53.3 hours (0.693/0.013=53.3) and mean transit time was 400 hours, or 16.7 days. The disease progression rate was 0.001 per hour and drug effect was 0.355 per AUC ng/ml*h. The precision of parameter estimates seemed good since all RSE of parameter estimates were below 30%. To check any bias in model prediction, goodness of fit plots were generated in

**Table 5. Parameter estimates of procalcitonin model.**

| Model | PCT_model |
|---|---|
| **Parameter** | **Population estimate (%RSE)** |
| **Structural parameter** | |
| $k_{tr}$ (/h) | 0.007 (8.91) |
| $k_{out}$ (/h) | 0.016 (16.4) |
| PCT_INI (ng/ml) | 1.334 (25.3) |
| $K_p$ (/h) | 0.05 (13.4) |
| α | 2.22 (0.01) |
| **Between subject variability** | |
| $\omega^2_{PCT\_INI}$(CV¶(%)) | 193.3 (8.55) |
| $\omega^2_{Kp}$(CV (%)) | 121.6 (3.43) |
| $\omega^2_{\alpha}$ (CV (%)) | 0.05 (49.2) |
| **Residual variability** | |
| $\sigma^2_{proportional}$ _(CV %)) | 50.6 (8.81) |
| $\sigma^2_{additive}$ __(ng/ml) | 0 FIX |

¶CV %: Coefficient of variation

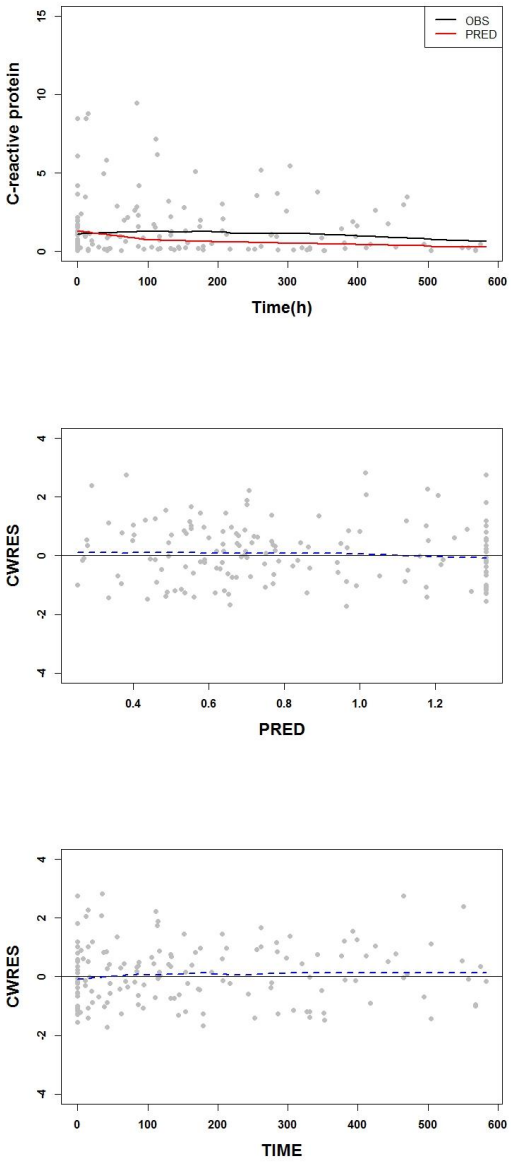



**Figure 12. Goodness of fit plots (Procalcitonin model) (Upper : PRED vs TIME, middle : CWRES vs PRED, lower : CWRES vs TIME).**
CWRES and PRED means conditional weighted residual errors and predictions.

Figure 12. Based on CWRES vs PRED and CWRES vs TIME plots, no significant bias appeared in our model. In PRED vs TIME plot, it was observed that there was almost no mismatch between observations and predictions.

**Table 6. Parameter estimates of absolute neutrophil count model.**

| **Model** | **ANC model** |
|---|---|
| **Parameter** | **Population estimate (%RSE)** |
| **Structural parameter** | |
| **$k_{tr}$ (/h)** | 0.010 (4.30) |
| **$K_{out}$ (/h)** | 0.013 (2.35) |
| **γ** | 1.028 (7.00) |
| **CIRC0 (cells/$10^9$/L)** | 6.476 (7.49) |
| **$K_p$ (/h)** | 0.001 (29.4) |
| **S_ANC** | 0.001 (17.1) |
| **α** | 0.355 (10.1) |
| **Between subject variability** | |
| **$\omega^2_{ktr}$(CV¶(%))** | 60.3 (7.56) |
| **$\omega^2_{CIRC0}$(CV (%))** | 88.8 (3.09) |
| **Residual variability** | |
| **$\sigma^2_{proportional}$ _(CV %))** | 33.7 (1.03)) |
| **$\sigma^2_{additive}$ _(cells/$10^9$/L)** | 0.019 (7.54) |

¶CV %: Coefficient of variation

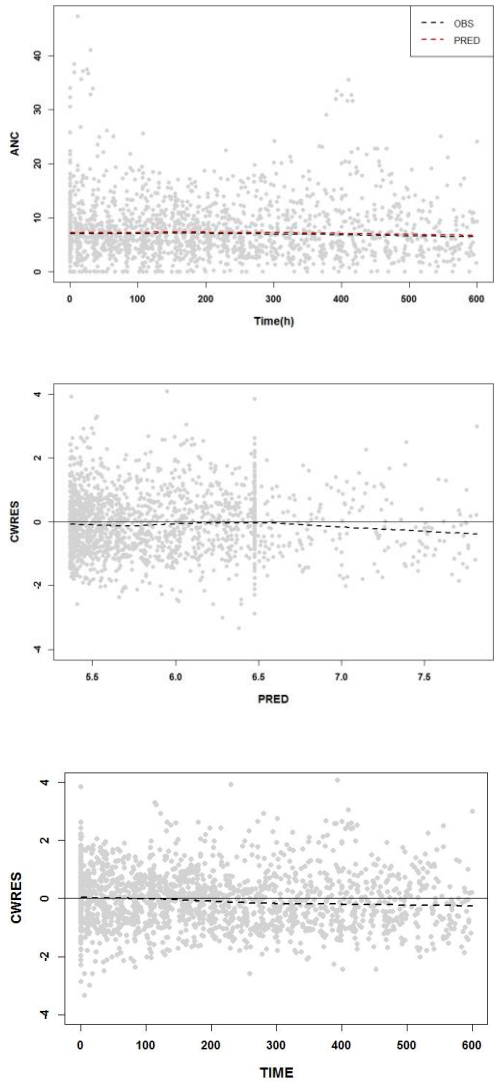



**Figure 13. Goodness of fit plots (Absolute neutrophil count model) (Upper : PRED vs TIME, middle : CWRES vs PRED, lower : CWRES vs TIME).**
CWRES and PRED means conditional weighted residual errors and predictions.

### D. Simulation results

As a user friendly tool to apply the developed model in clinical practice, a web-based application for simulating an optimal dosage regimen of vancomycin was developed using R shiny, as partly displayed in Figure 8. When patients' demographics, medical information, dosing frequency, and infusion duration are entered in a left panel, predicted concentration profiles of vancomycin are generated and drawn in a right Plot panel (Figure 13) and a summary of dose recommendation and biomarker levels assuming 2 weeks-therapy is presented in a right Result panel (Figure 14).

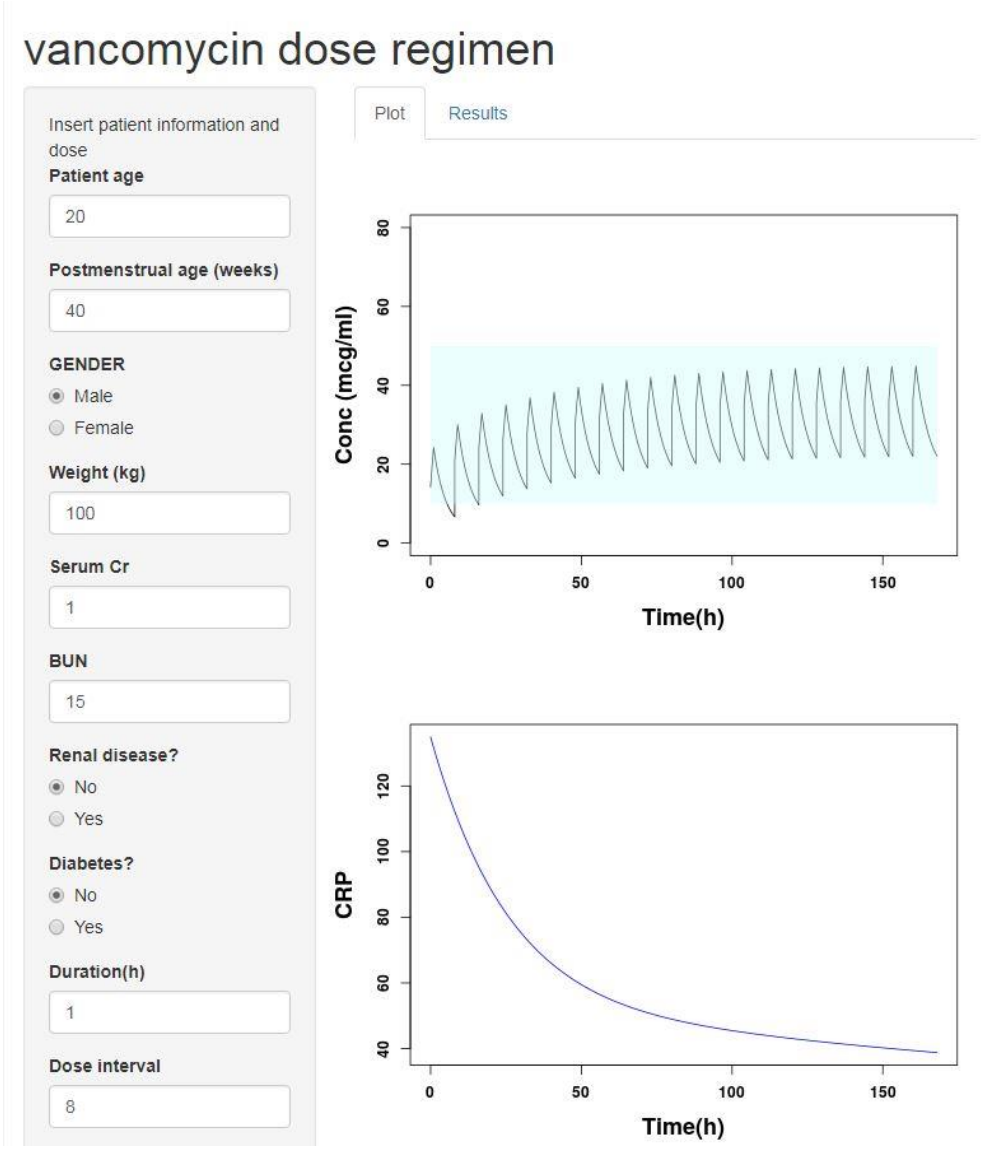



**Figure 14. Demonstration of an application for vancomycin concentration prediction using R shiny.**

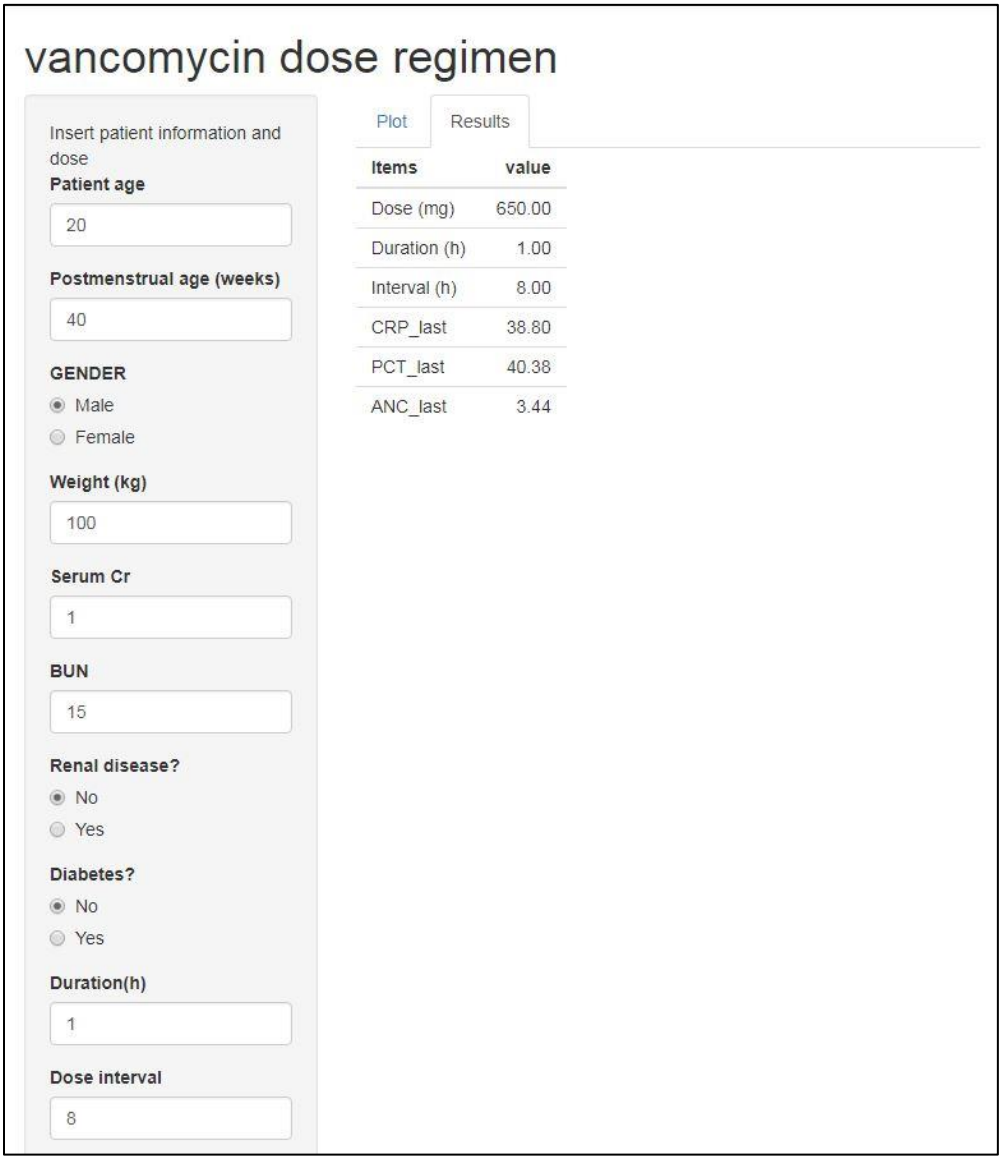



**Figure 15. Demonstration of an application for vancomycin dosing recommendation using R shiny.**

## IV. DICUSSIONS

Making a decision to discontinue antibiotic therapy is becoming a more important issue and non-invasive biomarkers such as CRP, PCT and ANC have been suggested as useful markers for monitoring patients' status.[44] Model development for predicting latent disease severity using easily measurable biomarkers allow clinicians to understand disease progression pattern, to prepare appropriate therapeutic regimens, and to make an evidence-based scientific decision. Furthermore, optimal dose regimen can be proposed by simulation with developed models, which can be a supportive tool for effective therapy in antibiotics.

In recent years, CRP and PCT have been suggested to be used in diagnosis and monitoring in order to distinguish bacterial infection from other diseases such as viral infection or inflammation.[38] Originally, these markers have been well-known as acute inflammatory proteins since substantial increase in CRP and PCT levels were observed in acute phase of inflammation. However, it has been reported that the levels of CRP and PCT rise even higher with bacterial infections- than viral infection or mild inflammation.[37] Moreover, there have been various difficulties in measuring bacterial burden at the infected site in our body and monitor changes of patients' status in real-time. For these reasons, many researches and/or guidelines have recommended to monitor the effect of antibiotic therapy using easily available serum biomarkers; such attempt may promote the utilization of modeling and simulation which can be designed to reflect real situations.[45,46] On the other hands, neutrophil has been traditionally regarded as a marker pertaining to immunologic response. When infection is detected in bloodstream by innate immune response, neutrophils move to infected extracellular tissue via extravasation, which lead to temporarily decreased neutrophils in bloodstream. Subsequently, decreased circulating levels of neutrophils become a signal to stimulate cell proliferation of

neutrophils in the bone marrow. Additionally, maturation of neutrophils is also enhanced, which is called left-shift.[40] In our study, it was presumed that infection-induced latent disease severity was a driving force to alter the dynamics of these biomarkers and the relationship between disease severity and biomarkers were assumed to be linear as disease status records were not available, particularly the bacterial burden. With this assumption, latent disease severity may simply reflect the bacterial burden or the combination of symptomatic inflammation and immune response caused by bacterial infection. This approach allows the developed model to focus on patients' symptoms and signs in terms of therapeutics, instead of focusing on the count of bacterial burden. Furthermore, our model has an advantage to provide optimal vancomycin dose based on patients' demographics since these biomarker models was linked with AUC calculated from an established PK model.

In our PK analysis, there are few noticeable points in regard to physiology. As listed in Table 3, creatinine clearance following age, maturation, BUN, sex, the presence of diabetes and renal diseases, aging effect were statistically significant covariates. First of all, creatinine clearance was used as renal function, which was modeled using serum creatinine based on physiology rather than calculated with equations because most of the formula to calculate renal function had limitations and was limitedly applied to sub-population. For examples, MDRD formula has been broadly used in estimating creatinine clearance but this formula has not been validated in special population including pediatrics, the elderly, and pregnant women.[47] Alternatively, Schwartz formula can be applied in calculating creatinine clearance for pediatrics. However, when pediatric and adult patients were analyzed at the same time, estimated creatinine clearance should be calculated by different formula, which will make a discontinuity of creatinine clearance at the age where pediatric become adults.[47] CKD-EPI could be a solution to this problem because it

covers all aged population and it is reported to be more accurate than MDRD formula.[48] However, it was empirically developed using about 8,000 patients and its prediction in several sub population was not validated.[49,50] In our model, creatinine production and creatinine clearance was modeled using a turn-over model which is widely used in PK-PD modeling. Creatinine clearance is determined by creatinine production rate that is changed over age and serum creatinine concentration assuming steady-state. This is intuitively comprehensive and can be simply used for all aged population. For validation of our method, a comparison with representative method to estimate renal function, particularly CKD-EPI, MDRD, and Cockcraft-Gault equation, was carried out for adult group. As displayed in Figure 15, our method showed good correlation with other methods and correlation coefficient was the highest, indicating that results from our method was quite comparable to others.

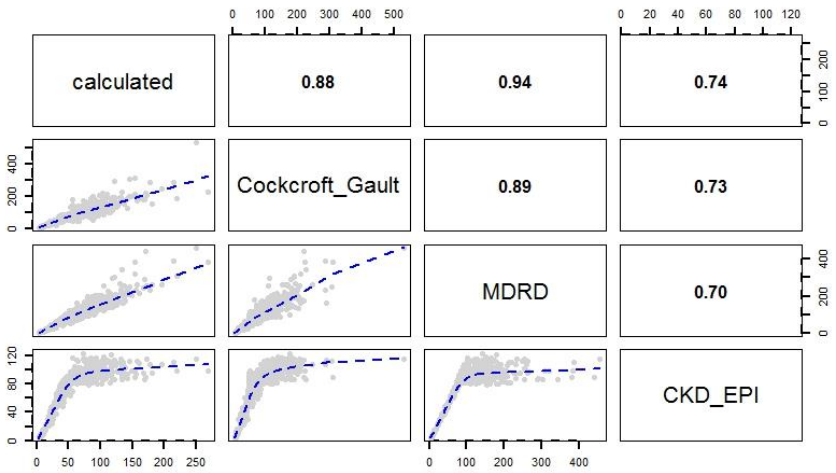



**Figure 16. Comparisons of a method for estimating renal function to other methods.**

Additionally, we compared the performance of our model to that of eGFR based model in predicting vancomycin concentrations of adult patients. CKD-EPI equation was used to calculate GFR. As a result, AIC values were 6558.659 for our model and 6888.123 for eGFR based model, which indicates that predictability of our model is superior to that of eGFR based model.

Secondly, physiological maturation in a lifetime was incorporated. Organ maturation and aging effect cannot be ignored in determining appropriate dose to avoid toxicity. In this study, maturation until age 4 was described by sigmoid function and aging effect was expressed by exponentially decreasing function, which was already validated in several studies. By doing so, our model can be applied in extrapolation for other age groups including pre-term since PMA was used to described maturation in renal clearance. Moreover, PMA50 corresponding to PMA of half-completed renal function was 50.65 weeks, which is consistent with the fact that maturation of glomerular filtration rate is completed within at latest 2 years old.[51,52] For the elderly, at the initiation of vancomycin therapy, lower dose was already recommended through previous researches and carried out in clinical practice due to enhanced volume of distribution and decreased renal function. [53,54] According to estimated parameters about aging effect on volume, the volume of distribution increases exponentially with the rate of 0.0096 per year after 40 year-old.

Third, potential factors to reduce renal clearance or to represent reduced renal function were also included. BUN is synthesized by liver but eliminated via renal route. As a result, increased BUN allows to make an inference about lowered renal clearance. It is well known that comorbidity such as diabetes and renal diseases is undoubtedly responsible for decrease in renal function. Gender effect was also plausible because an adjusting factor for female is often seen in formulae used to

estimate creatinine clearance. All in all, the developed PK model is physiologically feasible and its application for an optimal vancomycin dosing in various populations would be expected.

When it comes to vancomycin-induced renal toxicity, several probable mechanisms and the association between dose and prevalence of renal toxicity have been reported but it is still controversial.[14,55] The reduced creatinine clearance model empirically developed was able to improve model prediction and it is conjectured that prolonged therapy might be one of the reasons to lower renal function.[56] However, other risk factors such as high trough vancomycin concentration, concomitant treatment with nephrotoxic drugs, and prolonged admission were not tested due to the scarcity of information. Therefore, this renal toxicity is necessary to be more studied in further studies.

Although PK-PD model presented in this study shows fairly good prediction for most observations and is well supported by physiological principles, there are some limitations. First, there were no records of patients before drug treatment and the lack of pre-treatment or placebo data made it impossible to purely predict disease progression. In addition, the rise of biomarkers beyond normal range was failed to be captured, which ultimately led to obstacles in more mechanistic latent and biomarker models. Moreover, due to the sparse sampling of biomarkers and computation power, integrated biomarker models sharing latent disease severity were not successful. Also, our analysis was carried out using retrospective routine clinical data. In theory, it is hard to draw a strong inference through this kind of data analysis because there are many compounding factors. Therefore, additional validation with controlled clinical trials is needed to generalize our results. For optimal dose regimen, recovery of three biomarkers was more significantly affected by initial levels rather than drug dose and regimen because their size of effects was

not considerable. Alternatively, trough concentration and peak concentration were adopted for optimal dose for patients. In spite of these limitations, this modeling framework has a potential to give an insight about an effective vancomycin treatment in patient using non-invasive biomarkers.

## V. CONCLUSION

PK-PD model for optimal dose regimen of vancomycin in patients were well established and individualized vancomycin dose can be calculated using patients' demographics and disease information. In order to predict vancomycin concentration and disease progression over time using easily accessible measurements, especially CRP, PCT and ANC, this approach could be a supportive tool for a suggestion of optimal dose regimen for vancomycin therapy.

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ABSTRACT (IN KOREAN)

# Vancomycin 적정 용량 설계를 위한 혈중 약물농도 및 임상대리지표의 정량적 모델링

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국진주

본 연구는 vancomycin 치료를 받은 환자에게서 질병진행양상을 예측하는 약동-약력학 모델을 구축하며 이를 바탕으로 최적화된 용량을 제시하고자 한다. 2013년 세브란스 병원을 방문하여 vancomycin을 투여 받았고 치료적 약물농도 모니터링을 받은 환자들의 자료를 이용한 후향적 연구이다. 수집한 환자 정보는 vancomycin의 최고 및 최저 농도, 투약 정보, 인구학적 정보, C-reactive protein, procalcitonin, absolute neutrophil count 를 포함한 임상실험실결과 및 환자의 동반질환으로 이러한 정보는 모델의 모수에 유의한 공변량으로서 활용 가능한지 알아보는데 이용되었다. 약동학분석에서 1구획 모형 및 2구획 모형이 시도 되었고, allometry scaling이 사용되었다. 또한, 시간에 따른 신기능 감소가 유의한지도 평가되었다. 약력학분석에서는 turnover 모형 및 transit 모형이 평가되었으며, 수집되지 않은 bacterial 수는 latent variable로 취급하여 모형화 하였다. 약물의 효과는 latent로 대변되는 bacterial count로

인한 대리지표들의 생성을 억제를 가정하여 모델에 고려하였고, 최종적으로 이러한 방법을 통해 환자에서의 vancomycin 투여 후 약동학-약력학적 양상을 예측하였다. 본 연구에서 사용된 분석은 NONMEM 7.3과 R.3.2.2를 이용하여 진행되었다. 총 542명의 환자의 정보를 수집하였고, 130명의 환자에 대해서만 약동학-약력학 연구를 진행할 수 있었다. 약동학 모델 결과, 2구획 모형이 가장 적절하다고 판단되며, 공변량으로는 성별, 크레아티닌 청소율, postmenstrual age를 이용한 소아의 발달정도, BUN, 당뇨병력, 신질환 여부 등이 약물의 청소율에 영향을 미치는 것으로 확인되었으며, 약물의 분포용적에 대해 나이가 영향을 미치는 것을 확인하였다. 집단약동학적 관점에서 40세 성인 70kg를 기준으로 했을 때 약물의 청소율은 4.31 L/h, 분포용적은 38.6 L로 계산되었다. 약물에 의한 신기능의 감소는 통계적으로 유의했으며, 그 속도는 0.006 $day^{-1}$로 계산되었다. 약력학 모델에서는 CRP, PCT, ANC의 변화가 transit 모형에 의해 잘 기술되었다. 모든 모델의 모수들은 정밀하게 잘 추정되었으며 중대하게 편향되었다고 보이는 모수는 없었다. 개발된 모델을 바탕으로 R shiny를 이용하여 simulation을 할 수 있는 application을 성공적으로 만들었으며, 이러한 application을 통해 환자의 인구학적 정보 및 치료 정보를 이용하여 vancomycin 농도 및 임상대리지표의 추이를 예측할 수 있게 되었다. 개발된 약동-약력학적 모델은 추후 vancomycin의 비침습적인 대리지표를 이용한 최적화된 치료 계획을 세우는데 보조적인 수단으로 활용 될 수 있다.

핵심되는 말 : 반코마이신, 약동-약력학 모델, 최적 용량 설계