COMPARISON OF AREA UNDER THE CURVES FOR VANCOMYCIN FROM ONE- AND TWO-COMPARTMENT MODELS USING SPARSE DATA

Miss Nyein Hsu Maung

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Thesis Title	COMPARISON OF AREA UNDER THE CURVES FOR VANCOMYCIN FROM ONE- AND TWO-COMPARTMENT MODELS USING SPARSE DATA
By	Miss Nyein Hsu Maung
Field of Study	Clinical Pharmacy
Thesis Advisor	Assistant Professor Thitima Wattanavijitkul, Ph.D.

Accepted by the FACULTY OF PHARMACEUTICAL SCIENCES, Chulalongkorn University in Partial Fulfillment of the Requirement for the Master of Science in Pharmacy

..... Dean of the FACULTY OF PHARMACEUTICAL SCIENCES
(Assistant Professor RUNGPETCH SAKULBUMRUNGSIL, Ph.D.)

THESIS COMMITTEE

..... Chairman
(Associate Professor THITIMA PENGSUPARP, Ph.D.)

..... Thesis Advisor
(Assistant Professor Thitima Wattanavijitkul, Ph.D.)

..... Examiner
(TATTA SRIBOONRUANG, Ph.D.)

..... External Examiner
(Assistant Professor Janthima Methaneethorn, Ph.D.)

เนียน ซู เมือง :

การเปรียบเทียบพื้นที่ใต้โค้งสำหรับแวนโคมัยซินจากแบบจำลองหนึ่งและสองห้องโดยใช้ข้อมูลที่มีน้อย. (COMPARISON OF AREA UNDER THE CURVES FOR VANCOMYCIN FROM ONE- AND TWO-COMPARTMENT MODELS USING SPARSE DATA) อ.ที่ปรึกษาหลัก : ผศ. ภญ. ดร.ธิติมา วัฒนวิจิตรกุล

เภสัชจลนศาสตร์ของแวนโคมัยซินถูกอธิบายได้ด้วยแบบจำลองทั้งหนึ่งและสองห้อง แบบจำลองหนึ่งห้องที่สร้างจากข้อมูลการติดตามดูแลผู้ป่วยซึ่งมักเป็นข้อมูลระดับยาต่ำสุดมักถูกใช้ในการทำนายค่าพื้นที่ใต้กราฟความเข้มข้นกับเวลา (AUC) ซึ่งเป็นค่าที่ใช้ในการทำนายประสิทธิศักย์ของยาแวนโคมัยซิน ยังไม่มีการพิสูจน์ยืนยันว่าค่า AUC จากแบบจำลองหนึ่งห้องที่สร้างจากข้อมูลจำนวนน้อยสามารถเป็นตัวแทนของ AUC ที่แท้จริงได้หรือไม่ การศึกษานี้มีวัตถุประสงค์เพื่อเปรียบเทียบ AUC จากแบบจำลองหนึ่งและสองห้องที่สร้างจากข้อมูลจำนวนน้อย นำแบบจำลองที่มีการรายงานก่อนหน้ามาสร้างข้อมูลเต็มสำหรับผู้ป่วย 100 ราย คำนวณ AUC อ้างอิง (AUC ref) จากข้อมูลชุดนี้ และสร้างชุดข้อมูลจำนวนน้อยสองชุด คือ ชุดข้อมูลที่มีเฉพาะระดับยาต่ำสุด (trough only) กับชุดข้อมูลที่มีระดับยาสูงสุดและระดับยาต่ำสุด (peak-trough) สร้างแบบจำลอง 1 และ 2 ห้องจากชุดข้อมูลทั้งสองโดยใช้ NONMEM® คำนวณค่า AUC จากกราฟความเข้มข้นกับเวลาที่สร้างจากแบบจำลองโดยวิธีหาพื้นที่สี่เหลี่ยมคางหมู วิเคราะห์ความแตกต่างของ AUC กับ AUC ref จากมุมมองทางสถิติและทางคลินิก แบบจำลองสองห้องที่สร้างจากชุดข้อมูล peak-trough ทำนายค่า AUC ได้ใกล้เคียงค่า AUC ref แต่ที่สร้างจากชุดข้อมูล trough only นั้นแตกต่างจาก AUC ref อย่างมีนัยสำคัญ ค่าความแตกต่างเฉลี่ยระหว่าง AUC ref และ AUC จากแบบจำลองสองห้องที่สร้างจากชุดข้อมูล trough only สูงถึงร้อยละ 25.16 ($p < 0.05$) ซึ่งถือว่ามีนัยสำคัญทางสถิติ แบบจำลองหนึ่งห้องที่สร้างจากชุดข้อมูลทั้งสองชุดสามารถประมาณค่า AUC ได้อย่างเหมาะสม ค่าความแตกต่างเฉลี่ยมีค่าสูงถึงร้อยละ 4.38 และ 6.23 สำหรับชุดข้อมูล peak-trough และ trough only ตามลำดับ ดังนั้น แบบจำลองหนึ่งห้องที่สร้างจากข้อมูลจำนวนน้อยจึงมีความเหมาะสมที่จะใช้ทำนาย AUC ของแวนโคมัยซินในทางคลินิกปฏิบัติ

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Nyein Hsu Maung : COMPARISON OF AREA UNDER THE CURVES FOR VANCOMYCIN FROM ONE- AND TWO-COMPARTMENT MODELS USING SPARSE DATA. Advisor: Asst. Prof. Thitima Wattanavijitkul, Ph.D.

Vancomycin pharmacokinetics has been described by 1- and 2-compartment models. One-compartment models built from routine monitoring data, which were mainly trough samples, are commonly used to predict area under the curves (AUC), the useful indicator for vancomycin efficacy. The question stands whether AUCs from 1-compartment models with sparse data can sufficiently represent the true AUC. This study aimed to compare AUCs from 1- and 2-compartment models using sparse data. A previously published model was used to simulate full individual profiles for 100 patients. From these data, the reference AUC (AUC_{ref}) was calculated and two depleted datasets (trough-only and peak-trough) were also created. Both 1- and 2-compartment models were built from the depleted datasets using NONMEM®. AUC was calculated from concentration-time profiles of each model by linear trapezoidal method. Deviation of each AUC from the AUC_{ref} was examined from statistical and clinical perspectives. A two-compartment model from peak-trough data provided similar AUCs with the AUC_{ref}, but not that from trough-only data. The mean difference of AUC_{ref} and AUCs from the 2-compartment model with trough only data was up to 25.16% ($p < 0.05$) which were considered clinically significant. One-compartment models from both datasets could adequately estimate the AUCs with no significant differences ($p > 0.05$) from the AUC_{ref}. The mean differences were up to 4.38% and 6.23% for peak-trough and trough only data, respectively. Therefore, 1-compartment models from sparse data may be trustable to predict vancomycin AUC in clinical practice.

Field of Study:	Clinical Pharmacy	Student's Signature .....
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Chapter I

INTRODUCTION

1. Background and rationale

Vancomycin was discovered from *Streptomyces orientalis.* It is a glycopeptide antibiotic having bactericidal effect against a wide range of gram positive bacteria.[1] The use of vancomycin in hospital settings became popular in 1980s due to the emergence of methicillin resistant *Staphylococcus aureus* (MRSA).[2] Since vancomycin possesses poor oral absorption, it is mainly administered by intravenous route. Distribution of the drug varies throughout the body space. It is mainly eliminated by renal route with nearly 90% of the drug remained unchanged in urine.[3]

Due to its narrow therapeutic index and nephrotoxicity, it is advised to perform therapeutic drug monitoring (TDM) in patients receiving vancomycin treatment. Although the ratio of area under the curve to minimum inhibitory concentration (AUC/MIC) is the pharmacokinetic/pharmacodynamic (PK/PD) index of vancomycin, trough concentration (C_t) monitoring was the most useful practical method in clinical setting and C_t was used as a TDM parameter assuming it is an optimal surrogate for AUC.[4, 5] However, several studies later pointed out poor correlation between C_t and AUC.[6-9] For this reason, the consensus guideline has been updated with some changes suggesting to estimate AUC directly instead of using C_t as a marker in vancomycin TDM.[10] The revised consensus guideline and review by American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Pediatric Infectious Diseases Society (PIDS) and the Society of Infectious Diseases Pharmacists (SIDP) suggested to maintain AUC/MIC 400-600 for serious MRSA infections with isolates having MIC value of ≤1.

There are mainly two strategies to compute AUC.[11] In one approach, AUC is calculated from two samples collected within the same dosing interval (peak and

trough) using first order pharmacokinetic equations. The other is the prediction of AUC based on published population model parameters. Population models of vancomycin have been described as 1-compartment and 2-compartment models.[12-14] Clinicians tend to use 1-compartment models because of mathematical simplicity although vancomycin pharmacokinetics follows 2-compartment nature.[3] In fact, there are limited data comparing AUCs from 1- and 2-compartment models.

Shingde et al[15] assembled richly sampled vancomycin data from 30 patients with over 300 concentrations and developed both 1-and 2-compartment models. Single-dose AUCs derived from these models were compared. They found a statistically significant underestimation of AUC from 1-compartment model when compared to the reference AUC from 2-compartment model. But the difference was unlikely to be clinically significant with respect to dose adjustment.

Neely et al[7] applied richly sampled vancomycin data from 47 patients with 569 concentrations and developed a 2-compartment population model from which the reference AUC was derived. Then, they created trough-only and peak-trough datasets by removing other concentrations from the full dataset. And 2-compartment population models were again developed from these two depleted datasets. This offered average daily AUCs from trough-only model (AUC_T) and peak-trough sampled model (AUC_{PT}). Trough-only model under predicted the true AUC with 23% bias which is higher when compared to peak-trough model having 14% bias.

Population-based modeling approach is a useful tool to analyze the sparse sampling data and has been widely used to analyze TDM data which mainly contains trough concentrations. This study aimed to compare AUCs from 1- and 2-compartment models using trough-only dataset and peak-trough dataset simulated from a previously published robust 2-compartment model and to assess the clinical applicability of AUCs provided by the models constructed from trough-only dataset in terms of both 1- and 2-compartment modeling.

2. Objectives

To compare AUCs of 1-compartment model and 2-compartment model using trough-only dataset and peak-trough dataset and to assess the AUC predictability of the population models developed from trough-only data.

3. Scope of the study

This study used the 2-compartment population model introduced by Goti et al[16] to produce concentration-time profiles via simulation. Because this model used the largest sample size of around 1800 subjects with various clinical conditions, AUCs derived from this model will offer a good generalizability.

4. Hypothesis of the study

By using a non-linear mixed effect modeling approach, 1-compartment models developed from sparse data would sufficiently predict the AUC with reasonable bias and precision when compared to 2-compartment models. Both 1- and 2-compartment pharmacokinetic models using trough-only samples would yield biased AUC when compared to AUCs from peak-trough models.

5. Significance of the study

This study is the first study that compares three AUCs (AUC_{0-24}, AUC_{24-48} and average AUC_{24} within the first 48 hours) obtained after multiple doses from 1-compartment and 2-compartment models with sparse data considering TDM practice in real clinical setting. Thereby, decision could be made whether 1-compartment model should be used to predict AUC in clinical practice. Besides, this study examined the AUC predictability of population models developed from trough-only data.

Chapter II

LITERATURE REVIEW

1. Physicochemical properties of vancomycin

Vancomycin is a large tricyclic glycopeptide antibiotic (figure 1) having a molecular weight of 1448 g/mol and a strong solubility in water.[17]

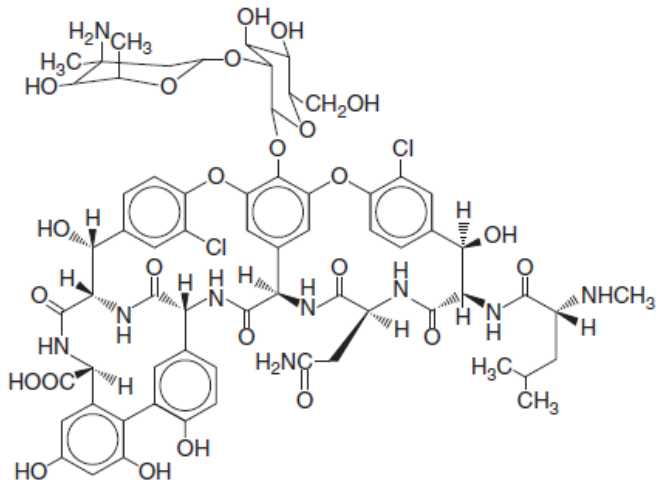


Figure 1 Chemical structure of vancomycin[18]

2. Pharmacokinetics of vancomycin

2.1 Absorption

Vancomycin has poor oral absorption with less than 5% of the drug absorbed into systemic circulation. Oral formulation is used for the treatment of enterocolitis caused by overgrowths of gram positive bacteria in gastro-intestinal tract. Because of poor oral absorption, it is mainly administered via intravenous route.[3, 19]

2.2 Distribution

The volume of distribution ranges from 0.4 to 1 L/kg for adults. As vancomycin exhibits multi-compartmental pharmacokinetics, concentration-time profile can be described by mono-exponential, bi-exponential and tri-exponential curves.[3] So far, 1- and 2-compartment models were reported by several pharmacokinetic studies.[12-14] Distribution half-life (alpha phase) takes 0.5-1 hour in 2-compartment models for patients with normal renal function.[3] Vancomycin has moderate protein binding effect with around 55% of the drug binding to albumin. Penetration of the drug into body space varies according to site of infection and is also influenced by the presence of inflammation. Normally, vancomycin has poor penetration into central nervous system (CNS) and lung tissues. But in patients with meningitis, inflammation improves penetration of the drug into CNS and higher concentration can be seen in cerebrospinal fluid.[3, 19]

2.3 Metabolism

Vancomycin metabolism is negligible in humans with non-renal route elimination of less than 5% of total body clearance.[17]

2.4 Excretion

Vancomycin is mainly excreted by glomerular filtration with over 80% of the drug remained unchanged in urine. Therefore, clearance of the drug is mainly influenced by renal function. Elimination half-life ranges from 6 to 12 hours in patients with normal renal function and it takes nearly a week in patients with end stage renal disease.[3, 19]

3. Summary of literature review on compartmental models of vancomycin

Compartmental pharmacokinetics of vancomycin has mostly been described as 1- and 2-compartment models. Broeker et al[14] evaluated the predictive performance of 31 vancomycin models including both 1- and 2-compartment models by encoding all models in NONMEM 7.4 and using patient data from two hospitals. First, they created a standard patient of 50-year male having body weight of 75 kg, height of 1.7 m and serum creatinine of 85 µmol/L. Then, pharmacokinetic profiles of the standard patient was calculated using 31 models and their concentration-time profiles were found to differ with a wide variability. Furthermore, 1221 concentrations of 292 patients were also predicted by inputting patient covariate values in 31 models. Predicted concentrations were compared to observed concentrations in terms of relative bias and precision (rBias and rRMSE). Of all, the 2-compartment model by Goti et al[16] was found to show the best predictive performance having rBias -4.41% and rRMSE 44.3%.

AUC_{0-24} for 292 patients were also predicted using those 31 models by means of two methods. The first method involved application of only covariate values in models. The second method was Bayesian forecasting by using 31 models and patient data such as drug concentrations and dosing history. The difference between AUCs from both methods were compared. Again, the model by Goti et al[16] offered the lowest bias between two AUCs showing the difference of only 2.22 mg.h/L. For all these, it was advised that the model by Goti et al[16] is the most suitable model to predict AUC in clinical setting.

The summary of 35 published vancomycin models (15 one-compartment models and 20 two-compartment models) is mentioned in table 1 and 2.[13, 16, 20-53] Pharmacokinetic parameters were calculated by inserting median or mean covariates of particular participants into final models. It can be seen that some studies were conducted on specific patient populations such as extremely obese patients or critically ill patients. Most of models discovered renal function markers and body

weight as significant covariates which are currently applied for dosing purposes in clinical practice. Among the models with generalized clinical conditions, the 2-compartment model by Goti et al[16] included the largest number of participants and their model also contained commonly used factors (renal function and body weight) as the significant covariates.

Table 1 One-compartment models of vancomycin

Study	Patients	No. of samples	Cl (L/h)	V_d (L)	Significant covariates
Buelga et al[20] (2005)	215 (hematological malignancy) Age (years) = 51.5 ± 15.9 Wt (kg) = 64.7 ± 11.3 CLCR (ml/min) = 89.4 ± 39.2	1004	5.79	63.41	-CLCR on Cl -TBW on V_d
Staatz et al[21] (2005)	102 (cardiothoracic surgery patients) Age (years) = 66 (17-87) Wt (kg) = 74 (44-110) CLCR (ml/min) = 60 (12-172)	408	2.94	85.1	-CLCR on Cl -TBW on V_d
Revilla et al[22] (2010)	191 (ICU) Age (years) = 61.1 ± 16.3 Wt (kg) = 73 ± 13.3 CLCR (ml/min) = 74.7 ± 58	569	3.37	59.86 (Scr < 1 mg/dL) 148.92 (Scr ≥ 1 mg/dL)	-CLCR, age on Cl -TBW, Scr on V_d (Scr was included as categorical coviate)

Study	Patients	No. of samples	CL (L/h)	V_d (L)	Significant covariates
Tanaka et al[23] (2010)	86 (MRSA infections) Age (years) = 74 (17-95) Wt (kg) = 53 ± 10 CLCR (ml/min) = 65 (14-261)	181	3.097	45.79	-GFR on Cl -TBW on V_d
Roberts et al[24] (2011)	206 (septic, critically ill) Age (years) = 58.1 ± 14.8 Wt (kg) = 74.8 ± 15.8 CLCR (ml/min/1.73m^2) = 90.7 ± 60.4	579	4.17	112.2	-CLCR on Cl -TBW on V_d
Chung et al[25] (2013)	678 (Korean, normal Scr) Age (years) = 57 (18-96) Wt (kg) = 60.8 (27-140) Scr (mg/dL) = 0.9 (0.39-1.2)	1373	4.9	46.2	-Cystatin C, age, TBW, Scr, sex on Cl -TBW, age, sex on V_d

Study	Patients	No. of samples	CL (L/h)	V_d (L)	Significant covariates
Deng et al[26] (2013)	72 (Chinese) Age (years) = 54.07 ± 18.36 Wt (kg) = 61.12 ± 10.70 CLCR (ml/min) = 82.09 ± 36.19	167	4.90	47.76	CLCR on Cl
Udy et al[27] (2013)	81 (Septic CRRT) Age (years) = 61 ± 15.6 Wt (kg) = 83.4 ± 22.1 No renal function measure	199	2.90	66.72	TBW on V_d
Adane et al[28] (2015)	29 (extremely obese) Age (years) = 43 (38.5-53) Wt (kg) = 147.9 (142.8-178.3) CLCR (ml/min) = 207.1 (157-229.8)	93	4.74	75.45	-CLCR on Cl -TBW on V_d

Study	Patients	No. of samples	CL (L/h)	V_d (L)	Significant covariates
Lin et al[29] (2016)	100 (Chinese post cranial meningitis patients) Age (years) = 51.6 ± 16.9 Wt (kg) = 59.1 ± 10 CLCR (ml/min) = 104.7 ± 43.9	179	7.56	101.0	CLCR on Cl
Medellin-Garibay et al[30] (2017)	54 (critically-ill) Age (years) = 65 ± 12.3 Wt (kg) = 75 ± 20.1 CLCR (ml/min) = 106.3 ± 64.5	641	2.64	77.25	-CLCR, mechanical ventilation on Cl -TBW on V_d

Study	Patients	No. of samples	CL (L/h)	V_d (L)	Significant covariates
Usman et al[31] (2018)	144 (hospitalized patients, TDM) Age (years) = 62 (16-88) Wt (kg) = 79.5 (40-177) CLCR (ml/min) = 89.8 (11.3 – 316.6)	256	2.32	19.2	CLCR on Cl
Heffernan et al[32] (2019)	27 (sepsis or septic shock, ICU) Age (years) = 37 (26-49.3) Wt (kg) = 75 (65.5 – 84.8) CLCR (ml/min/1.73m^2) = 107 (77.3 – 137.8)	At least one trough and peak per patient	7.23 (<72hrs) 5.75 (>72hrs)	53.36 41.61	CLCR by Jelliffe equation on Cl

Study	Patients	No. of samples	CL (L/h)	V_d (L)	Significant covariates
Jing et al[33] (2020)	99 (Chinese neurosurgical) Age (years) = 46.95 ± 12.71 Wt (kg) = 60.22 ± 11.77 sGFR (ml/min) = 115.8 ± 44.64	436	6.49 (Scr group)	60.2	Age, Wt, Cys C on CL
			6.40 (Cys C group)	62	Age, Scr on CL
Chu et al[34] (2020)	95 (Chinese ARC) Age (years) = 45 (30-57) Wt (kg) = 70 (60-80) CLCR (ml/min) = 175.90 (142.2-198.1)	186	8.52	155.4	Age on Cl

No. - number, Cl - clearance, V_d – volume of distribution, CLCR - creatinine clearance, TBW - total body weight, Scr - serum creatinine, ICU – intensive care unit, sGFR – glomerular filtration rate estimated from Scr, CRRT - continuous renal replacement therapy, ACR – augmented renal clearance, Cys C – cystatin C. Patient data were described as mean ± SD and median (range).

Table 2 Two-compartment models of vancomycin

Study	Patients	No. of samples	Cl (L/h)	V_c (L)	V_p (L)	Q (L/h)	Significant covariates
Yasuhara et al[35] (1998)	190 (MRSA infections) Age (years) = 64.3 ± 13.8 Wt (kg) = 52.3 ± 9.6 CLCR (ml/min) = 77.1 ± 50.9	1235	3.67	17.5	43.2	9.17	CLCR on Cl
Schaedeli et al[36] (1998)	26 (Patients on intermittent renal replacement therapy) Age (years) = 62 ± 15.2 Wt (kg) = 64.7 ± 13.6 CLCR (ml/min) = 4.5 ± 4.3	162	4.88	10.61	57.33	9.25	-CLCR, urea dialysis clearance on Cl -TBW on V_c and V_p

Study	Patients	No. of samples	CL (L/h)	V_c (L)	V_p (L)	Q (L/h)	Significant covariates
Llopis-Salvia et al[37] (2006)	30 (critically ill) Age (years) = 67 ± 21 Wt (kg) = 75 ± 12.5 CLCR (ml/min) = 68.45 ± 32	234	3.46	31.1	99	7.48	-CLCR, TBW on Cl -TBW on V_c and Vp
Thomson et al[38] (2009)	398 (patients on TDM) Age (years) = 66 (16-97) Wt (kg) = 72 (40-159) CLCR (ml/min) = 64 (12-216)	1557	3	48.6	52.71	2.28	-CLCR on Cl -TBW on V_c and V_p

Study	Patients	No. of samples	CL (L/h)	V_c (L)	V_p (L)	Q (L/h)	Significant covariates
Yamamoto et al[39] (2009)	106 (patients with gram+ infections and healthy volunteers) -Characteristics of 100 patients with infection Age (years) = 65.4±15.1 Wt (kg) = 52.6±12.7 CLCR (ml/min) = 79.6±41.8	356	2.88	25.14 (with infection)	60.6 (with infection)	8.81	-CLCR on Cl -TBW, infection status on V_c -Infection status on V_p
Sanchez et al[41] (2010)	141 (hospitalized patients) Age (years) = 55 ± 14.58 Wt (kg) = 73.2 ± 17.48 Scr (mg/dl) = 1.05 ± 0.65	254	3.14	20.72	33.1	8.25	-CLCR on Cl -TBW on V_c and Q -Age on V_p

Study	Patients	No. of samples	CL (L/h)	V_c (L)	V_p (L)	Q (L/h)	Significant covariates
Dolton et al[40] (2010)	70 (total) Age (years) = 72 (38-95) Wt (kg) = 67 (48.9-111) CLCR (ml/min) = 75±47.8 (Patients without burn, n= 33)	4 samples per patient	3.4 (without Burn)	65.5	69.9	4.54	-CLCR on Cl -TBW, severe burn on V_c -TBW on V_p
	Age (years) = 34 (15-88) Wt (kg) = 69 (425-116) CLCR (ml/min) = 124.4 ± 55.5 (Patients with burn, n=37)	2 samples per patient	5.9 (with burn)	34.3	71.95		
Purwonugroho et al[42] (2012)	221 (patients at any ward) Age (years) = 66.62 ± 18.38 Wt (kg) = 57.64 ± 11.62 CLCR (ml/min) = 35.07 ± 29.83	391	1.56	36.1	44.2	6.95	-CLCR on Cl -Age on V_c

Study	Patients	No. of samples	CL (L/h)	V_c (L)	V_p (L)	Q (L/h)	Significant covariates
Donadello et al[43] (2014)	22 (critically ill with and without ECMO) -Patients with ECMO (n= 11) Age (years) = 43 (19-59) Wt (kg) = 70 (46-85) CLCR (ml/min) = 64 (39-99) -Patients without ECMO (n= 11) Age (years) = 55 (24-64) Wt (kg) = 70 (47-95) CLCR (ml/min) = 61 (46-109)	66	2.22 (with CRRT) 3.7 (without CRRT)	31.8	57.1	3.6	CRRT on Cl
Mangin et al[44] (2014)	30 (critically ill with post sternotomy mediastinitis) Age (years) = 63 (35-81) Wt (kg) = 82 (62-104) Scr (mg/dl) = 1.56 (0.36-6.85)	359	1.58	25.6	79.56	5.71	-Sex, TBW, Scr, SAPSII-score on Cl -TBW on V_c and V_p -TBW, diabetes mellitus on Q

Study	Patients	No. of samples	CL (L/h)	V_c (L)	V_p (L)	Q (L/h)	Significant covariates
Li et al[45] (2015)	16 (postoperative neurosurgical patients) Age (years) = 46.8 ± 14 Wt (kg) = 69.8 ± 9.9 CLCR (ml/min) = 116.2 ± 31.5	284	7.98	15.2	46.1	36.97	CSF albumin on $Cl_{intercompartmental\ CSF}$
Li et al[46] (2016)	20 (postoperative neurosurgical patients) Age (years) = 45.25 ± 15.96 Wt (kg) = 68.9 ± 12.07 Scr (mcgmol/L) = 64.2 ± 13.28 Scr (mg/dl) = 0.73 ± 0.15	400	8.75	27.84	19.8	17.6	-CSF albumin on $Cl_{intercompartmental\ CSF}$ -TBW on V_c
Medellin-Garibay et al[47] (2016)	118 (trauma patients) Age (years) = 74.3 ± 14 Wt (kg) = 72 ± 15 CLCR (ml/min/1.73m^2) = 70.7 (16-273)	392	2.66	53.2 (age < 65) 77.04 (age > 65)	424.8	0.81	-CLCR, furosemide taking on Cl -TBW, age on V_c (age was inserted as categorical factor) -TBW on V_p

Study	Patients	No. of samples	CL (L/h)	V_c (L)	V_p (L)	Q (L/h)	Significant covariates
Moore et al[48] (2016)	14 (ECMO patients) Age (years) = 47 ± 16 Wt (kg) = 95 ± 27 CLCR (ml/min) = 84 ± 37	70	2.83	24.2	32.3	11.2	-CLCR on Cl -TBW on V_c and V_p
Li et al[49] (2017)	25 (postoperative neurosurgical patients) Age (years) = 50.2 ± 17 Wt (kg) = 69.4 ± 11.9 CLCR (ml/min) = 142.8 ± 51.7	262	7.25	11.9	21.5	15.46	-CLCR on Cl -Drainage amount, elapsed time on Cl_{CSF}
Alqahtani et al[50] (2018)	28 (open heart surgery) Age (years) = 51.7 ± 15.9 Wt (kg) = 79.6 ± 17 CLCR (ml/min) = 83.5 ± 29.3	168	6.13	40	3.88	0.22	-CLCR, albumin on Cl -TBW on V_c

Study	Patients	No. of samples	CL (L/h)	V_c (L)	V_p (L)	Q (L/h)	Significant covariates
Okada et al[51] (2018)	95 (patients undergoing stem-cell transplantation) Age (years) = 49 (17-69) Wt (kg) = 59.4 (39.4-104.5) CLCR (ml/min/1.73m^2) = 113 (47-253) Scr (mg/dl) = 0.62 (0.29-1.63)	285	4.25	39.2	56.1	1.95	-CLCR on Cl -TBW on V_c
Goti et al[16] (2018)	1812 Age (years) = 57 (17-101) Wt (kg) = 79 (33-255) CLCR (ml/min) = 62 (4-150)	2765	2.65	65.99	38.4	6.5	-CLCR and dialysis status on CL -Wt and dialysis status on Vc

Study	Patients	No. of samples	CL (L/h)	V_c (L)	V_p (L)	Q (L/h)	Significant covariates
Kim et al[52] (2019)	99 (Korean TDM) Age (years) = 64.8 ± 12.6 Wt (kg) = 59.70 ± 10.98 CLCR (ml/min) = 54.49 ± 36.25	328	2.21	32.6	45.8	3.06	cGFR on CL
Vu et al[53] (2019)	55 (Vietnamese, critically ill in ICU) Age (years) = 55 ± 18 Wt (kg) = 55.9 ± 11.1 CLCR (ml/min) = 76.5 ± 36.4	274	3.63	56.46	133.6	1.92	-CLCR on Cl -Allometric wt on Vc, Vp

No. - number, Cl - clearance, V_c – central volume of distribution, V_p – peripheral volume of distribution, Q – inter-compartmental clearance, CLCR - creatinine clearance, TBW - total body weight, Scr - serum creatinine, cGFR – glomerular filtration rate estimated using cystatin C, CRRT - continuous renal replacement therapy, ECMO – extracorporeal membrane oxygenation, CSF – cerebrospinal fluid. Patient data were described as mean ± SD and median (range).

4. Mechanism of action

Vancomycin inhibits bacterial cell wall synthesis (figure 2) by forming a complex with peptidoglycan precursors (D-alanyl-D-alanine), thereby, blocking incorporation of those subunits into peptidoglycan.[19]

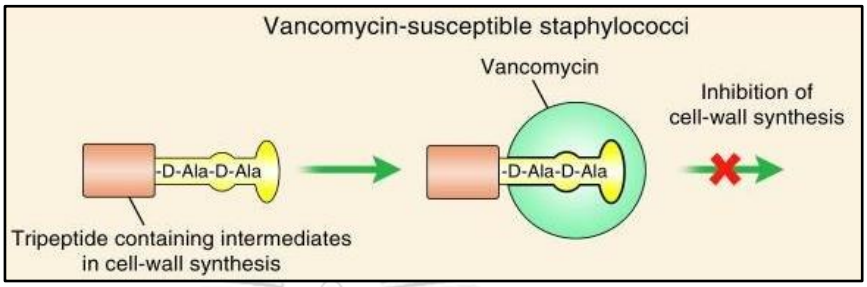


Figure 2 Mechanism of action of vancomycin[54]

5. Therapeutic uses and dosage

Vancomycin is used in infections caused by gram positive bacteria such as skin and soft tissue infections, bacteremia, endocarditis, pneumonia, meningitis, ventriculitis, osteomyelitis and pseudomembranous colitis. It plays an important role in the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections.[55]

Dosage varies according to renal function and weight. Usual adult maintenance dose is 15-20 mg/kg to be given 8 or 12 hourly with intermittent infusion. Loading dose of 25-30 mg/kg is sometimes recommended to achieve steady state in early treatment period. Continuous infusion is also sometimes given due to the ease of drug level monitoring.[4]

6. Untoward effects

Adverse drug reactions involving local phlebitis, Red Man Syndrome, neutropenia, thrombocytopenia, hypersensitivity, ototoxicity and nephrotoxicity are major concerns and are assumed to be dose related. It is suggested to infuse over at least 1 hour to avoid infusion-related side effects or antihistamine can be given

before the start of infusion. It is also recommended to perform therapeutic drug monitoring to prevent development of some dose-related side effects.[5]

7. Therapeutic drug monitoring of vancomycin and importance of area under the curve (AUC)

Therapeutic drug monitoring (TDM) is the practice of measuring drug levels and maintaining them within the therapeutic range for the purpose of dosage individualization. In the case of vancomycin, TDM is mainly provided for patients with high risk of nephrotoxicity, those who need long duration of treatment (greater than 3-5 days). Once-a-week monitoring is recommended for stable patients requiring long duration of treatment.[4, 5]

Having concentration-independent activity, the ratio of area under the curve to minimum inhibitory concentration (AUC/MIC) is more likely to be an indicative of efficacy and toxicity of vancomycin. AUC is the measure of drug exposure on a certain time interval. Considering some practical feasibility, steady-state trough concentration (C_t) monitoring was the most useful TDM method assuming C_t as a surrogate marker for AUC. And it was suggested to maintain C_t between 15-20 mg/L for MRSA infections and complicated infections like bacteremia, meningitis, endocarditis and osteomyelitis.[4] However, several studies[6-9, 56-62] later indicated that trough concentration tends out to be unreliable TDM parameter because of these three main reasons:

(1) Trough concentration was found to be poorly correlated with AUC

(2) Significant association between AUC and nephrotoxicity

(3) Significant association between AUC and other patient outcomes

Therefore, the updated consensus guideline (2020) no longer supports C_t monitoring in serious MRSA infections. A new decision was made to apply AUC monitoring in patients with serious MRSA infections and it is suggested to maintain AUC/MIC of 400-600 in MRSA infections with isolates having MIC ≤ 1.[10]

7.1 Poor correlation between trough concentration and AUC

Several studies showed therapeutic discordance between C_t and AUC. Patel et al[6] found a wide variability of AUC values given by similar trough concentrations from different dosage regimens (1 g, 1.5 g and 2 g twice a day) and the probability of achieving target AUC was 70% in spite of having lower C_t than the recommended value. Similarly, in the study conducted by Neely et al,[7] 50-60 % of simulated patients achieving AUC/MIC≥400 were found to have trough concentration less than 15 mg/L. (Table 3)

Unlike above studies, Bel Kamel et al[8] analyzed correlation of AUC and trough concentration by using actual patient data. And around one-third of patients showed AUC_{24} value of greater than 400 mg.h/L with trough concentrations less than 15 mg/l. Chart analysis conducted by Hale et[9] also pointed out that C_t > 15 mg/L would not necessarily be needed to obtain AUC/MIC≥400 in patients infected with MRSA having MIC value of 1 mg/L. (Table 4)

Table 3 Simulation studies showing trough concentration as a poor predictor of AUC

Authors (year)	Study Design	Objective	AUC Method	Results
Patel et al[6] (2011)	-Monte Carlo simulation from published 2-compartment model -Simulation across different dosage regimens-0.5 g, 1 g, 1.5 g and 2 g (q12 each) with assumed MIC values of 0.5-2 mg/L	To observe PD profile of the drug in response to guidelines	Steady-state AUC was calculated from integrated concentration-time profiles	70% of subjects with AUC/MIC ≥ 400 had C_t < 15 mg/L
Neely et al[7] (2014)	- Population pharmacokinetic analysis with Pmetrics 1.1.1 for R 3.0.1 - Simulation from 2-compartment model with 2 dosage regimens (5000 profiles each) with Cl_{CR} = 100 mL/min • 1 g inf over 1h q12 5days • 1.5 g inf over 1h q12 5days	To access whether assumption of C_t being a good surrogate for AUC is true or not	AUC was calculated from simulated concentration-time profiles with 1h interval	50-60% of subjects achieving AUC/MIC ≥ 400 had C_t < 15 mg/L assuming MIC of 1 mg/L

Table 4 Studies indicating trough concentration as a poor predictor for AUC with actual patient data

Authors (year)	Study Design	Objective	AUC Method	Results
Bel Kamel et al[8] (2017)	Retrospective analysis of TDM data (n=95, elderly) PK parameters estimated by Bayesian approach with BestDose	To analyze correlation between C_t and AUC and assess how well AUC could be predicted from C_t	AUC was estimated by Bayesian approach with BestDose	-Moderate correlation between AUC_{24} and C_t (R^2 = 0.51) -1/3 of patients achieved AUC target with C_t < 15 mg/L -C_t = 10.8 mg/L was optimal predictor for AUC_{24} ≥ 400 mg.h/L
Hale et al[9] (2017)	Retrospective chart review (n=100) with MRSA infections 94% of isolates had MIC 1 mg/L	To find association between attainment of AUC/MIC and different trough concentration ranges	AUC obtained via daily dose divided by Cl using published equation Cl = (0.79 CrCl + 15.4) ×0.06	52.4% of patients achieving AUC/MIC target attainment had C_t < 15 mg/L

7.2 Association between AUC and nephrotoxicity

After finding out trough concentration as a poor surrogate for AUC, several studies attempted to point out association between AUC and nephrotoxicity by conducting researches in clinical settings. Zasowski et al[57] found out the risk of nephrotoxicity increases by 3-4 times with daily AUC value between 600-800 mg.h/L (Table 5). Finch et al[56] and Neely et al[58] compared AUC-guided dosing strategy and trough-based dosing strategy. The former method was superior to the latter in terms of nephrotoxicity occurrence. Besides, AUC-based monitoring was also related to

shorter duration of therapy and fewer additional blood samples per patient in the study by Neely et al[58] (Table 6).

Table 5 Summary of the study by Zasowski et al[57]

Authors (Year)	Study design	Objective	AUC estimation method	Results
Zasowski et al[57] (2017)	Multi-center, retrospective cohort study	To observe association between AUC and nephrotoxicity	AUC was estimated by Bayesian method with ADAPT V	- AUC threshold of 600-800 mg.h/L was produced by CART analysis - 3-fold increase of nephrotoxicity in patients with $AUC_{24-48} \geq 683$, Poisson regression, RR = 2.982 (95%CI=1.293 to 6.878) - 4 fold increase of nephrotoxicity in patients with $AUC_{0-24} \geq 677$, Poisson regressing, RR = 3.734 (95% CI = 1.646 to 8.470)

CART analysis = classification and regression tree analysis

Table 6 Literature review of comparing trough-based monitoring and AUC-based monitoring

<table>
<tr><th>Authors (year)</th><th>Study design</th><th>Objective</th><th>Outcomes</th></tr>
<tr><td>Finch et al[56] (2017)</td><td>Single-center, retrospective quasi-experiment
N = 1280 (546 in C_t group and 734 in AUC group)</td><td>To determine incidence of nephrotoxicity in two groups</td><td>Association of AUC-based monitoring and lower nephrotoxicity
• by multivariable regression, Adjusted OR =0.52 (95%CI=0.34 to 0.80) p=0.003
• by Cox proportional hazard regression, HR=0.53 (95%CI=0.35 to 0.78) p=0.002</td></tr>
<tr><td rowspan="3">Neely et al[58] (2018)</td><td colspan="3">Prospective 3-year study
(n = 252)</td><td rowspan="3">-To compare AUC-guided dosing and C_t guided dosing
-To assess nephrotoxicity between those mentioned groups</td><td rowspan="3">Lower proportion of patients suffered nephrotoxicity in AUC-guided group - 0% in year 2, 2% in year 3 when compared with trough-based group (8%)
(Fisher’s exact test, p=0.01)</td></tr>
<tr><td>Year1</td><td>Year2</td><td>Year3</td></tr>
<tr><td>N=75
Trough based monitoring</td><td>N = 88
Bayesian AUC monitoring (from trough samples)</td><td>N = 89
Bayesian AUC monitoring (from optimally collected samples)</td></tr>
</table>

7.3 Association between AUC and other patient outcomes

It has already been known that AUC/MIC has an association with clinical and bacteriological outcomes in terms of therapeutic success and eradication of bacteria.[63]

Kullar et al[59] and Holmes et al[60] studied the association of AUC/MIC and patient outcomes. The rate of treatment failure was higher in patients with AUC/MIC ≤ 421 when compared to those above that cut off value according to the first study. Also, patients having AUC/MIC ≤ 373 were found to have 12% higher 30-day mortality in the latter study (Table 7).

Table 7 Literature review on association of AUC and patient outcomes

Authors (year)	Study design	Objective	AUC method	Results
Kullar et al[59] (2011)	Single-center, retrospective analysis, N = 320 with MRSA infections	To examine impact of exposure and patient outcomes	AUC = Daily Dose divided by Cl (from study of their institution)	AUC/MIC cut off = 421 from CART analysis Failure rate in subjects below cut off was higher than those above the cut off (61.2% Vs 48.6%, p = 0.038)
Holmes et al[60] (2013)	Observational study N= 182 with *S.aureus* bacteremia	To assess AUC/MIC≥400 is related to improved outcome or not	AUC=Dose/CL Cl=(0.79CrCl+15.4) ×0.06	AUC/MIC cut off = 373 from CART analysis Probability of survival in subjects above cut off was higher than those below the cut off (84.3% Vs 71.6%, p=0.043) by Kaplan-Meier curve and log-rank test

Moreover, there was significant association between AUC/MIC and treatment failure, persistent bacteremia and mortality in the meta-analysis conducted by Prybylski et al[61] which involves 14 cohorts with *Staphylococcus aureus* bacteremia. Regression analysis yielded AUC/MIC threshold of 418 mg.h/L. Patients above the threshold were found to have lower risks of treatment failure (OR=0.4, 95% CI=0.31 to 0.53), persistent bacteremia (OR=0.41, 95% CI=0.33 to 0.86) and mortality (OR=0.47, 95%CI=0.33 to 0.65).

Men et al[62] also conducted a meta-analysis which involves 9 cohorts having different types of serious infections with MRSA isolates. They evaluated the evidence of association between AUC/MIC and clinical outcomes in terms of mortality and treatment failure. Outcomes were compared between patient groups having targeted AUC/MIC greater than 400 and below. Patients with higher exposure were noticed to have lower mortality rate (RR=0.47, 95% CI=0.31 to 0.70 p<0.001) and treatment failure (RR=0.39, 95% CI=0.28 to 0.55, p=0.001) when compared to those below AUC/MIC 400.

8. Methods to predict AUC

Linear trapezoidal approach is the one which can predict the most precise AUC. But, a series of blood samples are needed to obtain AUC with linear trapezoidal approach and this is the reason which makes it impossible to implement the linear trapezoidal method in real clinical practice. Alternatively, there are a variety of methods to estimate AUC with reasonable precision and less bias ranging from specific AUC calculator created by each institution to commercially and freely available online software.[11] Of these, 2-sample pharmacokinetic equation method and Bayesian method are the most popular among researchers and clinical settings.

8.1 Simplified pharmacokinetic equation method

This strategy was originally introduced by Begg, Barclay and Duffull and it was dedicated for aminoglycosides.[64] Pai et al[65] modified this method which was later

renowned as Pai innovative approach in estimation of AUC for vancomycin. In this method, 2 serum levels (peak and trough) during steady state are required and they must also be collected from the same dosing interval so that mono-exponential pharmacokinetic equation could be applied for mathematical simplicity. There are two options in Pai innovative method.

As for the first option, elimination rate constant (K_e) was first derived from collected samples as below:

$$K_e = \frac{Ln\,(\frac{C1}{C2})}{t}$$

C1 = peak concentration

C2 = trough concentration

t = time difference between two concentrations

After this step, K_e can be used to obtain theoretical peak and trough concentrations through backward and forward extrapolations as follow:

$$Cmax = C1 \,.\, e^{k.(t1-t')}$$

Cmax = theoretical concentration at the end of infusion

t1 = sampling time of C1

t' = infusion time

$$Cmin = = C2 \,.\, e^{-k.(\tau-t2)}$$

Cmin = theoretical concentration at the end of dosing interval

τ = dosing interval

t2 = sampling time for C2

After extrapolations, AUC for one dosing interval can be calculated as follow:

$$AUC_{0\text{-}\tau} = \frac{t' \times (Cmax+Cmin)}{2} + \frac{Cmax-Cmin}{k}$$

Finally, AUC_{24} can be calculated by multiplying AUC of one dosing interval with the number of doses during 24-hr period. There was some area which could not be captured by this method and it was believed to under-predict the true AUC for a certain extent (figure 3). So, the authors also invented another option.

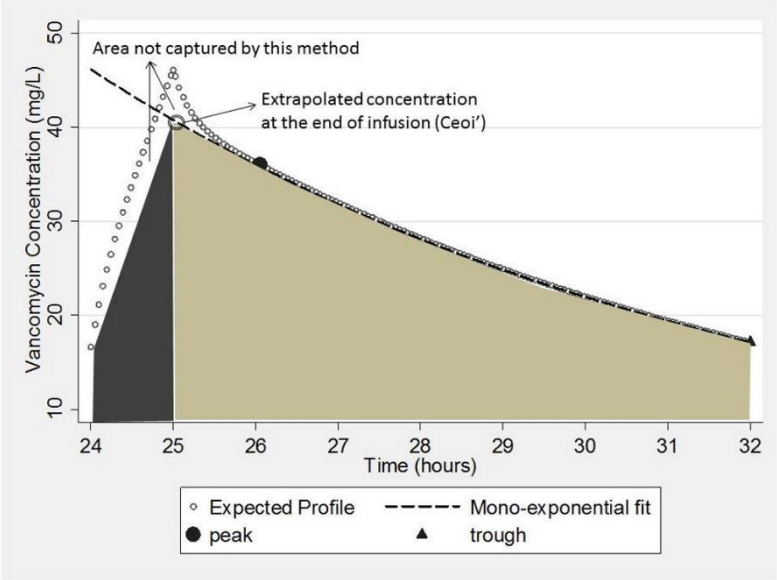


Figure 3 Area uncaptured by the first option[65]

As for the second option, AUC for one dosing interval can be calculated by using extrapolated concentration at the start of infusion (Csoi) and AUC_{24} can be obtained as mentioned above.

$$\text{AUC}_{0\text{-}\tau} = \frac{Csoi - Cmin}{k}$$

$$\text{Csoi} = \text{C1} \cdot e^{k.(t1)}$$

In contrast to the first option, AUC_{24} appeared to over predict the true AUC for a slight amount (figure 4).

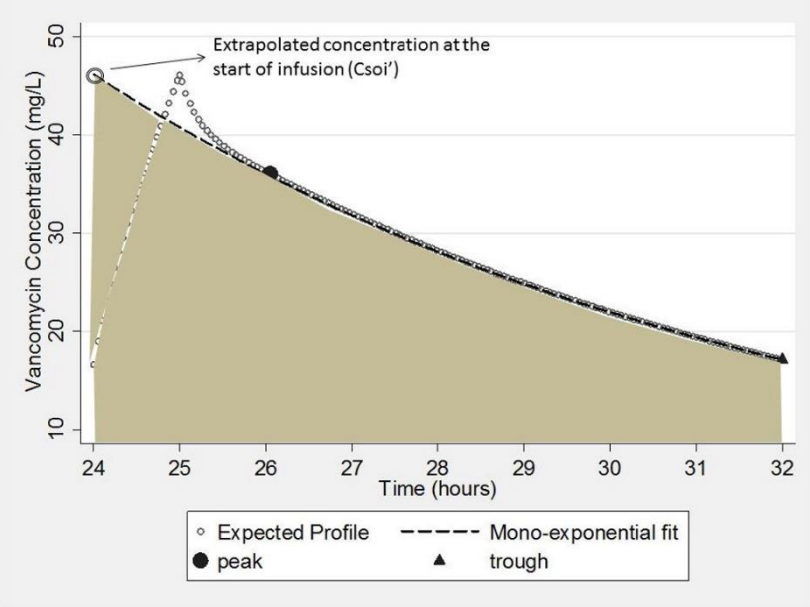


Figure 4 A slight overprediction of AUC by the second option[65]

Suchartlikitwong et al[66] applied these two options to determine their predictability of AUCs for vancomycin in clinical settings and the first option was found to be superior to the second one. Their study involved 43 pediatric patients with normal renal function. Vancomycin was given as intermittent infusion over 1-2 hours every 6 hour. For two-sample equation method, peak and trough concentrations were collected after the fourth dose. Peak concentrations were collected at 2 hours after the completion of infusion and trough concentrations were collected at 30 minutes before the subsequent dose. Using the mentioned option 1 and option 2 along with these samples, two AUCs were obtained. Then, they analyzed the agreement between these two AUCs and their reference AUC by means of Bland-Altman analysis. Reference AUC was calculated from 1-compartment intermittent short infusion model as follow:

$$AUC_{24} = \frac{Total\ daily\ dose}{CL}$$

$$CL = \frac{Dose\ (mg)\left(1 - e^{-kt_{inf}}\right) e^{-k(t-t_{inf})}}{C_t . t_{inf} . (1 - e^{-k\tau})}$$

AUC_{24} = area under the curve over 24 hours (mg.h/L)

CL = clearance (L/h)

K = rate constant ($hours^{-1}$)

t_{inf} = infusion time (hours)

C_t = concentration at certain time t (mg/L)

t = sampling time (hour)

τ = dosing interval (hour)

According to Bland-Altman analysis, AUC obtained from the option 1 showed less bias than the AUC from the option 2 when comparing to the reference AUC. In other words, the option 1 provided the bias of 1.3 mg.h/L and the option 2 offered the bias of -72.1 mg.h/L.

8.2 AUC estimation by Bayesian software

AUC estimation by Bayesian approach is based on Bayes' theorem in which parameters are included as probability distributions instead of a single value. In this method, known parameter distribution and variability from previous population models such as clearance (Cl) or volume of distribution (V_d) are inputted as Bayesian priors into the software. Inputted parameters are again re-estimated based on patient data such as blood samples, dosing history and demographic figures to gain revised version of parameter distribution (Bayesian conditional posteriors). Unlike simple pharmacokinetic equation method, clinicians do not need to pick serum levels at the steady state.[11] Only one random concentration is enough to predict AUC with the aid of Bayesian software.[11, 67] However, the revised consensus guideline suggested to use at least one trough sample with the belief that including trough concentration alone or a pair of peak and trough concentrations offers more precise AUC.[10]

There are a wide range of software available for this method, say, Adult and Pediatric Kinetics (APK), BestDose, Dose Me, InsightRx, Pmetrics, Precise PK, Rxkinetics, Target Intervention Software Program and MM-USCPACK. Among the aforementioned software, only BestDose and Target Intervention Software Program are freely available. Some published population pharmacokinetic models have already been

embedded in these software. The level of precision and bias of estimating AUC between these software may vary due to the different input models and the samples. Of note, it has been said that clinicians should be aware of the chosen population model to input as a prior into the software.[68, 69] In other words, patients to whom dosing individualization wants to be performed should have similar characteristics with participants in the model. Furthermore, it is still unclear that AUCs yielded from 1-and 2-compartment models inputted as priors have similar precision or not. And there are very few studies that compare AUCs from 1-compartment model and 2-compartment model.

8.3 Comparing Bayesian approach and simplified pharmacokinetic equation approach

Both Bayesian approach and 2-sample equation method were proved to have sufficient predictive ability when estimating the true AUC. Alsultan et al[70] compared two AUCs derived from Bayesian method using only one trough concentration and 2-sample based equation method to the reference AUC in pediatric patients who are 1-12 years old. First, 1-compartment model was built from 76 patients with the use of Monolix 4.3. Using that model, concentration-time profiles for 500 virtual patients were created via simulation and the reference AUCs were calculated from those profiles with trapezoidal rule. Using trough sample collected at 5.5 h ($C_{5.5}$), patient data and their model parameters as Bayesian priors, clearance (CL) was revised (Bayesian posterior). And revised CL was used to obtain Bayesian AUC as follow.

$$AUC_{0-24} = \frac{total\ dose\ in\ 24\ hours}{revised\ CL}$$

In 2-sample equation method, peak concentrations were obtained at 1-hour after the end of infusion and trough concentrations were collected at 30 minutes before fifth dose. AUCs were calculated according to equations by Pai innovative method. The comparisons of AUCs were conducted in terms of coefficient of determination (R^2),

bias, and precision. Bias and precision were calculated according to the following equations.

$$\%\ Bias = \frac{\sum(predicted\ AUC - observed\ AUC)}{N} \times \left(\frac{100}{mean\ AUC}\right)$$

$$\%\ Precision = \sqrt{\frac{\sum(predicted\ AUC - observed\ AUC)^2}{N}} \times \left(\frac{100}{mean\ AUC}\right)$$

Predicted AUC = AUCs from Bayesian approach and 2-sample equation approach were

Observed AUC = Reference AUC

N = number of observed AUCs

Mean AUC = the average value of predicted AUC and observed AUC

Both AUCs from Bayesian approach and 2-sample equation method showed strong correlations with the reference AUC having R^2 values of 0.93 and 0.92 respectively. AUCs obtained by Bayesian approach showed bias of -3.19% and precision of 9.6%. AUCs from 2-sample equation method offered bias of 0.71% and precision of 10.5%.

Turner et al[68] also compared AUCs from Bayesian approach and simplified pharmacokinetic equation approach to the reference AUC using adult data. The study involved rich data from previously published study with 19 critically ill participants. The original dataset consisted roughly of 6 samples per patient – collected during infusion, at the end of infusion, 1 hour post infusion, 2 hours post infusion, 5 hours post infusion and immediately before the next dose. Reference AUC (AUC_{ref}) was obtained from that full data set using linear-log trapezoidal formula. They also examined the variability of AUCs between five Bayesian software programs – Adult and Pediatric Kinetics (APK), BestDose, DoseMe, InsightRx and Precise PK. Researchers assessed Bayesian AUCs from different sampling designs. In this case, five subsets of dataset with different sampling designs were created. Two subsets included one sample per patient - trough only subset giving AUC_T and another

subset used samples at 5-hour post infusion level giving AUC_{5h}. Three remaining subsets include two samples per patient – trough and peak from 1-hour post infusion ($AUC_{T,1h}$), trough and peak from 2-hour post infusion ($AUC_{T,2h}$), trough and the sample collected 2.8 hours before the trough level ($AUC_{T,next}$). Therefore, each Bayesian software program yielded five Bayesian AUCs with different sampling designs. AUC_T and AUC_{5h} provided similar estimates in all programs except in APK. Therefore, each of remaining Bayesian AUCs except AUC_{5h} was compared to AUC_{ref} in terms of bias and accuracy (table 8 and 9). Bias was calculated by the following equation in terms of percentage.

$$\%\ Bias = \frac{|AUC_{pred} - AUC_{ref}|}{AUCref} \times 100$$

AUC_{pred} = AUC predicted from each Bayesian software

AUC_{ref} = reference AUC calculated from full dataset using log-linear trapezoidal rule

Table 8 Bias of Bayesian AUCs when compared to the reference AUC in the study by Turner et al[68]

Software	AUC_T	$AUC_{T,1h}$	$AUC_{T,2h}$	$AUC_{T,next}$
APK	13.1 (7.4 – 18.9)	-	-	-
BestDose	11.2 (5.1 – 18.3)	8.1 (3.6 – 18.3)	8.8 (4.4 – 11.6)	10.6 (5.7 – 20.2)
DoseMe	21.2 (16.3 – 24.6)	8.4 (4.6 – 13.2)	13.3 (6.6 – 16.1)	16.8 (13.8 – 21.0)
InsightRx	16.4 (11.8 – 22.6)	12.2 (8.0 – 16.9)	12.6 (9.1 – 14.5)	13.9 (9.5 – 22.1)
Precise PK	5.1 (3.0 – 11.2)	8.9 (1.8 – 12.2)	4.7 (2.9 – 12.8)	5.2 (3.3 – 8.9)

Biases are described as median percentage (25^{th} percentile to 75^{th} percentile). From APK, AUCs estimated with 2 levels were assumed unreliable by researchers due to errors during analysis.

Accuracy was calculated in terms of the median ratio of predicted AUC to the reference AUC (AUC_{pred} /AUC_{ref}). The ratio value greater than 1 means overestimation and less than 1 means underestimation.

Table 9 Accuracy of Bayesian AUCs when compared to the reference AUC in the study by Turner et al[68]

Software	AUC_T/AUC_{ref}	$AUC_{T,1h}/AUC_{ref}$	$AUC_{T,2h}/AUC_{ref}$	$AUC_{T,next}/AUC_{ref}$
APK	0.87 (0.81 – 0.94)	-	-	-
BestDose	1.01 (0.84 – 1.08)	1.03 (0.86 – 1.06)	1.02 (0.91 – 1.06)	1.01 (0.82 – 1.06)
DoseMe	0.79 (0.75 – 0.84)	0.92 (0.87 – 0.97)	0.87 (0.84 – 0.93)	0.83 (0.79 – 0.86)
InsightRx	0.84 (0.77 – 0.88)	0.88 (0.83 – 0.92)	0.87 (0.86 – 0.91)	0.86 (0.78 – 0.91)
Precise PK	1.03 (0.92 – 1.05)	1.07 (1.01 – 1.12)	1.04 (1.01 – 1.12)	1.03 (0.95 – 1.06)

Date were described as median (25^{th} percentile to 75^{th} percentile). From APK, AUCs estimated with 2 levels were assumed unreliable by researchers due to errors during analysis.

Looking above AUCs estimated with five Bayesian software using only one trough sample, bias ranges from 5.1 to 21.2% and accuracy ranges from 0.79 to 1.03. Among these software, Precise PK showed the least bias of 5.1%.

They also predicted AUCs by means of 2-sample pharmacokinetic equations based method with three sampling designs - trough and peak from 1-hour post infusion ($AUC_{T,1h}$), trough and peak from 2-hour post infusion ($AUC_{T,2h}$), trough and the sample collected 2.8 hours before the trough level ($AUC_{T,next}$). Bias and accuracy of AUCs estimated by PK equation method in comparison of AUC_{ref} are mentioned in

table 10. This PK equations also offered similar estimates of AUCs when compared to AUC estimates from Bayesian method.

Table 10 Bias and accuracy of AUCs from PK equations when compared to the reference AUC in the study by Turner et al[68]

% Bias			
PK equations	**$AUC_{T,1h}$**	**$AUC_{T,2h}$**	**$AUC_{T,next}$**
Equation option 1	6.5 (2.0 – 12.2)	7.1 (3.3 – 11.9)	15.1 (10.8 – 19.1)
Equation option 2	11.0 (3.9 – 14.4)	5.5 (1.3 – 10.1)	11.3 (7.6 – 15.3)
Accuracy			
PK equations	**$AUC_{T,1h}/AUC_{ref}$**	**$AUC_{T,2h}/AUC_{ref}$**	**$AUC_{T,next}/AUC_{ref}$**
Equation option 1	1.0 (0.93 – 1.05)	0.94 (0.88 – 0.97)	0.88 (0.81 – 0.93)
Equation option 2	1.09 (0.96 – 1.14)	0.98 (0.92 – 1.01)	0.89 (0.85 – 0.97)

Date were described as median (25^{th} percentile to 75^{th} percentile).

All in all, both Bayesian and PK equation methods were assumed as reliable approaches to predict AUC according recent studies.[42, 68, 70] Bayesian method is preferred where technical aid and experts are readily available when compared to 2-sample equation approach due to some superiorities over the later method.[10, 11] Benefits and drawbacks of these two methods are summarized in table 11.

Table 11 Advantages and disadvantages of simplified pharmacokinetic equation method and Bayesian approach for prediction of AUC

Method	Advantages	Disadvantages
Simplified pharmacokinetic equation method	Easy to use by inputting formula into excel spreadsheet	-More levels (peak and trough) are required when compared with Bayesian approach -Not adaptive to physiologic changes as samples were collected from one dosing interval at steady state
Bayesian approach	-Require only one sample regardless of sampling time (might be advantageous especially for neonates, pediatrics and ICU patients) -Dose optimizing could be performed at early period because of no requirement to wait until steady state -Adaptive to physiologic changes as covariates like creatinine clearance (CrCl) representing patient's renal function can be inputted into software	-Extensive training is required to use complicated software -Some software are not freely available

9. Comparison of AUCs from rich-data and sparse-data models

Neely et al[7] tried to compare AUCs from 2-compartment models using trough-only and peak-trough samples (figure 5). They extracted data from three previous studies with rich samples and built 2-compartment models by Bayesian estimation with the use of Pmetrics 1.1.1 for R 3.0.1. Their model gave parameter distributions (Bayesian posteriors) of linear elimination rate constant (K_e), volume of central compartment (V_c), transfer rate constants between compartments- K_{cp} (from central to peripheral) and K_{pc} (from peripheral to central). From these parameter distributions, concentration-time profiles with 12-minute intervals were created for each subject. Reference AUC (AUC_{full}) was calculated from these full concentration-time profiles by using trapezoidal method.

Then, only trough concentrations were remained in the data set by setting other concentrations as missing value which is zero and built a 2-compartment model from this data depleted dataset. Concentration near 1 hr before next dose was assumed as trough concentration. AUC was calculated as before (AUC_T).

Another data depleted version was also created by removing non-trough and non-peak concentrations from the full dataset. Concentrations around 1 hr post infusion were remained as peak concentrations. Another 2-compartment model was built from this dataset containing only peak and trough concentrations. AUC was estimated as above (AUC_{PT}).

AUC_T and AUC_{PT} were compared to the reference AUC by Wilcoxon signed-rank test and linear regression. AUC_T was found to underestimate the true AUC by 23% (95% CI=11 to 33%, p=0.0001) and AUC_{PT} also underestimated the true AUC by 14% (95% CI=7 to 19%, p<0.0001).

This points out that models constructed from trough-only data could under estimated the true AUC with more biased than AUC from peak-trough sampled models.

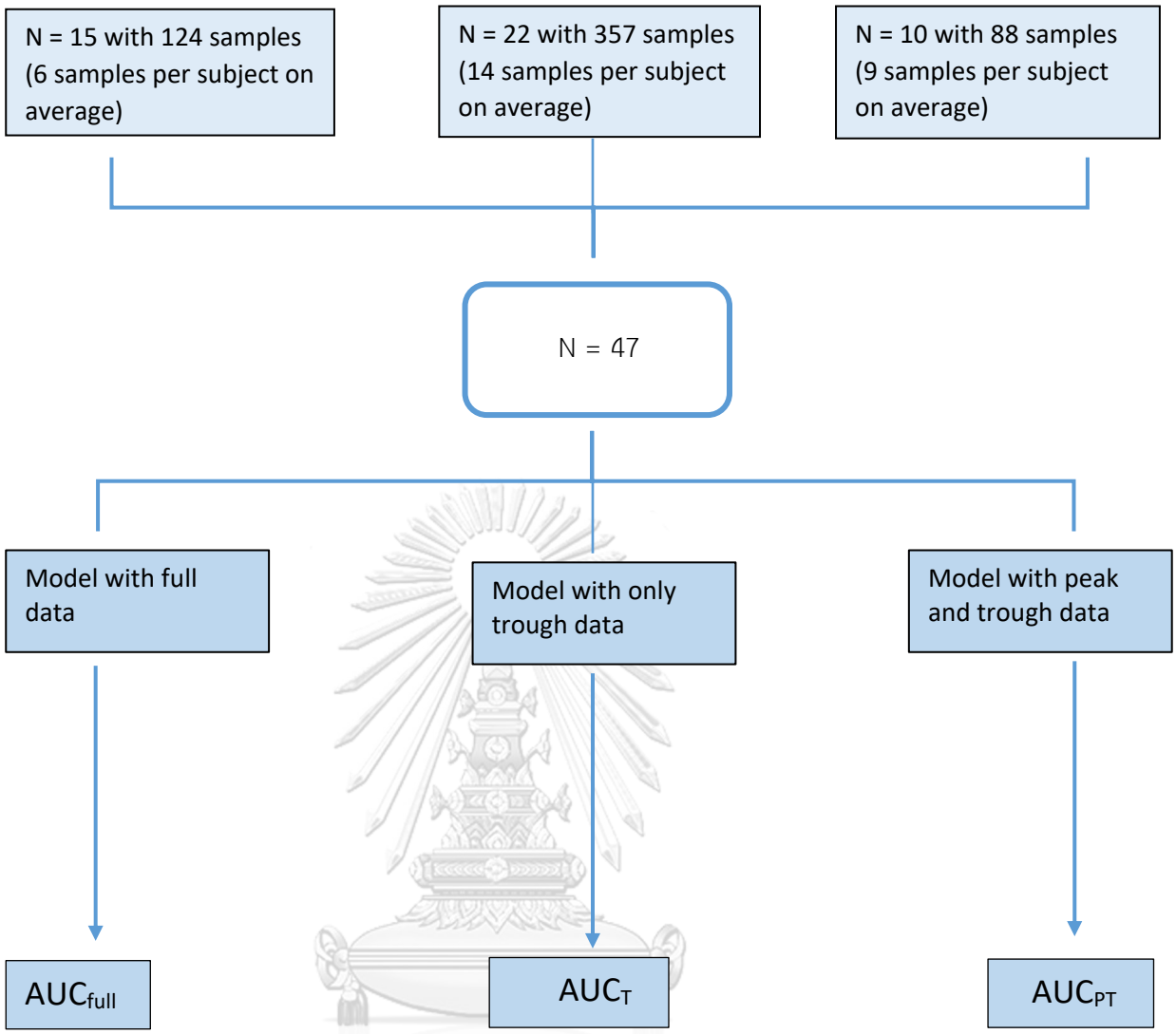


Figure 5 Brief illustration of AUCs derivation in the study by Neely et al[7]

10. Comparisons of AUCs from non-compartmental and compartmental models

The study conducted by Shingde et al[15] was the first study attempting to compare single-dose AUCs from non-compartmental models and 1-, 2- and 3-compartment models. They combined extensively sampled data from three different studies and analyzed the data with the use of PK solver 2.0 which is an add-in software for Microsoft Excel. Model fits were based on Akaike information criterion (AIC) and visual inspection of residual plots for 1- and 2-compartment models. Due to incomplete convergence, 3-compartment model was excluded from the study. Therefore, AUCs from non-compartment model (AUC_N), 1-compartment model (AUC_{1CMT}), and 2-compartment model (AUC_{2CMT}) were compared by setting AUC_{2CMT} as a gold-standard (reference AUC).

As for the outcomes from statistic perspective, AUC_{1CMT} and AUC_{2CMT} were inspected to be significantly different while AUC_N was similar to AUC_{2CMT}. There was a slight underestimation of AUC from 1-compartment model when compared to both AUC_{2CMT} and AUC_N (8.3% and 7.2%, respectively).

From clinical perspective, these differences were considered to be insignificant when using AUC values of 400-600 mg.h/L as the therapeutic target and 700 mg.h/L as the threshold for nephrotoxicity. To be clear, the authors accepted the difference between AUCs up to 20% according to the following equation.

$$\frac{700 - 600}{600} \times 100 = 17\% \cong 20\%$$

For these reasons, the investigators suggested that 1-compartment model can sufficiently predict the true AUC with a negligible imprecision. The summary of this study is described in table 12.

Table 12 Summary of the study by Shingde et al[15]

Objective	Study design	AUC estimation methods	Results showing AUC values (mean ± SD) and their difference (mg.h/L)
To compare single-dose $AUC_{0-\infty}$ from 1-, 2- and 3-compartment models and non-compartment models	Retrospective pharmacokinetic data analysis from combined data of 3 different studies (N=30) n_1 = 10 (21 samples per patient) n_2 = 11 (5 samples per patient) n_3 = 10 (8 samples per patient) AUCs were compared by 1-way repeated measures analysis of variance and post-hoc analysis (Tukey contrasts with Bonferroni correction) with the use of R 3.5.0.	For AUC_N, data were fitted by non-compartmental infusion model and AUC_N was calculate by linear ascending, log-linear descending trapezoidal approach For compartmental AUCs, data were fitted by compartmental modelling Concentration-time profiles and AUCs were calculated by using equivalent standard PK equations.	AUC_N = 180 ± 86 AUC_{1CMT} = 167 ± 79 AUC_{2CMT} = 183 ± 88 $AUC_{2CMT} - AUC_{1CMT}$ =15.1 ($p = 5.4 \times 10^{-14}$) $AUC_{2CMT} - AUC_N$ = 2.1 ($p = 0.85$) $AUC_N - AUC_{1CMT}$ = 13.0 ($p = 1.3 \times 10^{-10}$)

Chapter III

Methodology

1. Study Design

This is a pharmacokinetic study employing simulated profiles conducted using a previously published robust model. The overview of the study design is illustrated in figure 6.

2. Original Study

Broeker et al[14] evaluated the predictive performance of 31 vancomycin models by encoding and processing all models in NONMEM 7.4. The 2-compartment model by Goti et al[16] showed the best predictive performance and provided the most precise AUC. Furthermore, it is believed to offer a good generalizability as it was developed from the largest sample size composed of 1812 adult patients with 2765 samples. Also, they found creatinine clearance and body weight as significant covariates, which are the common factors used for dosing purposes in clinical practice. For all these reasons, the model by Goti et al[16] was used in the simulation process.

Their model was parameterized by clearance (Cl), central volume of distribution (V1), peripheral volume of distribution (V2) and inter-compartmental clearance (Q). Inter-individual variability (IIV) was described by exponential function and residual error model was described by a combined additive and proportional error model. Creatinine clearance (CrCL) and the presence of dialysis (DIAL) were found to be significant covariates for Cl. V_c was influenced by body weight (WT) and the presence of dialysis. The final model is as follow:

$$TVCL\ (Lh^{-1}) = 4.5 \times \left(\frac{CrCL}{120}\right)^{0.8} \times {\theta_3}^{DIAL}$$

$$TVV1\ (L) = 58.4 \times \left(\frac{WT}{70}\right) \times {\theta_5}^{DIAl}$$

TVCL = typical value of clearance

TVV1 = typical value of central volume of distribution

CrCL = creatinine clearance

DIAL = dialysis status

3. Data simulation

Full concentration-time profiles with 15 min interval for 100 patients were created by simulation with the use of NONMEM 7.3. Median covariate values (Wt = 79 kg and CLCR = 62 ml/min) were inserted to the final model equation by Goti et al[16] assuming there is no dialysis in virtual population. Obtaining parameters used in the simulation process are shown in table 13. Dosing regimen of 1000 mg given 12 hourly with 2 hour infusion time was used in NONMEM input dataset. As for the residual error model, the original error components were manipulated to an acceptable level – proportional component to 10% and additive component to the standard deviation (SD) of 0.5 to avoid erratic-looking concentration-time profiles from which the reference AUC was calculated. The NONMEM control file for the simulation is mentioned in appendix.

Table 13 Parameter estimates used in the simulation process

Parameters	Values
CL ($\boldsymbol{\Theta}_1$) in L/h	2.65
V1 ($\boldsymbol{\Theta}_4$) in L	65.99
V2 in L	38.4
Q in L/h	6.5
IIV on CL in variance (%CV)	0.158 (39.8%)
IIV on V1 in variance (%CV)	0.666 (81.6%)
IIV on V2 in variance (%CV)	0.326 (57.1%)
Proportional error component in variance (%CV)	0.01 (10%)
Additive error component in variance (SD)	0.25 (0.5)

CL – clearance, V1 – central volume of distribution, V2 – peripheral volume of distribution, Q – inter-compartmental clearance, IIV – inter-individual clearance.

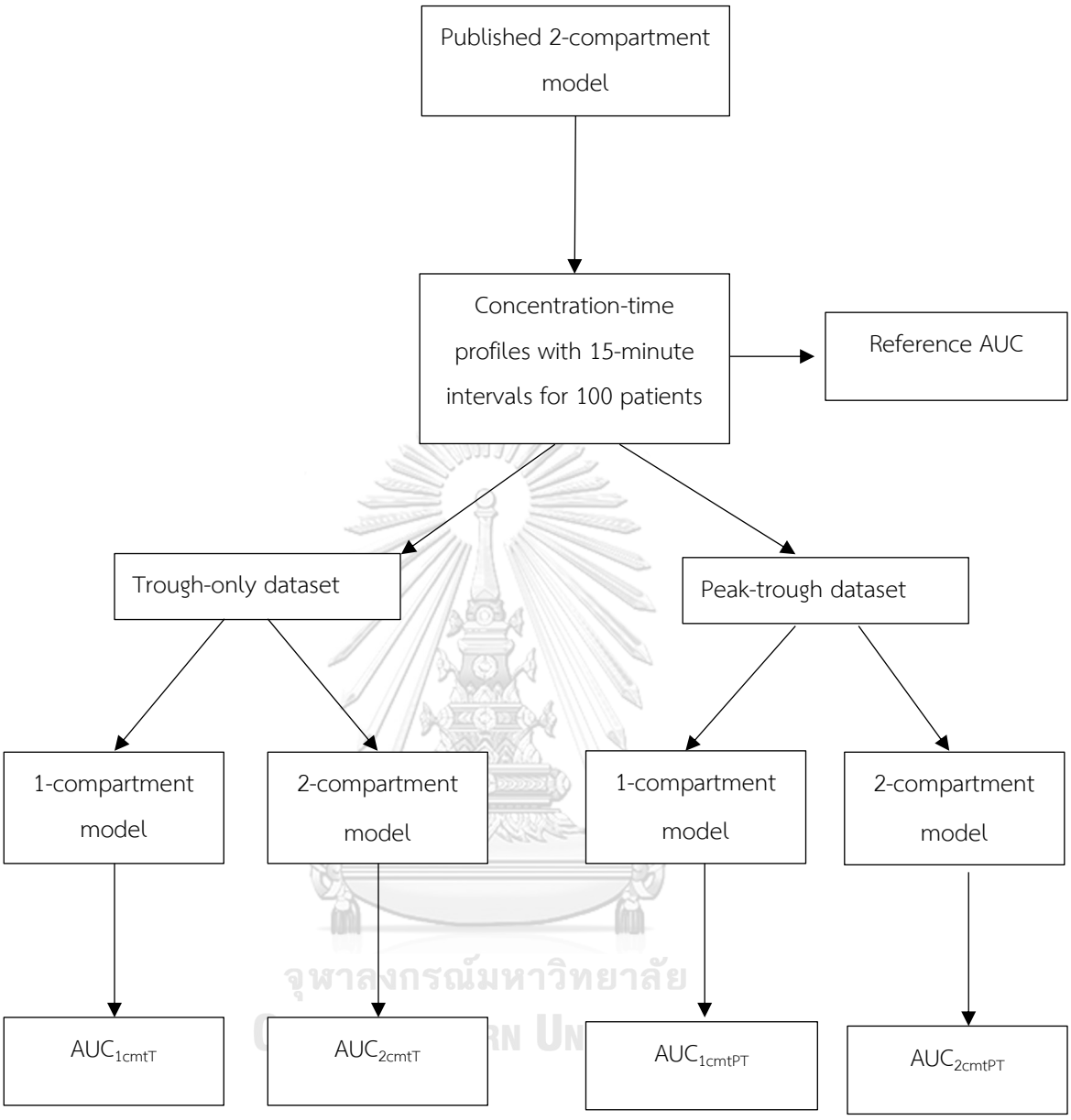


Figure 6 Overview of the study design

AUC_{1cmtT} and AUC_{2cmtT}: AUCs from 1- and 2-compartment models using trough-only dataset, AUC_{1cmtPT} and AUC_{2cmtPT}: AUCs from 1- and 2-compartment models using peak-trough dataset

4. Estimation of the reference AUC

From simulated full concentration-time profiles, three reference AUCs – AUC_{0-24}, AUC_{24-48} and average daily AUC within 48 hours (AUC_{avg}) were calculated by means of linear trapezoidal rule. The following equation was used in this case.

$$AUC = \frac{1}{2}(C_1 + C_2)(t_2 - t_1)$$

C_1 and C_2 are concentrations within a given time interval of t_1 and t_2.

5. Creating data-depleted versions of dataset

Two versions of depleted dataset such as trough-only and peak-trough datasets were created by simulation with NONMEM® 7.3 and PDx-Pop® 5.2 (ICON Development Solutions, Ellicott city, MD, USA). Each dataset includes 100 patients. Trough-only dataset contains one sample per patient. Peak-trough dataset includes two samples per patient. Concentrations at 30 minutes before 4th dose ($C_{35.5h}$) from the previous simulated full profiles were used as trough concentrations and concentrations obtained at 1 hour post infusion (C_{27h}) were used as peak concentrations. Other remaining concentrations were removed from the simulated profiles and set up as missing value that is zero.

6. Population Model Building

Both 1- and 2-compartment models were built from each of two depleted datasets, thereby, four population models were obtained. Models were developed by using non-linear mixed effect modelling software, NONMEM 7.3® and PDx pop 5.2® (ICON Development Solutions, Ellicott city, MD, USA). First-order conditional estimation method with interaction (FOCE-I) was used to estimate model parameters. ADVAN1 TRANS2 were used for 1-compartment modeling and ADVAN3 TRANS4 were used for 2-compartment modeling. Inter-individual variability (IIV) was described by exponential function. Residual variability was tested with additive, proportional, combined additive and proportional error models.

In modeling from trough-only dataset, only clearance and its variability were estimated and other parameters were fixed to the values in literature. In that case, the literature search was performed via PubMed using key words - 'vancomycin' and 'population' and 'pharmacokinetics'. The summary of 15 studies (1-compartment models) and 19 studies (2-compartment models) in adults was mentioned in literature review section (tables 1 and 2).[20-53]. Number of participants, patient characteristics, covariates and physiological plausibility of the parameters were mainly considered for assigning reasonable volume parameters into the models. Studies with less than 100 patients were excluded. As body weight was found to have an impact on volume of distribution in most studies, those with participants having similar weight as in our virtual population were mainly focused. As for the 1-compartment model, three models from studies by Staatz et al[21], Revilla et al[22] and Roberts et al[24] were selected. Likewise, studies by Thomson et al[38] and Sanchez et al[41] were chosen for V1, V2 and Q in 2-compartment model. And then, PK parameters to be fixed were calculated by standardizing these models with median covariate values of the patient population in the study by Goti et al[16]. Residual errors were also fixed and described as constant proportional error when modeling from trough-only datasets.

The most appropriate model was chosen according to physiological plausibility, precision of parameter estimates and objective function values (OFV). Model evaluation was performed by using goodness-of-fit plots: observed versus population and individual predicted concentrations (DV Vs PRED, DV Vs IPRED), conditional weighted residuals versus population predictions and time (CWRES Vs PRED, CWRES Vs TIME). Condition numbers were also checked to test the model stability. Bootstrap procedure with 1000 replications was performed for model validation.

7. Simulation and obtaining AUCs from four population models

Final model parameter estimates with their variability from each model were used to create concentration-time profiles until 48 hour for 100 patients per model. The same seed was used to generate concentrations from all four models.

8. Comparison of AUCs from four models

The difference between AUCs from 1- and 2-compartment models was examined in terms of both statistical and clinical significance. As for statistical comparison, one-way repeated measure analysis of variance (ANOVA) was used with Bonferroni post hoc analysis. The difference around 17% was accepted as clinically insignificant level according to the study by Shingde et al.[15] By pairwise comparison, AUCs from each of four models were also compared to the AUC_{ref} to assess the AUC predictability between models from trough-only data and models from peak-trough data.

Chapter IV

Results

1. Simulated data

Full concentration-time profiles with 15-min interval for 100 patients were obtained through simulation from the model by Goti et al.[16] For trough-only dataset, the average trough concentration was 14.21 mg/L ranging from 3.56 mg/L to 30.86 mg/L. For peak-trough dataset, the average peak concentration was 23.3 mg/L with minimal concentration of 3.56 mg/L and the maximal concentration of 59.83 mg/L. According to the original study where concentrations below 5 mg/L were regarded as below limit of quantification (BQL) data, there was one point which fell below the limit of quantification in both depleted datasets. In terms of percentage, this BQL data point accounted for 1% in trough-only dataset and 0.5% for peak-trough dataset.

2. Modeling

As for 1-compartment model from peak-trough dataset, both clearance (Cl) and volume of distribution (V_d) along with their variabilities could be estimated with reliable precision. For residual variability, proportional error model best described the data with lowest objective function value (OFV) having 919.89 when compared to additive error with OFV 926.25. Both of the error models gave similar PK parameter values. The model did not converge successfully when using the combined error model. When dealing with trough-only dataset, fixing V_d from the model by Staatz et al[21] showed the lowest OFV and condition number (Table 14).

Table 14 Comparison of fixed volume of distribution parameters for 1-compartment model from trough-only data

Study	Patient population	OFV	Condition number	Parameter estimate (%RSE)
Staatz et al[21] (2005)	N = 102 (cardiothoracic surgery) Age (years) = 66 (17-87) Wt (kg) = 74 (44-110) CLCR (ml/min) = 60 (12-172)	442.51	2.5	Cl = 3.8 L/h (5.5%) V_d = 90.8 L (fixed)
Revilla et al[22] (2010)	N = 191 (ICU) Age (years) = 61.1 ± 16.3 Wt (kg) = 73 ± 13.3 CLCR (ml/min) = 74.7 ± 58	594.23	10	Cl = 1.58 L/h (19.1%) V_d = 160 L (fixed)
Roberts et al[24] (2011)	N = 191 (septic, critically ill) Age (years) = 58.1 ± 14.8 Wt (kg) = 74.8 ± 15.8 CLCR (ml/min/1.73m^2) = 90.7 ± 60.4	462.93	4.6	Cl = 3.13 L/h (8.53%) V_d = 119 L (fixed)

Wt weight, CLCR creatinine clearance, ICU intensive care unit, OFV objective function value, %RSE percent relative standard error, Cl clearance, V_d volume of distribution. Median values were shown with range and mean values were shown with ± SD.

As for 2-compartment model from peak-trough dataset, all fixed-effect parameters - clearance (Cl), central volume of distribution (V1), peripheral volume of distribution (V2) and inter-compartmental clearance (Q) could be estimated.

Regarding random effect parameters, inter-individual variabilities on V2 and Q could not be estimated. Proportional error model best described the data with OFV 904.66 when compared to additive error with OFV 909.46. Combined error model could not be run successfully. As for trough-only model, the most appropriate model was obtained by fixing with PK parameters from Sanchez et al[41] with the smallest OFV and conditional number (Table 15).

Table 15 Comparison of fixed pharmacokinetic parameters for 2-compartment model from trough-only data

Study	Patient population	OFV	Condition number	Parameter estimate (%RSE)
Thomson et al[38] (2009)	N = 398 (patients on TDM) Age (years) = 66 (16-97) Wt (kg) = 72 (40-159) CLCR (ml/min) = 64 (12-216)	441.89	2.3	Cl = 2.82 L/h (5.46%) V_1 = 53.3 L (fixed) V_2 = 57.8 L (fixed) Q = 2.28 L/h (fixed)
Sanchez et al[41] (2010)	N = 141 (hospitalized patients) Age (years) = 55 ± 14.58 Wt (kg) = 73.2 ± 17.48 Scr (mg/dl) = 1.05 ± 0.65 CLCR (ml/min) = 82.3	436.68	1.2	Cl = 3.48 L/h (3.71%) V_1 = 22.4 L (fixed) V_2 = 34.3 L (fixed) Q = 8.77 L/h (fixed)

TDM therapeutic drug monitoring, Wt weight, Scr serum creatinine, CLCR creatinine clearance, OFV objective function value, %RSE % relative standard error, Cl clearance, V_1 and V_2 central and peripheral volumes of distribution respectively, Q inter-compartmental clearance. Median values were shown with range and mean values were shown with ± SD.

3. Model evaluation

Goodness-of-fit plots showed acceptable models. Shrinkage was found when looking at dependent variable versus population predictions plots (DV Vs PRED) and dependent variable versus individual predictions plots (DV Vs IPRED). There was a symmetric distribution of points at each side of the identity line in each plot. Observed concentration points fell within ± 3 SDs in conditional weighted residuals versus population predictions plots (CWRES Vs PRED) and in conditional weighted residuals versus time plots (CWRES Vs TIME). Goodness-of-fit plots for all models from the depleted datasets are illustrated in Figure 7, 8, 9 and 10.

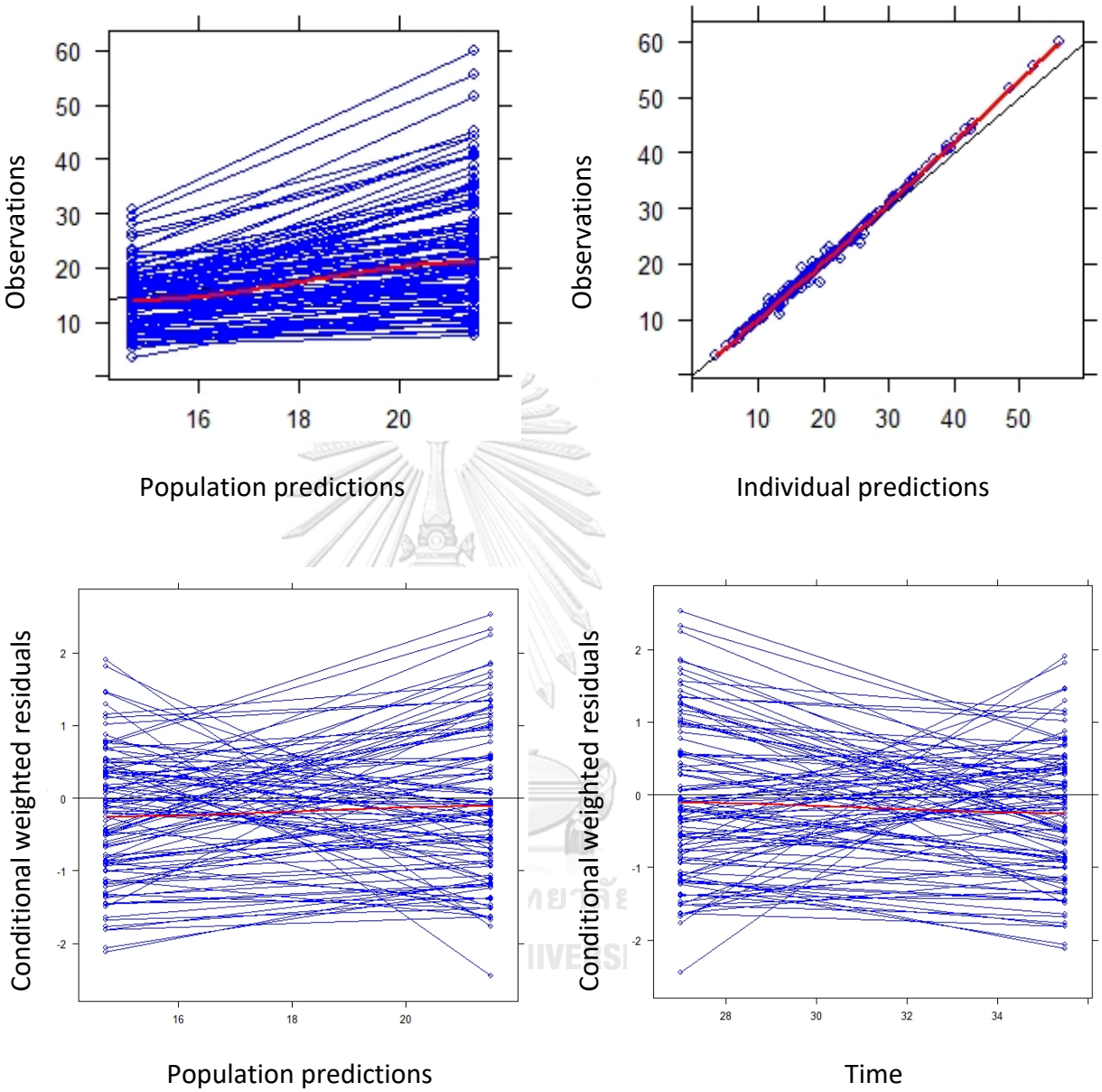


Figure 7 Goodness-of-fit plots for 1-compartment model from peak-trough data

The red line represents the local regression line which tracks well with the black line which is the identity line.

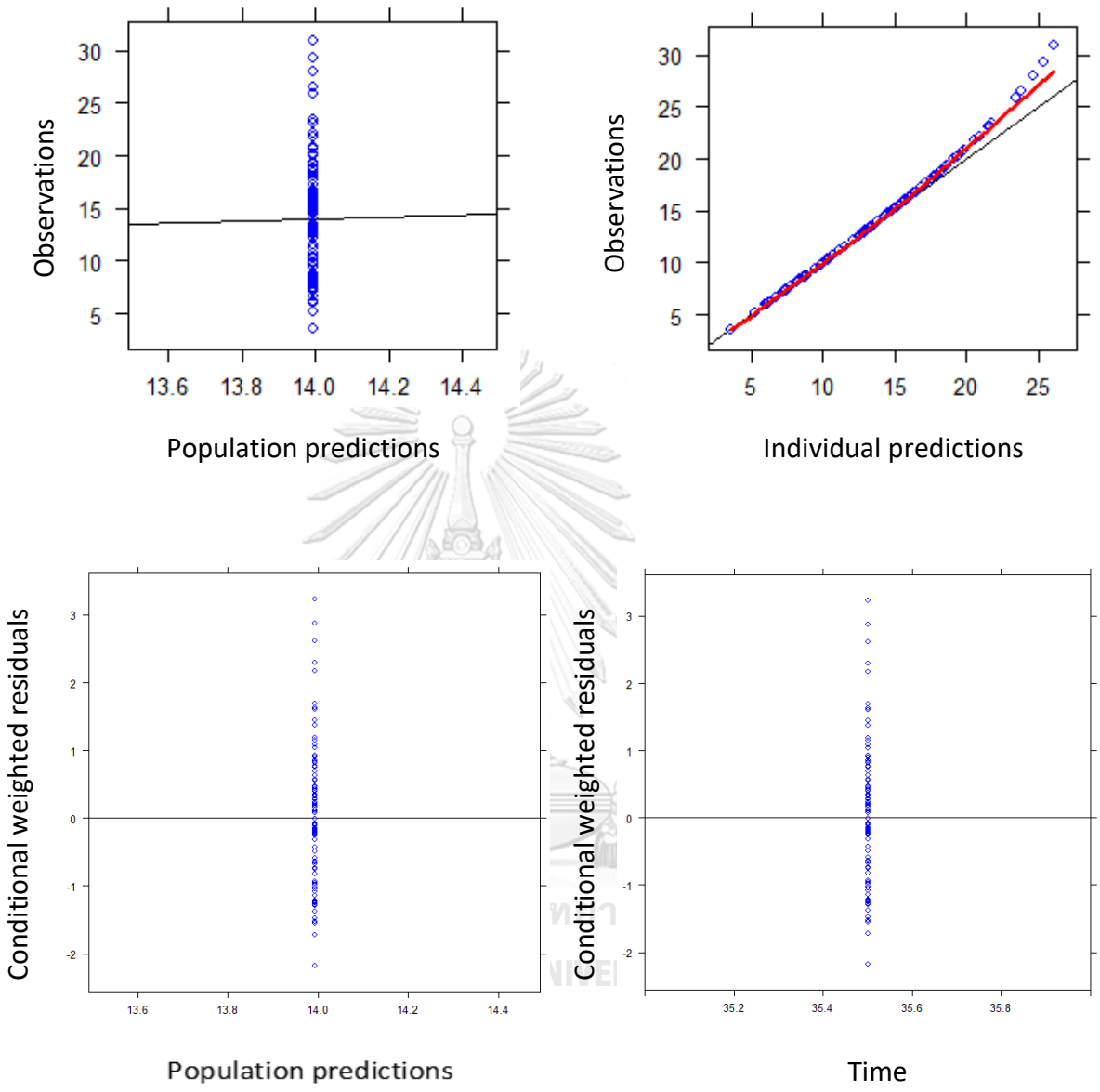


Figure 8 Goodness-of-fit plots for 1-compartment model from trough-only data

The red line represents the local regression line which tracks well with the black line which is the identity line.

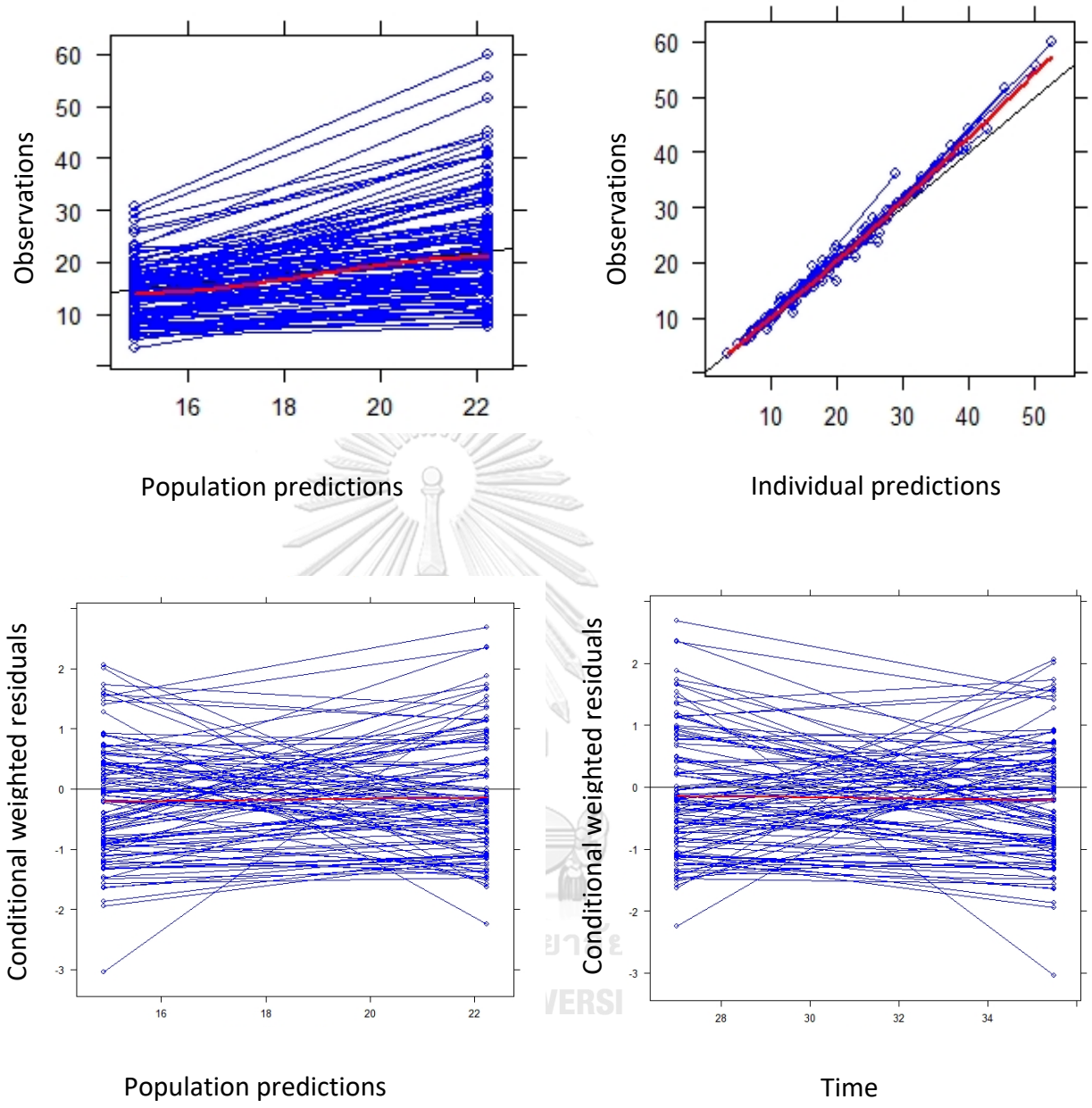


Figure 9 Goodness-of-fit plots for 2-compartment model from peak-trough data

The red line represents the local regression line which tracks well with the black line which is the identity line.

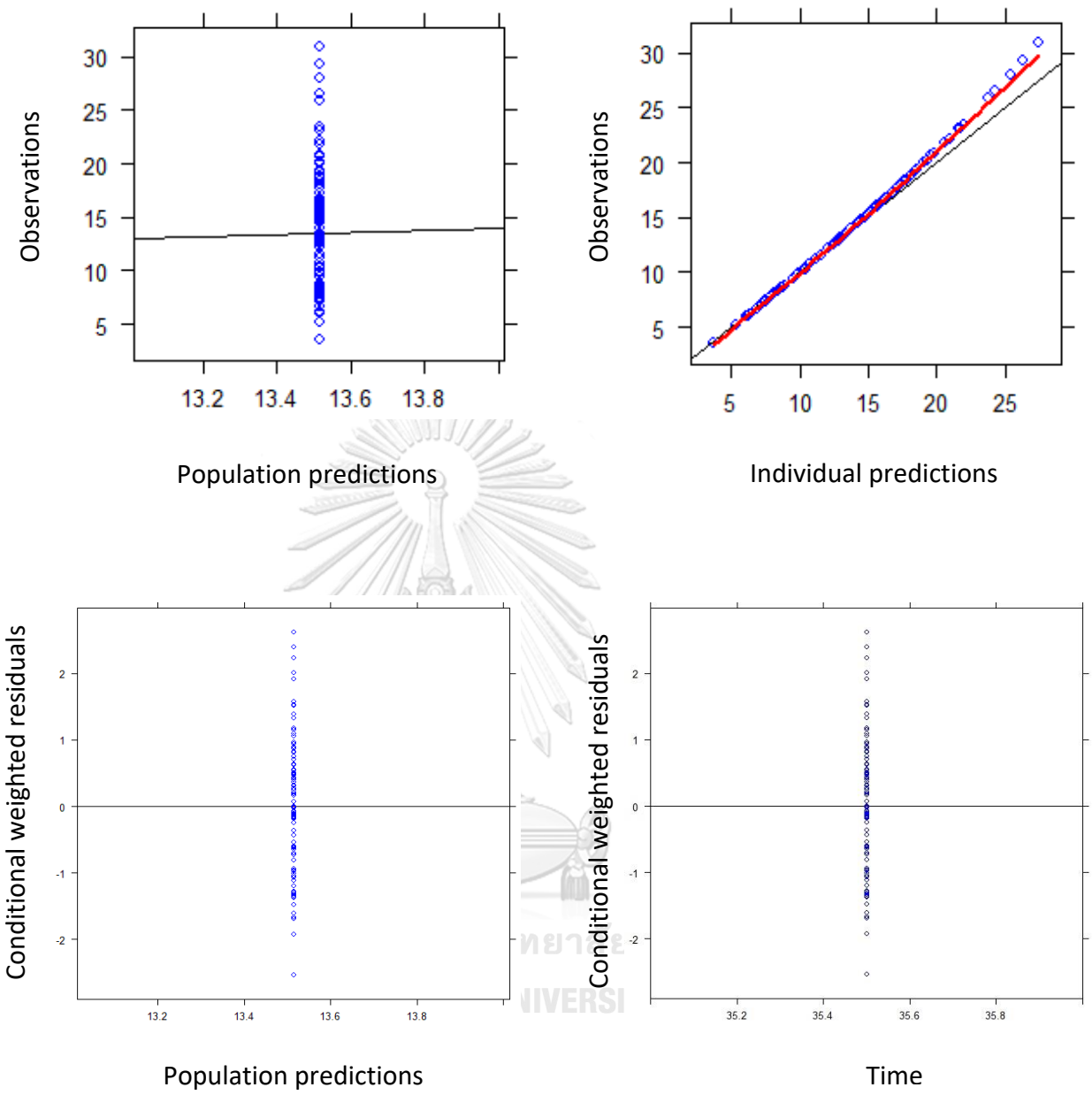


Figure 10 Goodness-of-fit plots for 2-compartment model from trough-only data

The red line represents the local regression line which tracks well with the black line which is the identity line.

Model validation by bootstrap procedures also provided good results. Typical parameter estimates from all models fell within 95% confidence intervals of bootstrap estimates (Table 16 and 17). Out of 1000 replications for each model, success rate was over 95% in all fixed and random effect parameter estimates.

Table 16 Summary of 1-compartment models with bootstrap results

Parameters		1000 Bootstraps	
Model from peak-trough dataset	**Values (%RSE)**	**Median**	**95% CI**
Cl (L/h)	3.66 (4.43)	3.63	3.22 - 3.95
V_d (L)	82.2 (7.02)	83.43	71.9 - 96.7
IIV on Cl in %CV	39.7 (16.4)	37.84	20.9 – 45.60
IIV on V_d in %CV	66.9 (12.9)	67.29	58.48 – 75.76
Residual variability (proportional, %CV)	9.75 (38.0)	11	5.3 – 18.28
Model from trough-only dataset			
Cl (L/h)	3.80 (5.50)	3.798	3.39 – 4.2
V_d (L)	90.8 (fixed)	-	-
IIV on Cl in %CV	51.6% (17.6%)	51.69	43.24 – 60.75
Residual variability (proportional, %CV)	9.75 (fixed)	-	-

Cl; clearance, V_d; volume of distribution, IIV; inter-individual variability, %CV; percent coefficient of variation, %RSE; percent relative standard error

Table 17 Summary of 2-compartment models with bootstrap results

Parameters		1000 Bootstraps	
Model from peak-trough dataset	**Values (%RSE)**	**Median**	**95% CI**
Cl (L/h)	2.20 (15.2)	2.25	1.54 – 3
V_1 (L)	65.20 (23.6)	83.43	51.5 – 80.9
V_2 (L)	63 (16.7%)	60.15	34.3 – 86.6
Q (L/h)	5.87 (47.2%)	5.95	3.41 – 8.61
IIV on Cl in %CV	63.5 (26.6%)	59.01	32.25 – 79.75
IIV on V1 in %CV	84.5 (37.3%)	86.52	70.71 – 104.88
Residual variability (proportional, %CV)	10.9 (42.6%)	12.08	6 – 20.69
Model from trough-only dataset			
Cl (L/h)	3.48 (3.71%)	3.47	3.22 – 3.72
V_1 (L)	22.4 (fixed)	-	-
V_2 (L)	34.3 (fixed)	-	-
Q (L/h)	8.77 (fixed)	-	-
IIV on Cl in %CV	35.6% (14.7%)	35.59	30.61 – 40.74
Residual variability (proportional, %CV)	10.9 (fixed)	-	-

Cl; clearance, V1; central volume of distribution, V2; peripheral volume of distribution, Q; inter-compartmental clearance, IIV; inter-individual variability, %CV; percent coefficient of variation, %RSE; percent relative standard error

4. Areas under the curve (AUC)

Predicted vancomycin exposures from three time periods (0 to 24 hr, 24 to 48 hr and average exposure within 48 hrs) are mentioned in table 18.

Table 18 Reference AUCs and AUCs from the models with depleted datasets

Models	AUC_{0-24} (mean ± SD)	AUC_{24-48} (mean ± SD)	AUC_{avg} (mean ± SD)
Reference AUC	283.14 ± 124.69	470.63 ± 176.28	376.88 ± 149.24
2-compartment model (peak-trough)	267.05 ± 104.88	458.72 ± 171.43	362.89 ± 136.62
2-compartment model (trough-only)	379.92 ± 62.59	559.06 ± 140.28	469.49 ± 101.28
1-compartment model (peak-trough)	290.84 ± 125.17	450.02 ± 163.33	370.43 ± 140.09
1-compartment model (trough-only)	265.51 ± 40.23	459.78 ± 124.64	362.64 ± 82.3

AUC_{0-24} exposure between the time period of 0 to 24 hour, AUC_{24-48} exposure between the time period of 24 to 48 hour, AUC_{avg} average 24-hour exposure within first 48 hours.

4.1 Comparison of AUCs

When conducting one-way repeated measure analysis of variance (ANOVA), the Mauchly's test of sphericity was violated. Therefore, degrees of freedom were adjusted using Greenhouse-Geisser correction. ANOVA and the pairwise comparisons with the post-hoc analysis using Bonferroni correction showed there were significant differences within pairs of mean AUCs ($p < 0.05$).

When comparing AUCs from each of models with the depleted dateset to the AUC_{ref}, AUCs from 1-compartment models from both depleted datasets were not statistically significant from the AUC_{ref}. Two-compartment model with peak-trough data also offered similar AUCs with the AUC_{ref} . However, AUCs from 2-compartment model with trough-only dataset showed significant differences ($p < 0.05$) when compared to the AUC_{ref} – 25.16% for $AUC_{0\text{-}24}$, 15.92% for $AUC_{24\text{-}48}$ and 19.45% for AUC_{avg} (table 19). In other words, AUCs from 2-compartment model with trough-only data were incomparable to the remaining AUCs (figure 11). Besides, there were statistically significant differences between AUCs from 1- and 2-compartment models with both versions of depleted datasets (table 20).

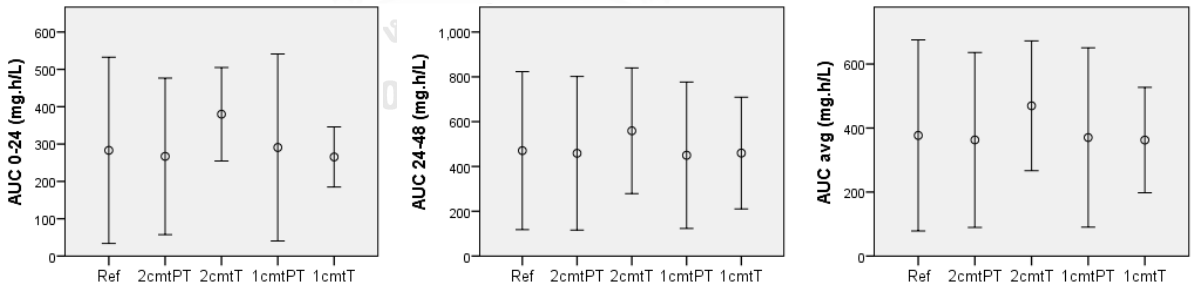


Figure 11 Comparison of AUCs from 1- and 2-compartment models and the reference AUCs

The small circles are means and the bars show standard deviations. Ref reference model, 2cmtPT 2-compartment model from peak-trough dataset, 2cmtT 2-compartment model from trough-only dataset, 1cmtPT 1-compartment model from peak-trough dataset, 1cmtT 1-compartment model from trough-only dataset.

Table 19 Mean difference (%) of the reference AUCs and AUCs from the models with depleted datasets

Models	Mean difference for AUC_{0-24}	Mean difference for AUC_{24-48}	Mean difference for AUC_{avg}
2-compartment model (peak-trough)	5.68% (NS)	2.53% (NS)	3.71% (NS)
2-compartment model (trough-only)	25.16% * ($p < 0.05$)	15.92% * ($p < 0.05$)	19.45% * ($p < 0.05$)
1-compartment model (peak-trough)	2.65% (NS)	4.38% (NS)	1.71% (NS)
1-compartment model (trough-only)	6.23% (NS)	2.31% (NS)	3.78% (NS)

AUC_{0-24} exposure between the time period of 0 to 24 hour, AUC_{24-48} exposure between the time period of 24 to 48 hour, AUC_{avg} average 24-hour exposure within first 48 hours.

* significant difference from the reference AUC ($p < 0.05$), NS – not significant.

Table 20 Comparison of AUCs between 1- and 2-compartment models from the depleted datasets

	Mean difference (mg.h/L)	Mean difference (%)	P value
Peak-trough models			
AUC_{2cmt} - AUC_{1cmt} (0to24)	-23.79	8.09	< 0.0005
AUC_{2cmt} - AUC_{1cmt} (24to48)	8.7	1.9	= 0.037
AUC_{2cmt} - AUC_{1cmt} (average within 48 hours)	-7.54	2.04	< 0.0005
Trough-only models			
AUC_{2cmt} - AUC_{1cmt} (0to24)	114.41	29.75	< 0.0005
AUC_{2cmt} - AUC_{1cmt} (24to48)	99.28	17.87	< 0.0005
AUC_{2cmt} - AUC_{1cmt} (average within 48 hours)	106.84	22.44	< 0.0005

AUC_{1cmt} – AUC from 1-compartment model, AUC_{2cmt} – AUC from 2-compartment model

Chapter V

Discussion

Until recent years, trough concentration (C_t) was mostly used as TDM predictor in vancomycin therapeutic monitoring with the belief of having correlation with AUC, the therapeutic indicator for efficacy and toxicity. However, the updated consensus guideline (2020) recommended to apply AUC-guided monitoring system in MRSA infections with pathogens having MIC ≤ 1 after studies pointed out therapeutic discordance between C_t and AUC.[10] With the emergence of Bayesian dose-optimizing software like BestDose, DoseMe, Adult and Pediatric Kinetic (APK), InsightRx and Precise PK, AUC can be estimated using existing population models and patient data.[10, 68]As vancomycin pharmacokinetics has mostly been described by both 1- and 2-compartment models using TDM data, we examined whether the difference between AUCs from 1- and 2-compartment models are acceptable from clinical point of view. This study was pharmacokinetic data analysis using simulated concentrations from a previously published model. We also examined whether models with trough-only data could adequately estimate the true AUC when compared to models with peak-trough data.

According to findings from our study, there was a statistically significant difference between AUCs from 1- and 2-compartment models in both cases of using peak-trough data and using trough-only data. Using peak-trough dataset, the differences between AUCs from 1- and 2-compartment models were 8.09% for AUC_{0-24}, 1.9% for AUC_{24-48} and 2.04% for average AUC_{24} over 48-hour period. In spite of having significant differences from statistical analysis, the extent of difference was small with respective to clinical perspective as the percentages were less than 17% which was our assigned cut-off level for clinical significance. Shindge et al [15] compared single-dose AUCs between 1- and 2–compartment models using rich data. Their mean (±SD) AUCs were 183 ± 88 mg.h/L for 2-compartment model and 167 ± 79 mg.h/L for 1-compartment model. AUC_{2cmt} was higher than AUC_{1cmt} by 8.3% ($p <$

0.05). In our models using peak-trough data, AUC_{2cmt} was higher than AUC_{1cmt} by 1.9% for AUC_{24-48} whereas AUC_{1cmt} was higher than AUC_{2cmt} by 8.09% for AUC_{0-24} and 2.04% for AUC_{avg}. Our findings on the difference between AUCs were consistent with the findings by Shindge et al.[15] In both studies, the difference of AUCs between 1- and 2-compartment models was small with respect to dose adjustment (< 17%). Hence, it can be assumed that 1-compartment model using either rich or sparse data (in this case, one peak sample and one trough sample) could adequately predict AUC when compared to 2-compartment model.

Broeker et al[14] predicted AUC_{0-24} from the model by Goti et al[16] with two different methods – prior method and Bayesian method. In prior method, their patient covariate values were inserted into the final model equations of the study by Goti et al[16] and AUC was derived from these PK parameters. In Bayesian method, observed concentrations from their patients were also used along with the model by Goti et al[16] as Bayesian priors. The former method provided median AUC (10^{th} – 90^{th} percentiles) of 265mg.h/L (180 - 407) and the later method provided median AUC (10^{th} – 90^{th} percentiles) of 267 mg.h/L (174 - 415). Our study offered the reference AUC_{0-24} of 283.14 ± 124.9 mg.h/L in terms of mean ± SD and 261.15 mg.h/L (132.64 – 447.16) in terms of median (10^{th} – 90^{th} percentiles). It appears that our finding for the reference AUC_{0-24} from the model by Goti et al[16] is consistent with their findings. According to our findings, we would like to suggest that AUC_{24-48} could be the optimal predictor for therapeutic drug monitoring practice as recommended AUC target (> 400 mg.h/L) was achieved only within time period of 24-48hr. (Table 2).

In the study by Neely et al[7], AUCs from models with trough-only data and peak-trough data (AUC_T and AUC_{PT}) were compared to the true AUC (AUC_{ref}) from the model with rich data in terms of 2-compartment modeling. In their study, AUCs were compared in the form of the average daily AUC (AUC_{24}) between the time period of 0 to 120 hours. Their median reference AUC (range) was 445.2 (28.3 to 7172) mg.h/L. Our reference average daily AUC between 0-48 hour in terms of mean ± SD was 376.88 ± 149.24 mg.h/L and 363.95 (134.63 to 819.14) mg.h/L in terms of median

(range). The lower value of our reference average daily AUC (0-48 hour) could be explained by the shorter time interval used for calculating AUC from simulated concentrations. It seems that higher AUC could be expected with the longer time interval in their study. Furthermore, cumulative exposure should also be considered with more number of doses until 120 hours after the first dose. We decided to estimate AUCs over the time interval of 0-48 hour since the reviewed consensus guideline suggested to use AUC obtained within first 48 hours for dosing purposes. In their study, both peak-trough model and trough-only model underestimated the reference AUC by 14% and 23% respectively. Also, our 2-compartment model from trough-only data offered AUCs which are considerably different from the AUC_{ref} – 15.92 to 25.16% for for AUCs of three periods whereas 2-compartment model using peak-trough data provided similar AUC estimates with the reference AUCs.

AUCs derived from 1-compartment models (both trough-only and peak-trough datasets) did not show significant differences from the reference AUCs. From these findings, we could assume that 1-compartment model constructed from trough-only data might be dependable to predict AUC when rich-data population models are scarce to be used as Bayesian priors for intended population.

In our study, we decided to estimate only clearance and its inter-individual variability in modeling from trough-only data according to the following reasons. First, it is likely that volume parameter estimates do not yield good precision when modeling from trough-only data as the trough concentrations are more related to elimination process. Second, we fixed residual error (RE) due to the presence confounding effect between IIV and RE. [71] Besides, PK parameters seem to play more important role than residual error to predict AUC by Bayesian approach.

In the study by Goti et al[16], concentrations below 5 mg/L were regarded as below limit of quantification (BQL) data and treated by M3 method and by exclusion from analysis process. In our simulated data, we found only one concentration point having less than 5mg/L and we did not apply any special method to handle this BQL data for the following reasons. Keizer et al[72] showed that there is no significant

difference in model performance between BQL handling methods when the percentage of BQL is less than 5%. In addition, they found that model performance was superior when incorporating BQL data in analysis process when compared to the likelihood methods. Therefore, we decided to include this BQL data in our PK analysis.

We decided to compare the therapeutic outcome predictor in terms of AUC rather than in terms of the ratio of AUC over MIC (AUC/MIC) even though the suggested target was AUC/MIC 400-600. The reviewed guideline also favors to use AUC solely for dosing purposes regarding MIC as a less important parameter for the following reasons. The first reason is the narrow range of MIC values for vancomycin having MIC breakpoint of 2 mg/L and the reports showed that most of MIC values were less than 1 mg/L despite a slight MIC creep discovered. Second, the methods used to measure MIC differ among hospitals such as E test, broth micro dilution (BMD), Vitek 2, MicroScan and BD Phoenix methods. This brings about the variability in measured MIC values. As the therapeutic target AUC/MIC 400-600 was adopted from the study using BMD method, there might be the variability AUC/MIC results if different methods of MIC measurement are used. The third reason is the imprecision of measurement of MIC values with ± $\log_2$ dilution allowing for 10-20% measurement error. The fourth reason is that MIC values are usually available after 72 hours of admission in hospitals and this hampers to examine the therapeutic outcome in terms of AUC/MIC in the need for early monitoring within 48 hours after the first dose.[10, 73] For all these facts, it seems to be more sensible to apply AUC alone for TDM in clinical practice.

We have some limitations in our study. First, we did not apply Bayesian approach to predict AUC due to some technical difficulties. Instead, we decided to perform simulation to produce concentration-time provides at 15-min intervals until 48 hours with the use of NONMEM®. And then, we applied linear trapezoidal rules to calculate AUC by summing each trapezoids of 15-min interval. We believe that our AUCs were precise as we included as many trapezoids as possible when calculating AUCs. Besides, our reference AUC_{0-24} estimate was similar to Bayesian AUC_{0-24} of the

study by Broeker et al[14] having median AUCs (range) of 261.15 mg.h/L (86.03 to 657.74) and 267 mg.h/L (174 - 415) respectively considering the fact that both studies attempted to derive AUCs from the same model by Goti et al[16].

Another limitation is that we chose to perform modeling with simulated concentrations from Goti et al[16] as this model has been suggested as the most appropriate model to predict AUC [14]. Since this study was conducted on adults, our findings might not be applicable in pediatric populations. In addition, the original error components were bound to be reduced as small as possible so that an erratic concentration-time profile could be avoided and the residual error modeling process could be run successfully in our analysis plan. Therefore, these residual errors might not reflect the true assay errors which could be higher than our manipulated errors. Nonetheless, we believe that this could be ignored as the residual error appears to play less important role than pharmacokinetic parameters in the process of predicting AUC via Bayesian method.

Chapter VI

Conclusion

Vancomycin is a glycopeptide antibiotics which is effective against gram positive bacterial infections. The unique usefulness of vancomycin is the treatment of methicillin resistant *Staphylococcus aureus* (MRSA) infections.[3, 55] Therapeutic drug monitoring (TDM) is usually performed in patients receiving vancomycin treatment for major infections or serious MRSA infections. Being time dependent antibiotic, area under the curve (AUC) is the therapeutic indicator for vancomycin. Due to the difficulty to calculate AUC in clinical bedside in earlier years, the 2009 consensus guideline recommended to use trough concentration as TDM parameter with the belief that there is correlation between trough concentration and AUC.[4] However, later studies showed the therapeutic discrepancy between trough concentration and AUC.[6-9] Besides, AUC proved to be more related to nephrotoxicity and other patient outcomes.[56-62]

With the emergence of advanced dosing optimizing software in recent years, it is expected to be able to calculate AUC with less trouble and the updated consensus guideline do not suggest trough based monitoring anymore. Instead, AUC-based monitoring is preferred and it is recommended to maintain AUC/MIC 400-600 for MRSA infections with isolates having MIC ≤ 1. The guideline advised to apply Bayesian method or first-order pharmacokinetic equations based method to estimate AUC. To predict AUC with Bayesian method, population pharmacokinetic models are required.[10, 68] Vancomycin pharmacokinetics has been described as 1- and 2-compartment models.[12-14] As the AUC outcome depends on various factors including inputted model, it is important to examine the difference between AUCs from 1- and 2-compartment models. So far, only one study explored the difference between AUCs from 1-and 2-compartment models using rich data.[15] Considering the fact that the majority of vancomycin models have been derived from TDM data which are

sparse in nature, our study explored the difference of AUCs from 1- and 2-compartment models using sparse data in two scenarios – using peak-trough dataset and trough-only dataset. By comparing AUCs derived from models with these depleted datasets to the reference AUC, we also assessed the AUC predictability of peak-trough model and trough-only model.

The previously published 2-compartment model was used to produce full concentration-time profiles with 15-minute intervals until 48 hours after the first dose of vancomycin. The reference AUC (AUC_{ref}) was calculated by linear trapezoidal formula using these concentrations. AUCs were calculated for three different time periods – 0 to 24 hour, 24 to 48 hour and average daily AUC within 0 to 48 hour. AUC_{ref} values for these three periods were 283.14 ± 124.69 mg.h/L, 470.53 ± 176.28 mg.h/L and 376.88 ± 149.24 mg.h/L respectively. Then, 1- and 2-compartment models were constructed from depleted datasets and AUCs were derived from each model. AUC values for aforementioned three periods from 2-compartment model using peak-trough data were 267.05 ± 104.88 mg.h/L, 458.72 ± 171.43 mg.h/L and 362.89 ± 136.62 mg.h/L. Resulting AUCs from 2-compartment model with trough-only data were 379.82 ± 62.59 mg.h/L, 559.06 ± 140.28 mg.h/L and 469.49 ± 101.28 mg.h/L. As for 1-compartment model with peak trough data, AUCs of 290.84 ± 125.17, 450.02 ± 163.33 mg.h/L and 370.43 ± 140.09 mg.h/L were obtained. From 1-compartment model using trough-only data, AUC values were 265.51 ± 40.23 mg.h/L, 459.78 ± 124.64 mg.h/L and 362.64 ± 82.3 mg.h/L.

First, AUCs were compared between 1- and 2-compartment models from depleted datasets. And then, AUCs from each of those models were also compared to the AUC_{ref}. Statically significant difference was found between AUCs from 1- and 2-compartment models in both cases of depleted datasets. In models from peak-trough dataset, the percent differences were negligible (less than 17%) from clinical point of view – 8.09% for $AUC_{0-24,}$ 1.9% for AUC_{24-48} and 2.04% for AUC_{avg}. However, the percent differences were higher in models from trough-only dataset having around 17 % for all AUCs of three time periods. When comparing each AUC to the

AUC_{ref}, none of the pairs showed significant difference except in the pair of AUC_{ref} and AUCs from 2-compartment (trough-only) model. The results demonstrated that 2-compartment model with only trough concentrations should better be avoided for predicting AUCs for dosing purposes in clinical practice.

Taken together, 1-comparment model with sparse data that is a pair of peak and trough samples per patient could sufficiently describe the true AUC in clinical practice. Our findings also imply that there is a possibility of usefulness from 1-compartment model with single-trough data when models with rich data are not available for intended population to predict AUC by Bayesian software. Besides, 2-compartment model with at least one peak sample and one trough sample per patient could be reliably applied in prediction of AUC whereas 2-compartment model with only trough samples should better be avoided.

As our study is simulation study using previously published model with adult data, the question remains whether our findings are generalizable to pediatric population of neonates and children. We would like to suggest further studies to explore the idea of the difference between AUCs from 1- and 2-compartment models using sparse data in neonates and children as these are the population where it is inconvenient to collect rich data.

Appendix

1. The control stream used for simulation from the previously published model

```
$INPUT C ID TIME AMT RATE TAD DV MDV EVID
$DATA FULLPROFILE.CSV IGNORE=C
$SUBROUTINES ADVAN3 TRANS4
$PK
   TVCL=THETA(1)
   CL=TVCL*EXP(ETA(1))
   TVV1=THETA(2)
   V1=TVV1*EXP(ETA(2))
   TVV2=THETA(3)
   V2=TVV2*EXP(ETA(3))
   TVQ=THETA(4)
   Q=TVQ
   S1=V1
   S2=V2
   REP=IREP

$ERROR
 IPRE=F
   Y = F + F*EPS(1) + EPS(2)

$THETA
  2.65 ;[CL]
  65.99 ;[V1]
  38.4 ;[V2]
  6.5 ;[Q]
```

```
$OMEGA
  0.158 ;[P] omega(1,1)
  0.666 ;[P] omega(2,2)
  0.326 ;[P] omega(3,3)

$SIGMA
  0.01 ;[P] sigma(1,1)
  0.25 ;[A] sigma(2,2)
$SIMULATION (123456) ONLYSIM SUBPROBLEM=100
$TABLE ID TIME AMT RATE TAD DV MDV EVID REP ONEHEADER NOPRINT
FILE=072003sub.tab
```

2. The control stream used for modeling 1-compartment (peak-trough) model

```
$INPUT C ID TIME AMT ADDL II RATE TAD DV MDV EVID
$DATA PEAKTROUGHFOUR.CSV IGNORE=C
$SUBROUTINES ADVAN1 TRANS2
$PK
   TVCL=THETA(1)
   CL=TVCL*EXP(ETA(1))
   TVV=THETA(2)
   V=TVV*EXP(ETA(2))
   S1=V

 $ERROR
 IPRE=F
 W= IPRE
 IRES= DV-IPRE
 IWRE=IRES/W
   Y = F + W*ERR(1)

$EST METHOD=1 INTERACTION PRINT=5 MAX=9999 SIG=3    MSFO=0813pro001.msf
$THETA
  (0, 3) ;[CL]
  (0, 70) ;[V]
$OMEGA
  0.04 ;[P] omega(1,1)
  0.04 ;[P] omega(2,2)
$SIGMA
  0.04 ;[P] sigma(1,1)
$COV PRINT=E
```

```
$TABLE ID TIME ONEHEADER NOPRINT FILE=0813pro001.tab
$TABLE ID TIME CL V ONEHEADER NOPRINT FILE=PATAB0813pro001
$TABLE ID PRED RES WRES IPRE IWRE CPRED CWRES ONEHEADER NOPRINT
FILE=SDTAB0813pro001
$TABLE ID CL V FIRSTONLY NOAPPEND NOPRINT FILE=0813pro001.par
$TABLE ID ETA1 ETA2 FIRSTONLY NOAPPEND NOPRINT FILE=0813pro001.eta
```

3. The control stream used for modeling 1-compartment (trough-only) model

```
$INPUT C ID TIME AMT ADDL II RATE TAD DV MDV EVID
$DATA TROUGHFOUR.CSV IGNORE=C
$SUBROUTINES ADVAN1 TRANS2
$PK
   TVCL=THETA(1)
   CL=TVCL*EXP(ETA(1))
   TVV=THETA(2)
   V=TVV*EXP(ETA(2))
   S1=V

$ERROR
 IPRE=F
 W= IPRE
 IRES= DV-IPRE
 IWRE=IRES/W
   Y = F + W*ERR(1)

$EST METHOD=1 INTERACTION PRINT=5 MAX=9999 SIG=3    MSFO=091staatz001.msf
$THETA
  (0, 1) ;[CL]
  90.85 FIXED ;[V]
$OMEGA
  0.04 ;[P] omega(1,1)
  0 FIXED ;[P] omega(2,2)
$SIGMA
  0.00951 FIXED ;[P] sigma(1,1)
$COV PRINT=E
```

```
$TABLE ID TIME ONEHEADER NOPRINT FILE=091staatz001.tab
$TABLE ID TIME CL V ONEHEADER NOPRINT FILE=PATAB091staatz001
$TABLE ID PRED RES WRES IPRE IWRE CPRED CWRES ONEHEADER NOPRINT
FILE=SDTAB091staatz001
$TABLE ID CL V FIRSTONLY NOAPPEND NOPRINT FILE=091staatz001.par
$TABLE ID ETA1 ETA2 FIRSTONLY NOAPPEND NOPRINT FILE=091staatz001.eta
```

4. The control stream used for modeling 2-compartment (peak-trough) model

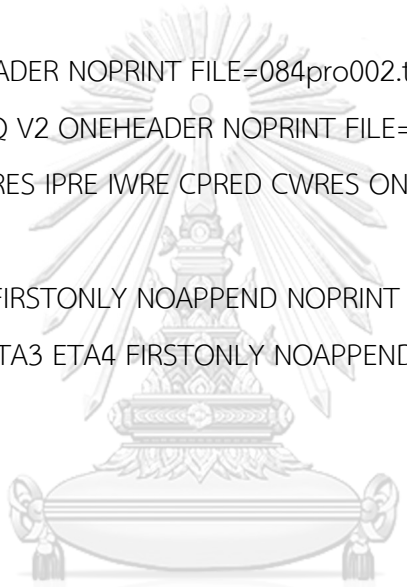
```
$INPUT C ID TIME AMT ADDL II RATE TAD DV MDV EVID
$DATA PEAKTROUGHFOUR.CSV IGNORE=C
$SUBROUTINES ADVAN3 TRANS4
$PK
   TVCL=THETA(1)
   CL=TVCL*EXP(ETA(1))
   TVV1=THETA(2)
   V1=TVV1*EXP(ETA(2))
   TVQ=THETA(3)
   Q=TVQ*EXP(ETA(3))
   TVV2=THETA(4)
   V2=TVV2*EXP(ETA(4))
   S1=V1
   S2=V2

 $ERROR
 IPRE=F
 W= IPRE
 IRES= DV-IPRE
 IWRE=IRES/W
   Y = F + W*ERR(1)

$EST METHOD=1 INTERACTION PRINT=5 MAX=9999 SIG=3    MSFO=084pro002.msf
$THETA
  (0, 1.385) ;[CL]
  (0, 59) ;[V1]
  (0, 5.8) ;[Q]
  (0, 34.56) ;[V2]
```

```
$OMEGA
  0.04 ;[P] omega(1,1)
  0.04 ;[P] omega(2,2)
  0 FIXED ;[P] omega(3,3)
  0 FIXED ;[P] omega(4,4)

$SIGMA
0.04 ;[P] sigma(1,1)
$COV PRINT=E
$TABLE ID TIME ONEHEADER NOPRINT FILE=084pro002.tab
$TABLE ID TIME CL V1 Q V2 ONEHEADER NOPRINT FILE=PATAB084pro002
$TABLE ID PRED RES WRES IPRE IWRE CPRED CWRES ONEHEADER NOPRINT
FILE=SDTAB084pro002
$TABLE ID CL V1 Q V2 FIRSTONLY NOAPPEND NOPRINT FILE=084pro002.par
$TABLE ID ETA1 ETA2 ETA3 ETA4 FIRSTONLY NOAPPEND NOPRINT
FILE=084pro002.eta
```



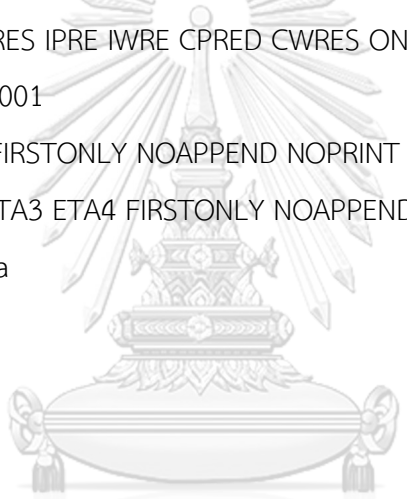
5. The control stream used for modeling 2-compartment (trough-only) model

```
$INPUT C ID TIME AMT ADDL II RATE TAD DV MDV EVID
$DATA TROUGHFOUR.CSV IGNORE=C
$SUBROUTINES ADVAN3 TRANS4
$PK
   TVCL=THETA(1)
   CL=TVCL*EXP(ETA(1))
   TVV1=THETA(2)
   V1=TVV1*EXP(ETA(2))
   TVQ=THETA(3)
   Q=TVQ*EXP(ETA(3))
   TVV2=THETA(4)
   V2=TVV2*EXP(ETA(4))
   S1=V1
   S2=V2

$ERROR
 IPRE=F
 W= IPRE
 IRES= DV-IPRE
 IWRE=IRES/W
   Y = F + W*ERR(1)

$EST METHOD=1 INTERACTION PRINT=5 MAX=9999 SIG=3
MSFO=091sanchez001.msf
$THETA
  (0, 1) ;[CL]
  22.36 FIXED ;[V1]
  8.77 FIXED ;[Q]
  34.29 FIXED ;[V2]
```

```
$OMEGA
  0.04 ;[P] omega(1,1)
  0 FIXED ;[P] omega(2,2)
  0 FIXED ;[P] omega(3,3)
  0 FIXED ;[P] omega(4,4)
$SIGMA
  0.0118 FIXED ;[P] sigma(1,1)
$COV PRINT=E
$TABLE ID TIME ONEHEADER NOPRINT FILE=091sanchez001.tab
$TABLE ID TIME CL V1 Q V2 ONEHEADER NOPRINT FILE=PATAB091sanchez001
$TABLE ID PRED RES WRES IPRE IWRE CPRED CWRES ONEHEADER NOPRINT
FILE=SDTAB091sanchez001
$TABLE ID CL V1 Q V2 FIRSTONLY NOAPPEND NOPRINT FILE=091sanchez001.par
$TABLE ID ETA1 ETA2 ETA3 ETA4 FIRSTONLY NOAPPEND NOPRINT
FILE=091sanchez001.eta
```



6. The control stream used for simulation from 1-compartment (peak-trough) model

```
$INPUT C ID TIME AMT RATE TAD DV MDV EVID
$DATA FULLPROFILE.CSV IGNORE=C
$SUBROUTINES ADVAN1 TRANS2
$PK
   TVCL=THETA(1)
   CL=TVCL*EXP(ETA(1))
   TVV=THETA(2)
   V=TVV*EXP(ETA(2))
   S1=V
   REP=IREP

$ERROR
 IPRE=F
   Y = F + F*ERR(1)

$THETA
  3.66 ;[CL]
  82.2 ;[V]
$OMEGA
  0.158 ;[P] omega(1,1)
  0.448 ;[P] omega(2,2)
$SIGMA
  0.00951 ;[P] sigma(1,1)
$SIMULATION (123456) ONLYSIMULATION SUBPROBLEM=100
$TABLE ID TIME AMT RATE TAD DV MDV EVID REP ONEHEADER NOPRINT
FILE=1cmtpeaktrough.tab
```

7. The control stream used for simulation from 1-compartment (trough-only) model

```
$INPUT C ID TIME AMT RATE TAD DV MDV EVID
$DATA FULLPROFILE.CSV IGNORE=C
$SUBROUTINES ADVAN1 TRANS2
$PK
   TVCL=THETA(1)
   CL=TVCL*EXP(ETA(1))
   TVV=THETA(2)
   V=TVV
   S1=V
   REP=IREP

$ERROR
 IPRE=F
   Y = F + F*ERR(1)

$THETA
  3.8 ;[CL]
  90.8 ;[V]
$OMEGA
  0.266 ;[P] omega(1,1)
$SIGMA
  0.00951 ;[P] sigma(1,1)
$SIMULATION (123456) ONLYSIMULATION SUBPROBLEM=100
$TABLE ID TIME AMT RATE TAD DV MDV EVID REP ONEHEADER NOPRINT
FILE=staatz.tab
```

8. The control stream used for simulation from 2-compartment (peak-trough) model

```
$INPUT C ID TIME AMT RATE TAD DV MDV EVID
$DATA FULLPROFILE.CSV IGNORE=C
$SUBROUTINES ADVAN3 TRANS4
$PK
  TVCL=THETA(1)
  CL=TVCL*EXP(ETA(1))
  TVV1=THETA(2)
  V1=TVV1*EXP(ETA(2))
  TVQ=THETA(3)
  Q=TVQ
  TVV2=THETA(4)
  V2=TVV2
  S1=V1
  S2=V2
  REP=IREP

$ERROR
  IPRE=F
  Y = F + F*ERR(1)

$THETA
 2.20 ;[CL]
 65.2 ;[V1]
 5.87 ;[Q]
 63 ;[V2]
```

```
$OMEGA
  0.403 ;[P] omega(1,1)
  0.714 ;[P] omega(2,2)
$SIGMA
  0.0118 ;[P] sigma(1,1)
$SIMULATION (123456) ONLYSIM SUBPROBLEM=100
$TABLE ID TIME AMT RATE TAD DV MDV EVID REP ONEHEADER NOPRINT
FILE=2cmtpeaktrough.tab
```

9. The control stream used for simulation from 2-compartment (trough-only) model

```
$INPUT C ID TIME AMT RATE TAD DV MDV EVID
$DATA FULLPROFILE.CSV IGNORE=C
$SUBROUTINES ADVAN3 TRANS4
$PK
   TVCL=THETA(1)
   CL=TVCL*EXP(ETA(1))
   TVV1=THETA(2)
   V1=TVV1
   TVQ=THETA(3)
   Q=TVQ
   TVV2=THETA(4)
   V2=TVV2
   S1=V1
   S2=V2
   REP=IREP

$ERROR
   IPRE=F
   Y = F + F*ERR(1)

$THETA
  3.48 ;[CL]
  22.4 ;[V1]
  8.77 ;[Q]
  34.3 ;[V2]
$OMEGA
  0.127 ;[P] omega(1,1)
```

```
$SIGMA
  0.0118 ;[P] sigma(1,1)
$SIMULATION (123456) ONLYSIM SUBPROBLEM=100
$TABLE ID TIME AMT RATE TAD DV MDV EVID REP ONEHEADER NOPRINT
FILE=sanchez.tab
```

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VITA

NAME	Nyein Hsu Maung
DATE OF BIRTH	24 May 1993
PLACE OF BIRTH	Yangon
INSTITUTIONS ATTENDED	University of Pharmacy, Mandalay, Myanmar
HOME ADDRESS	521/3-4 Soi Sriayuthaya 2-4, Room 403, Rangnam Apartment, Thung Phayathai, Ratchathewee, Bangkok, 10400.