DEVELOPMENT OF SERUM VANCOMYCIN CONCENTRATION MONITORING SERVICE AT RAMATHIBODI HOSPITAL

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DEVELOPMENT OF SERUM VANCOMYCIN CONCENTRATION MONITORING SERVICE AT RAMATHIBODI HOSPITAL

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ABSTRACT

The main objective of this study was to assess the appropriateness of serum vancomycin concentration monitoring (SVCM) including sampling time and serum concentration interpretation of vancomycin, and frequency of having vancomycin level within the therapeutic range. The study was limited to adult patients admitted into medical and surgical wards at Ramathibodi Hospital and who received vancomycin between 1st November 2006 and 15th December 2006 (pre-intervention period) and between 15th January 2007 and 28th February 2007 (intervention period). In-patient charts were reviewed retrospectively for the pre-intervention period, and during hospitalization in the intervention period. During the intervention period physicians and nurses were intervened for proper SVCM. In total, 52 patients were included in the study, 24 patients in the pre-intervention period and 28 patients in the intervention period. The appropriateness of SVCM was assessed using the serum drug concentration determination criteria, adopted from Winter, et al. The results demonstrated no statistically significant difference between the intervention group and the pre-intervention group in terms of weight, daily dose of vancomycin, peak concentration, trough concentration, frequency of having peak concentration within therapeutic range, frequency of having trough concentration within therapeutic range, and incidence of vancomycin-induced nephrotoxicity, except age. However, the appropriateness of SVCM was significantly increased from 38.1% in the pre-intervention group to 65.9% in the intervention group, $p < 0.001$. Pharmacist interventions were conducted in 92.9% of patients in the intervention group and 95.1% of the intervention were accepted. The acceptted interventions resulted in the proper data of vancomycin concentration to be further used for dosage adaptation.

It is concluded that the appropriateness of SVCM would be improved by the co-operation of the multidisciplinary team, and that pharmacists would play an important role in the team to run proper SVCM. This will improve the quality of patient care.

KEY WORDS: VANCOMYCIN/ SERUM CONCENTRATION MONITORING/ PHARMACIST/ TDM SERVICE

104 pp.

การพัฒนาการบริการติดตามตรวจวัดระดับยาในเลือดของยาvancomycin ในโรงพยาบาลรามาธิบดี (DEVELOPMENT OF SERUM VANCOMYCIN CONCENTRATION MONITORING SERVICE AT RAMATHIBODI HOSPITAL)

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บทคัดย่อ

การศึกษาครั้งนี้มีวัตถุประสงค์หลักเพื่อประเมินความเหมาะสมของการติดตามตรวจวัดระดับยาในเลือดของยา vancomycin ซึ่งประกอบด้วย การกำหนดเวลาในการเก็บตัวอย่างเลือด และการแปลผลค่าระดับยาในเลือด ตลอดจนการประเมินความถี่ของการมีระดับยา vancomycin ในเลือดอยู่ในช่วงการรักษา ทำการศึกษาเฉพาะผู้ป่วยผู้ใหญ่ที่นอนพักรักษาตัวในหอผู้ป่วยอายุกรรมและศัลยกรรม โรงพยาบาลรามาธิบดีและได้รับยา vancomycin ระหว่าง 1 พฤศจิกายน 2549 – 15 ธันวาคม 2549 (ช่วงก่อนมีการแทรกแซง) และ 15 มกราคม 2550 – 28 กุมภาพันธ์ 2550 (ช่วงมีการแทรกแซง) ทบทวนข้อมูลผู้ป่วยย้อนหลังในช่วงก่อนมีการแทรกแซงจากเวชระเบียนผู้ป่วย ส่วนในช่วงมีการแทรกแซง ทำการทบทวนข้อมูลผู้ป่วยร่วมกับการแทรกแซงโดยเภสัชกรไปยังแพทย์และพยาบาลเพื่อให้มีการติดตามตรวจวัดระดับยาในเลือดของยา vancomycin อย่างเหมาะสม ตลอดช่วงการศึกษามีผู้ป่วยจำนวนรวม 52 คน โดย 24 คนอยู่ในช่วงก่อนมีการแทรกแซง และ 28 คนอยู่ในช่วงมีการแทรกแซง การประเมินความเหมาะสมของการติดตามตรวจวัดระดับยาในเลือดของยา vancomycin ดำเนินการโดยอิงเกณฑ์ของ Winter และคณะ ผลการศึกษาพบความแตกต่างอย่างไม่มีนัยสำคัญทางสถิติระหว่างผู้ป่วยใน 2 ช่วงของการศึกษา ทั้งในเรื่อง น้ำหนัก ขนาดยาต่อวัน ระดับยาสูงสุดในเลือด ระดับยาต่ำสุดในเลือด ความถี่ของการได้ระดับยาสูงสุดที่ยังอยู่ในช่วงให้ผลการรักษา ความถี่ของการได้ระดับยาต่ำสุดที่ยังอยู่ในช่วงให้ผลการรักษา และอุบัติการณ์ของความเป็นพิษต่อไตจากยา vancomycin ยกเว้นอายุ แต่พบว่าความเหมาะสมของการติดตามตรวจวัดระดับยาในเลือดของยา vancomycin มีค่าเพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติ ($p < 0.001$) จากร้อยละ 38.1 ในช่วงก่อนมีการแทรกแซง เป็นร้อยละ 65.9 ในช่วงมีการแทรกแซง เภสัชกรดำเนินการแทรกแซงได้ในร้อยละ 92.9 ของผู้ป่วยในช่วงมีการแทรกแซง และได้รับการยอมรับร้อยละ 95.1 ผลของการยอมรับนี้ทำให้ได้ระดับยาในเลือดที่สามารถนำมาคำนวณเพื่อปรับขนาดยาใหม่

การศึกษานี้สรุปได้ว่าความเหมาะสมของการติดตามตรวจวัดระดับยา vancomycin ในเลือดจะประสบความสำเร็จได้ต่อเมื่อมีการทำงานร่วมกันแบบสหสาขาวิชาชีพ และเภสัชกรจะมีบทบาทสำคัญในการทำให้การติดตามตรวจวัดระดับยาในเลือดเป็นไปอย่างถูกต้อง ซึ่งจะเป็นการสนับสนุนคุณภาพการดูแลผู้ป่วยในที่สุด

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LIST OF ABBREVIATIONS

μg/mL	microgram/milliliter
ABW	actual body weight
AUC	area under the curve
CL	vancomycin clearance in milliliters per minute
CNS	central nervous system
CrCL	creatinine clearance
CSF	cerebrospinal fluid
Da	dalton
g	gram
h	hour
hr^{-1}	per hour
hrs	hours
hVISA	Heteroresistant vancomycin-intermediate *Staphylococcus aureus*
IBW	ideal body weight
IV	intravenous
Ke	elimination rate constant
Kg	kilogram
L	liter
L/kg	liter/kilogram
MBC	minimum bactericidal concentration
MD	physician
mg	milligram
mg/L	milligram/Liter
MIC	minimum inhibitory concentration
mL/min	milliliter/minut e
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*

LIST OF ABBREVIATIONS (continued)

Scr	serum creatinine
SD	standard deviation
SLE	systemic lupus erythematous
SVCM	Serum Vancomycin Concentration Monitoring
TBW	total body weight
TDM	therapeutic drug monitoring
Vd	volume of distribution

CHAPTER I
INTRODUCTION

Background and rationale

Vancomycin, a glycopeptide antibiotic**,** has been used widely in treating many susceptible infections**.** Current recommendation for vancomycin therapy includes the treatment of serious infections due to beta-lactam-resistant Gram positive bacteria, metronidazole-resistant organisms, or when the use of other antibiotics is contraindicated. A definitive relationship between vancomycin serum concentrations and oto- or nephrotoxicity has been clouded by several factors. In addition, concomitant drug therapy or underlying disease states that are associated with oto- or nephrotoxicity have been presented in many of the reported cases or selected reviews of these parameters. Toxicity is related to total vancomycin exposure. It would be logical to monitor some index of vancomycin accumulation, such as a trough concentration. Variability of vancomycin concentration in renal failure, renal replacement therapy and sepsis strengthen the necessity for monitoring in these conditions. Finally, in the intensive care situation where drugs with important hemodynamic effects are co-administered, therapeutic drug monitoring (TDM) is strongly recommended (1).

At Ramathibodi Hospital, a university teaching hospital, a tertiary care is provided. It is not surprising that drug are administered in individualized doses to patients. Before 2002, the individualizing was performed by physician alone. Pharmacy department started to offer pharmacokinetic consultation on the basis of requisition from physicians however physicians are allowed to consult or not to consult. The consultation mainly involved in dosage adaptation for individual patient based on his/her serum drug level. Since the start of service, the consulting pharmacist faced difficulties in the interpretation of serum drug concentration and the suggestion of dosage adjustment. This is due to no documented evidence and/or sampling time of

blood sampling. The drug level monitoring is thus turned out costly with less benefit. This study was conducted with the aim to improve the service and vancomycin was used as the object drug. The appropriateness of serum sampling time according to documentation and correctness were assessed during 2 phases, pre-intervention and intervention phase. In the pre-intervention phase, pharmacist played role upon physician's consultation while in the intervention phase, pharmacist immediately took action when vancomycin was firstly ordered by physician. The serum vancomycin concentrations were compared between pre-intervention and intervention period.

Objective

1. To assess and compare the appropriateness of serum sampling time and serum concentration interpretation of vancomycin at pre-intervention and intervention phase.
2. To determine and compare the frequency of having vancomycin level in therapeutic range at pre-intervention and intervention phase.

Expected outcomes and benefits

1. The increase in the appropriateness of serum sampling time and interpretation of vancomycin serum concentration.
2. The corporate service in multidisciplinary team for caring patients is implemented.
3. Vancomycin pharmacokinetic parameter of Thai patients are known and vancomycin dosage in Thai patients are suggested.

CHAPTER II
LITERATURES REVIEW

1. Pharmacology of vancomycin

Vancomycin, a glycopeptide antibiotic, was developed and released in late 1950s to treat aerobic Gram-positive infections, especially those caused by penicillin-resistant staphylococci. The compound was derived from *Amycolatopsis orientalis*, formerly known as *Streptococcus orientalis*, and a nickname "Mississippi mud" was used for vancomycin because of its brownish color from impurities in the early preparations (2). The drug is bacteriostatic against most enterococci and exhibits synergy when combined with aminoglycosides. Although vancomycin has been used widely to combat many susceptible organisms, the emergence of vancomycin-resistant enterococci has led to recommendations to restrict its use. Current recommendation for vancomycin therapy includes the treatment of serious infections of beta-lactam or metronidazole-resistant organisms or when the use of other antibiotics is contraindicated. However, vancomycin may be used prophylactically in some situations in which the patient is at risk for endocarditis or when methicillin-resistant *Staphylococcus aureus* or *S. epidermidis* is a risk.

2. Pharmacokinetics of vancomycin

Vancomycin is a large glycopeptide compound with a molecular weight of ~ 1450 Da. It is not appreciably absorbed orally and is eliminated primarily via the renal route, with > 80-90% recovered as unchanged form in urine within 24 hours after administration of single dose. The pharmacokinetic profile of vancomycin is complex and can be characterized by either a 2- or 3- compartment pharmacokinetic profile. The drug is administered intravenously, with a standard infusion time of at least 1 hour, to minimize infusion-related adverse effects. In patients with normal creatinine

clearance, vancomycin has an α-distribution phase of ~ 30 minutes to 1 hour and β-elimination half-life of 6 – 12 hours. The volume of distribution is 0.4-1 L/kg. The binding of vancomycin to protein has been reported in the literature to range from 10-50%. Factors that affect the overall activity of vancomycin include its tissue distribution, inoculum size, and protein-binding effects (3).

Oral bioavailability of vancomycin is poor (<10%), therefore systemic infections cannot be treated by this route of administration. However, patients with renal failure who have been given oral vancomycin for the treatment of antibiotic-associated colitis have accumulated therapeutic concentrations because gut wall inflammation increased vancomycin bioavailability and renal dysfunction decreased drug clearance (3).

Effect of disease states and condition on vancomycin pharmacokinetics and dosing (Table 2.1)

Nonobese adults with normal renal function (creatinine clearance > 80 mL/min) have an average vancomycin half-life of 8 hours (range, 7-9 hours), and an average volume of distribution (Vd) of 0.7 L/kg (range, 0.5-0.9 L/kg). Because of the moderate size of volume of distribution, fluid balance (under- or over-hydration) is less of an issue with vancomycin compared to the aminoglycoside antibiotics (4).

Renal dysfunction

- Since vancomycin is eliminated principally by glomerular filtration, renal dysfunction is the most important disease state that influences vancomycin pharmacokinetics. Vancomycin total clearance decreases proportionally to decrease in creatinine clearance.

Burns

- Major body burns (>30-40% body surface area) can cause large changes in vancomycin pharmacokinetics. Forty-eight to 72 hours after a major burn, glomerular filtration rate increases, which increases vancomycin clearance. Because of the increase in drug clearance, the average half-life for vancomycin in burn patients is 4 hours.

Obesity

- Obese individuals with normal serum creatinine concentrations have increased vancomycin clearance secondary to increased glomerular filtration rate and are best dosed using total body weight. Volume of distribution does not change significantly with obesity and is best estimated using ideal body weight (IBW) in patients who are more than 30% over ideal body weight (>30% over IBW, Vd = 0.7 L/kg IBW). Because the primary pharmacokinetic change for vancomycin in obesity is an increased drug clearance with a negligible change in volume of distribution, average half-life decreases to 3.3 hours.

Dialysis

- The effect of hemodialysis on vancomycin pharmacokinetics depends on the type of artificial kidney used for the procedure. Vancomycin is a relatively large molecule with a moderate-sized volume of distribution and intermediate protein binding. These characteristics lead to poor hemodilysis removal from the body. The mean vancomycin half-life for patients with renal failure is 120-140 hours.
    - Using traditional “low-flux” hemodialysis filters such as cuprophan, an insignificant amount (<10%) of the total vancomycin body stores is removed during a 3-4 hours of dialysis period.
    - Using a “high-flux” filters such as polysulfone, polyacrylonitrile and polymethylmethacrylate, vancomycin serum concentration decreases by one-third during the dialysis period but then slowly increases or “rebound” reaching nearly 90% of predialysis values.

Launay and cowoker (5) studied the pharmacokinetics of vancomycin in patients undergoing hemodialysis with high flux membranes demonstrated that there was a rebound in vancomycin plasma concentrations at the end of the session. The plasma profile of vancomycin concentrations versus time indicated that concentrations decreased dramatically during the session and then increased when the session was stopped for 3–6 hours (Figure 2.1). This rebound might result from drug recirculation from plasma protein binding sites. Recirculation from peripheral compartments was less likely to occur because of the low vancomycin volume of distribution, indicating that the drug remained mainly in

plasma. This rebound might be clinically significant, and it must be taken into account when determining vancomycin trough levels.

- Peritoneal dialysis removes only a negligible amount of vancomycin. Patients who develop peritonitis while receiving peritoneal dialysis can be treated by placing vancomycin into the dialysis fluid. Over a 6-hours dwell time, approximately 50% of a vancomycin dose (1000 mg in 2 L of dialysis fluid) is absorbed from the peritoneal cavity in renal failure patients without peritonitis. Peritonitis or inflammation of the peritoneal membrane facilitates absorption of vancomycin placed in the peritoneal dialysis fluid (up to 90% absorbed) and dialysis elimination of vancomycin from the body.

- Hemofiltration removes vancomycin from the body. Recommended doses for critically ill patients with acute renal failure undergoing continuous venovenous hemofiltration (CVVH) are a loading dose of 15-20 mg/kg followed by 250-500 mg every 12 hours. For patients undergoing continuous arteriovenous hemofiltration (CAVH), the recommended dose is 500 mg every 24-48 hours. Because of pharmacokinetic variability, vancomycin serum concentration should be measured in hemofiltration patients.

Table 2.1 Effect of disease states and condition on vancomycin pharmacokinetics and dosing (4)

Disease state/condition	Half-life (hours)	Volume of distribution (L/kg)	Comment
Normal renal function	8 (range; 7-9)	0.7 (range:0.5-1.0)	Usual dose 30 mg/kg in two divided doses
Renal failure	130 (range; 120-140)	0.7 (range:0.5-1.0)	Under- or overhydration does not affect the volume of distribution as much as with aminoglycosides
Burn patients	4	0.7	Because of shorter half-life, some patients may need a 6-8 hour dosage interval to maintain therapeutic trough concentration
Obese patients (>30% over IBW) with normal renal function	3-4	Vd = 0.7 IBW	Total daily doses are based on TBW, Vd estimates are based on IBW; because of shorter half-life, some patients may require an 8-hours dosage interval to maintain therapeutic trough concentration

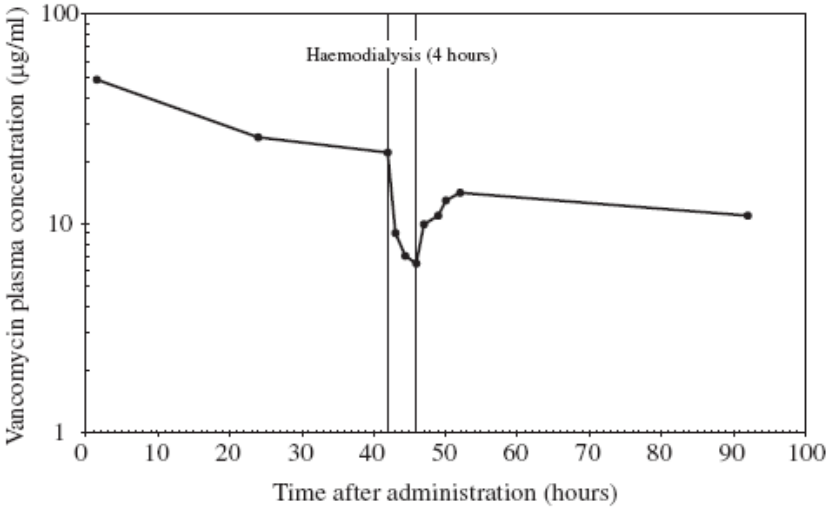

Figure 2.1 Plasma profile of vancomycin concentrations versus time in high flux hemodialysis (5)

Tissue distribution

Vancomycin penetrates into most body spaces, although the concentrations obtained are variable and somewhat dependent on the degree of inflammation present. In studies examining the penetration of vancomyin into the CSF of patients with uninflamed meninges, fairly low concentrations have been demonstrated (range, 0-3.45 mg/L), with corresponding CSF-to-serum ratios of 0-0.18. As expected, inflamed meninges improve penetration of vancomycin into CNS, with reported concentrations of 6.4-11.1 mg/L and CSF-to-serum ratios of 0.36-0.48 (3).

The penetration of vancomycin into lung is highly variable. Cruciani and coworker (6) investigated the penetration of vancomycin into the lung tissue of 36 patients undergoing a partial lobectomy. After intravenous administration of 1 g of vancomycin, concentrations ranged from 0 to 12.2 mg/L, with a mean concentration of 2.8 mg/L and a penetration of 41% were obtained. In a recent study investigating the penetration of vancomycin into the epithelial lining fluid of healthy volunteers given 1 g of vancomycin every 12 hours, the mean concentration at 12 hours was 2.4 mg/L, which represented a 52% of overall penetration rate (3). However, in critically injured patients, penetration of vancomycin into epithelial lining fluid was more variable,

ranging from 0 to 8.1 mg/L after several hours, with an overall blood-to-epithelial lining fluid penetration ratio of 6:1 (7).

3. Pharmacodynamics of vancomycin

There are very few human studies evaluating the pharmacodynamics of vancomycin, and the finding of most of those studies have not been conclusive in determining which parameter has the most value in predicting patient outcome. The majority of studies have involved relatively small patient populations and patients with a variety of infection types. One prospective evaluation randomized 106 patients with *S. aureus* infection, including bacteremia and endocarditis, to achieve 3 different trough concentration targets of 5-10 mg/L, 10-15 mg/L, and 15-25 mg/L. No relationships were found between peak concentrations, trough concentrations, or pharmacodynamic parameters (e.g., peak/MIC, time above the MIC, or AUC/MIC) and the organism eradication or overall patient outcome (3). On the other hand, Moise-Broder and coworker (8) examined the relationship between the vancomycin AUC/MIC and the outcome of 108 patients with methicillin-resistant *S. aureus* pneumonia. An AUC/MIC value of $\geq$ 400 was associated with a successful outcome, whereas an AUC/MIC of < 400 was associated with a lower eradication rate and a higher mortality rate (p=0.005). However, such relationship could not be demonstrated in a recent study performed in 168 patients with *S. aureus* bacteremia. In this study the MIC_{50} was 0.5 mg/L (range, 0.25-1.0 mg/L), and the median AUC/MIC value was 1072 (3).

Although susceptibility does not guarantee success, resistance certainly predicts failure, and several factors contribute to the failure of vancomycin in treating staphylococcal bacteremia and endocarditis. Firstly, in patients with endocarditis due to methicillin-susceptible *Staphylococcus aureus* (MSSA) infection, the rate of bacterial clearance is slower for vancomycin than for nafcillin (9-11). Recently, slower bacterial killing has also been demonstrated *in vitro*. For example, the rate of *in vitro* bacterial killing of MSSA isolates was comparatively lower for vancomycin than for nafcillin which significant reduction in mean cell count after 24 hours [The mean count for vancomycin had not significantly changed from that at 4 hours (reduction of

1.4 $\log_{10}$ CFU/mL from the initial inoculum; $p > 0.05$ by analysis of variance) compared with a significant reduction in counts after 24 hours for nafcillin (2.8 $\log_{10}$ CFU/mL; $p < 0.001$)], a finding that differs from those of studies performed with strains obtained during the 1960s and 1970s (12). Secondly, although most staphylococcal strains remain susceptible to vancomycin, minimum bactericidal concentrations (MBC) have been increasing over the course of several decades. The MBC and its relationship to the minimum inhibitory concentrations (MIC) determine whether an agent is bactericidal or bacteriostatic, and an antibiotic with an MBC:MIC ratio of 1 against a specific pathogen is defined as bactericidal for that agent. Generally, agents that are bacteriostatic have MBC: MIC ratios of 4-8. For antibiotics that are generally considered to be bactericidal against such pathogens as staphylococcus (e.g., beta-lactams), an MBC:MIC ration of > 32 is defined as denoting tolerance. Remarkably, MBC:MIC ratios of 4-16 have been reported for vancomycin (13). The emergence of glycopeptide-intermediate *S. aureus* (GISA), vancomycin intermediate *S. aureus* (VISA), and heterogenous GISA and VISA isolates among patients with serious infections have become problematic. High rate of treatment failure, heterogenous VISA infections, which are associated with prolonged bacteremia, high bacterial loads, and relatively lower vancomycin trough concentration have been reported (14). Thus, as MICs of vancomycin approach 2 mg/L, vancomycin treatment failure is more common, and mechanism could be either *agr* group II polymorphism or heterogenous GISA or both. Finally, since the late 1990s, vancomycin-resistant strains have been described in patients with previous exposure to vancomycin (e.g., patients undergoing renal dialysis) (12). In summary, the lack of good pharmacodynamic parameters to predict outcomes and emerging resistance among staphylococci and enterococci have posed medical dilemma to healthcare provider today.

4. Adverse effects of vancomycin

Soon after its introduction, vancomycin developed a reputation as being a relatively toxic antibacterial agent. Early preparations, often referred to as “Mississippi mud” contained many impurities that may have contributed to the frequency of

adverse effects. Improved purification procedures seem to have diminished the toxicity associated with vancomycin, and the frequency of serious toxicity is low. The most important potential adverse effect associated with the use of vancomycin is the damage to the auditory nerve and the consequent hearing loss. The potential for vancomycin to cause significant ototoxicity, as perpetuated in the medical literature, has probably been exaggerated. The risk of ototoxicity seems to be increased when vancomycin is administered in combination with an aminoglycoside. Although hearing occasionally improves when drug therapy is terminated, more commonly, it is permanent (15).

An infusion-associated reaction that is peculiar to vancomycin is referred to as the “red man” or “red neck” syndrome. Typically, it consists of pruritus, an erythematous rash that involves the face, neck, and upper torso, and occasionally hypotension. This reaction may occur within minutes after initiation of the drug infusion or may begin soon after its completion. Its manifestations are due to the nonimmunologically mediated release of histamine. This complication can be avoided by administering vancomycin over at least a 1-hour period. Smaller doses of vancomycin administered at shorter intervals (relative to the standard regimen) may also decrease the occurrence of this reaction. Because the red man syndrome is usually related to a rapid rate of infusion, vancomycin can be administered at a slower rate in a patient who has previously experienced these symptoms. Antihistamines such as hydroxyzine have been shown to be protective when given before infusion of vancomycin. Vasopressors may be needed if severe hypotension occurs. When used alone, vancomycin is rarely associated with nephrotoxicity. As with ototoxicity, however, the concomitant use of an aminoglycoside seems to enhance the risk of nephrotoxicity. Chemical thrombophlebitis occurs in as many as 13% of patients with peripheral venous cannulas. Hypersensitivity maculopapular or urticarial drug eruptions and drug-induced fever occur rarely. Reversible neutropenia has been noted in approximately 2% of vancomycin-treated patients. Its onset is usually delayed; the neutrophil nadir occurs 15 to 40 days after initiation of therapy (15).

5. Correlation of serum concentration with clinical response and toxicity of vancomycin

A close relationship between drug dosage, resultant serum drug concentration, and their relationship to minimum inhibitory concentration (MICs), minimum bactericidal concentration (MBCs), and therapeutic outcomes would be ideal. However, for vancomycin and many antibiotics, these relationships are influenced by many factor (16). It must either take into account underlying host factors and attainment of sufficient concentrations for sufficient duration at the site of infection, or have a reliable correlation between serum and tissue concentrations. Hence, given all these factors, specific comparative studies have not been able to show a direct relationship between vancomycin serum concentrations and therapeutic outcomes (17).

5.1 Vancomycin concentration and clinical efficacy

Although no correlation has been demonstrated between vancomycin levels and clinical response, some general conclusion can be drawn from the published reports of clinical trials. Studies in which patients with normal renal function were treated with fixed doses of vancomycin (1g IV q 12 hours) demonstrated the effectiveness of these regimens in the treatment of various staphylococcal or streptococcal infections and in the empirical treatment of febrile neutropenic patients with cancer. Whether higher or lower peak or trough concentrations of vancomycin would have been equally, more, or less effective is not known. Another problem in interpreting these levels is that the timing of determination of the peak concentration was not consistent between the studies. This is a critical issue, because vancomycin concentrations drop almost 50% within the first hour after the end of an intravenous infusion.

The patients in fixed dose studies generally had normal renal function. Although nomograms have been constructed to determine the proper dosage of vancomycin for patients with renal dysfunction, studies involving these nomograms generally focus on the pharmacokinetics of the drug rather than on the clinical outcomes of the patients. Certainly, vancomycin regimens that are based on the patient's age weight, and renal function or adjusted according to serum levels are effective in treating Gram-positive

infections. It is interesting to note that the vancomycin levels obtained with empirical dosing methods were similar to those noted in the studies in which serum levels were used to adjust the vancomyin dose. Although firm conclusions cannot be drawn, it would seem that deviations from the traditional therapeutic range of vancomycin that are seen with empirical dosing methods are probably unimportant in term of efficacy (18-21).

The development of staphylococcal resistance to vancomycin has been associated with prolonged exposure to low serum concentrations of the drug. GISA infection and subsequent failure of vancomycin therapy have been reported since the middle of the 1990s. By definition, these strains have a vancomycin MIC of 8-16 mg/L. The majority of cases of GISA infection have occurred among patients receiving peritoneal dialysis or hemodialysis who had received suboptimal, prolonged, and repeated courses of vancomycin. Most cases of GISA infection have involved serum concentrations of vancomycin that were consistently $\leq$ 10 mg/L. Although the number of case of GISA infection has remained low, there appears to be some evidences that this type of resistance has occurred in the past but may have been underreported because of our inability to detect these strains in the clinical laboratory (3).

5.2 Vancomycin concentration and toxicity

The major toxicities of vancomycin that have been suggested to be dose-related are ototoxicity and nephrotoxictiy. Vancomycin was not ototoxic in animal model and it is extremely rare reaction in clinical use. Furthermore, even when vancomycin monotherapy has been implicated as the cause of ototoxicity, the reactions have been irreversible in each case (18). Ototoxicity caused by vancomycin therapy has been reported in patients with decreased renal function and most frequently with high peak concentrations of more than 80 mg/L, although it has been reported with concentrations as low as 25 mg/L, with an estimated incidence of 1.5-5.5 %. Temporary tinnitus has been associated with serum concentrations of 40 mg/L (22).

The relationship between serum vancomycin concentrations and the drug's potential nephrotoxicity is enigmatic, because vancomyin is dependent on renal glomerular function for elimination. Therefore, as renal glomerular function decreases

secondarily to any cause, serum vancomycin concentrations increase. This situation inevitably results in the association of high serum vancomycin concentration with renal dysfunction. Determining that a causal relationship exists between these two events is virtually impossible. Nevertheless, attempts have been made to detect a relationship between serum vancomycin concentrations and its presumed nephrotoxicity (18).

Nephrotoxicity has been suggested to relate to trough concentrations of more than 20 mg/L, however it has occurred with concentrations as low as 10 mg/L. A potential link between duration of therapy and vancomycin nephrotoxicity has also been reported. A definitive relationship between vancomycin serum concentrations and oto- or nephrotoxicity has been clouded by several factors including purity of the product, concomitant drug therapy, and underlying disease states. Most of studies are retrospective, and definition for nephrotoxicity are highly variable. In many cases, serum vancomycin concentrations were measured after an elevation in serum creatinine level, making it uncertain which came first (3). However, despite the remarkably improved purity of the product over the course of nearly four decades of clinical use, vancomycin nephrotoxicity is still reported. In addition, concomitant drug therapy or underlying disease states that are associated with nephrotoxicity have been presented in many of the reported cases or selected reviews of these parameters. Reported incidence of vancomycin induced nephrotoxicity range between 0 and 5 % when use alone, and between 0 and 35 % with the addition of an aminoglycoside to the therapy (17).

In general, the use of serum drug concentrations to guide drug dosing in clinical practice can be rationalized only after several criteria are met. Firstly, a correlation between the drug concentration and the clinical efficacy or toxicity of the drug. This is a critical factor because if no correlation has been defined, then one cannot interpret the drug concentration measurements. Secondly, if a correlation between drug concentration and drug effect is known, then substantial interpatient variability in the pharmacokinetics of the drug must also exist. Otherwise, the desired drug concentration could be reliably obtained with empirical dosing method. Thirdly, the clinical efficacy or toxicity of the drug is difficult to measure or is delayed in

presentation. Finally, an assay with appropriate sensitivity and specificities must be readily available (23).

Some investigators have suggested that determination of vancomycin serum concentrations is unnecessary until the relationship between serum concentration and clinical outcome has been demonstrated. However, after waiting for such results for more than 30 years, it seems appropriate to continue monitoring vancomycin serum levels in order to ensure effective therapeutic concentrations until the results of well designed clinical studies become available (24).

6. Dosing regimens of vancomycin

6.1 Nomograms

Multiple approaches to dosing vancomycin exist, including empirical, nomogram, individualized and Bayesian. A small study in patients with normal renal function done by Healey and coworker (25) found the 2 g/day dosing divided as either 1000 mg every 12 hours or 500 mg every 6 hours to be appropriate as empiric dosing for patients with normal renal function. Trough levels from the two differently divided doses were 7.9 and 11.2 mg/L, respectively. The 12 hour dosing regimen had less accumulation. However, in patient with compromised renal function, trough levels will exceed these concentrations. Many authors therefore recommended to use nomograms proposed by Matzke (Figure 2.2), Moellering (Figure 2.3), Lake-Perterson (Table 2.2) and Rodvold (Table 2.3) in which the dose was based on a mg/kg basis and the one compartment model dosing interval was based on creatinine clearance. Others used the individualized dosing method based on the same approach that Sawchuk and Zaske used for aminoglycosides, and also used Bayesian model. The individualized and Bayesian methods are equally useful at achieving target concentrations and the latter method required a minimal number of serum samples which can accommodate 1- or 2- compartment models. Pyrka (17) reviewed a variety of dosing methods and found that the nomograms proposed by Moellering and Lake-Peterson (26, 27) had the best predictive performance.

Table 2.2 Vancomycin dosing interval based on estimated creatinine clearance (CrCL) by Lake-Peterson[a] (27)

Estimated CrCL [b] (mL/min)	Interval (hours)
> 90	6
70-89	8
46-69	12
30-45	18
15-29	24

[a] Patients received approximately 8 mg/kg. Calculated doses were rounded to the nearest 50 mg for convenience of preparation.

[b] CrCL estimated using the Cockcroft–Gault method and the patient's IBW. When the patient's measured serum creatinine was less than 1.0 mg/dL, substituted a value of 1.0 to the formulas.

Table 2.3 Vancomycin dosing interval as a function of CrCL by Rodvold (28)

CrCL [a] (mL/min/70 kg)	Dosing interval (hours)
> 65	8
40-65	12
20-39	24
10-19	48

[a] CrCL estimated using the Cockcroft–Gault method and the patient's IBW. When the patient's measured serum creatinine was less than 1.0 mg/dL, substituted a value of 1.0 to the formulas.

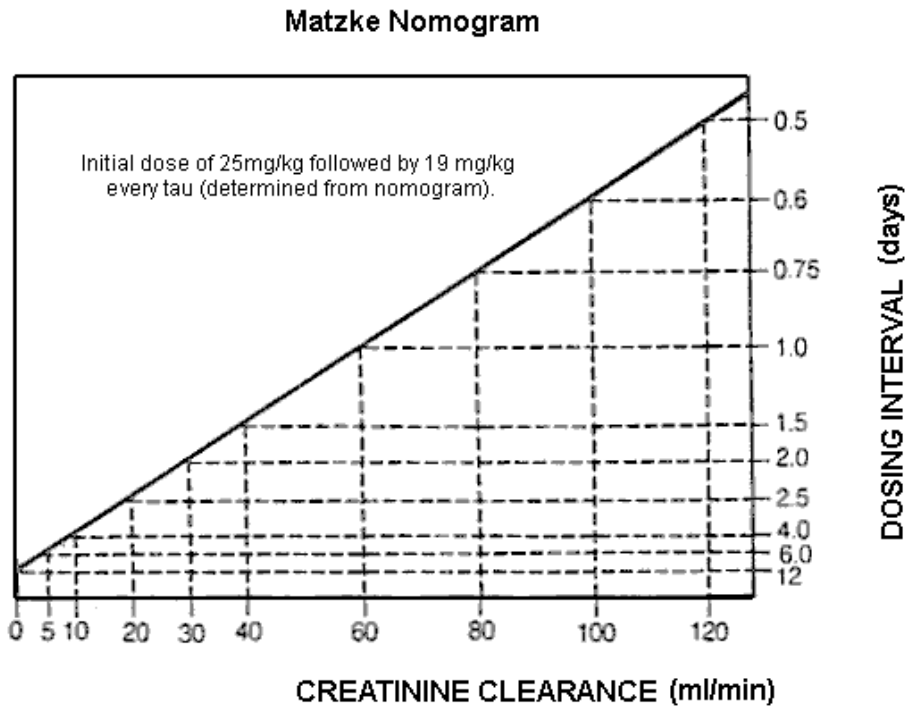

Figure 2.2 Matzke Nomogram (29)

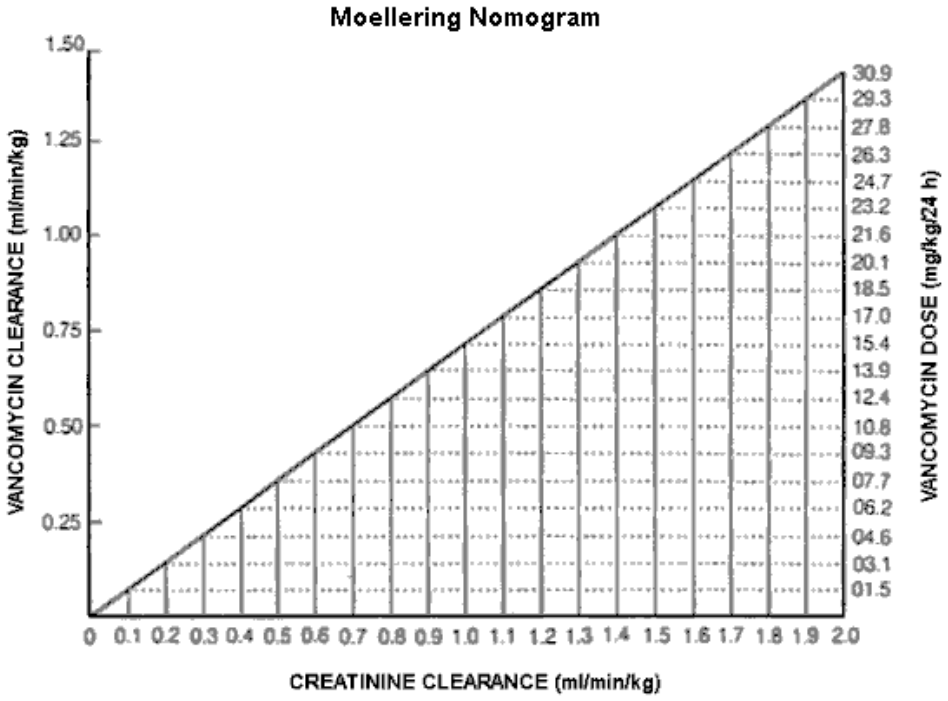

Figure 2.3 Mollering Nomogram (26)

6.2 Population pharmacokinetics

A number of predictor methods to determine dosing regimens based on estimations of a patient's pharmacokinetic parameters for vancomycin have been developed. Some of the more commonly cited predictors are the Birt, Matzke, Burton, and Rodvold methods. Depending on the specific patient population, one method may be better than another for estimating that population's vancomycin concentrations. Some of the calculation challenges associated with these predictors include selecting the best dosing weight and estimating vancomycin clearance from estimated creatinine clearance (CrCL), especially in the presence of diminished renal function. Determining the appropriate weight to estimate CrCL and volume of distribution is increasingly important. Knowing how dosing methods perform for a given patient population can be helpful. One study evaluating the utility of three methods found that the Lake–Peterson method typically provided the best vancomycin dosing estimates for individuals with a CrCL above 15 mL/min, while the Matzke method was best for CrCL of ≤15 mL/min. Because vancomycin pharmacokinetic parameters can vary widely among individuals, it may be necessary to develop institution-specific, population-based dosing methods and monitoring approaches.

Murphy and coworkers (30) studied seven methods for estimating vancomycin pharmacokinetic parameters and determine which method best predicted measured concentrations. The seven methods consisted of Birt, Matzke, Burton, Burton revised, Ambrose, Bauer, and Rodvold methods. Data from 189 patients were retrospectively reviewed. The Matzke method had the best combination of the least bias and the best precision. However, the seven methods were varied widely in predicting vancomycin trough concentrations compared with measured serum concentrations and were not sufficiently reliable to replace therapeutic monitoring of vancomycin serum concentrations (Table 2.4).

Table 2.4 Pharmacokinetic parameter prediction methods (30)

	Vancomycin clearance (mL/min)	Volume of distribution;Vd (L)
Matzke method[a,b]	(CrCL × 0.689) + 3.66	Vd = 0.72 L/kg if CrCL is >60 mL/min; Vd = 0.89 L/kg if CrCL is 10–60 mL/min; Vd = 0.9 L/kg if CrCL is <10 mL/min.
Rodvold method[a,c]	(CrCL × 0.79) + 15.7	Vd = 0.5 L/kg if CrCL is >70 mL/min/70 kg Vd = 0.59 L/kg if CrCL is 40–70 L/min/70 kg Vd = 0.64 L/kg if CrCL is 10–39 mL/min/70 kg
Birt method[a,c]	0.674 × CrCL + 13.45	Vd = 0.54 L/kg
Ambrose method[a,d]	CrCL	Vd = [0.17 × (age in years)] + [0.22 × (ABW in kg)] + 15
Burton method[e]	CLvanco(mL/min/kg) = [(CrCL (mL/min) × 0.0075]+ 0.04	Vd = 0.47 L/kg
Burton revised method[e,f]	CLvanco(L/hr) = CrCL (mL/min) × 0.048	Vd = 0.706 L/kg
Bauer method[g]	CLvanco (mL/min/kg) = [0.695 × CrCL (mL/min/kg)] + 0.05	Vd = 0.7 L/kg

Creatinine clearance (CrCL) units are stated for each method. The elimination rate constant (Ke) is determined from Ke = CLvanco/Vd.

a. Vd estimated using the patient's actual body weight (ABW).

b. CrCL estimated using the Cockcroft–Gault method and the patient's ABW.

c. CrCL estimated using the Cockcroft–Gault method, but the weight to be used is not stated. Since Cockcroft–Gault used ABW in their study, this approach is assumed and used.

d. CrCL estimated using the Cockcroft–Gault method, but the weight to be used is not stated. Elsewhere in the same textbook, it is recommended that an adjusted body weight (BWadj) be used, so this approach is assumed and used. The method for estimating BWadj is IBW + 0.4(ABW– IBW), where IBW = ideal body weight.

e. Vd estimated using BWadj if ABW > IBW;
ABW used if ≤ IBW. IBW = 0.73 × height (cm) – 59.42.

f. Burton developed the second equation after feedback from measured vancomycin concentrations and use of Bayesian iteration.

g. Uses the Salazar–Corcoran approach to estimate CrCL in obese patients (defined as ABW/IBW ≥ 1.3). Use Cockcroft–Gault and ABW to predict CrCL for nonobese patients. Vd estimated using ABW up to ABW/IBW = 1.3. After that IBW is used. IBW is calculated using the formula of Devine for all methods except Burton's.

IBW (males) = 50 kg + 2.3(height [in] – 60) kg
IBW (females) = 45.5 kg + 2.3(height [in] – 60) kg

Lee and coworkers (31) studied two predictive methods for determining serum vancomycin concentrations (SVCs) at a Veterans Affairs medical center. The data of 122 patients who received intravenous vancomycin and had vancomycin concentrations were retrospectively reviewed. Creatinine clearance was estimated by the Cockcroft and Gault equation. Volume of distribution and vancomycin clearance were calculated for each patient, using the Leonard and Boro method and the Rushing and Ambrose method. The Sheiner and Beal method for determining precision and bias was used to evaluate whether the two methods significantly differed in their ability to predict SVCs. There were no significant differences in 95% confidence intervals for relative precision and relative bias between the two methods. In patients whose weight was within 120% of their ideal body weight (IBW), the Leonard and Boro method was significantly more precise and less biased in predicting SVCs. In patients whose weight exceeded 120% of their IBW, the Rushing and Ambrose method was less biased and tended to be more precise, although the difference in precision was not significant.

Leonard and Boro method (32):

$$CL = 0.9 \times CrCL\ (mL/min/kg) \times ABW$$

$$Vd = 0.7\ L/kg \times ABW$$

Rushing and Ambrose method (33):

$$Vd = (0.17 \times age) + (0.22 \times ABW) + 15$$

$$CL = CrCL\ (mL/min/kg) \times (\text{lesser of ABW or IBW})$$

Where; Vd = volume of distribution,

ABW = actual body weight in kilograms

IBW = ideal body weight

CL = vancomycin clearance in milliliters per minute

(Cockcroft and Gault equation)

6.3 Therapeutic drug monitoring (TDM)

6.3.1 Rational for monitoring vancomycin concentrations

Vancomycin has a narrow therapeutic index, with nephrotoxicity and ototoxicity complicating therapy. It has been traditional to monitor peak and trough concentration, just as in the case of aminoglycosides. However, because the bactericidal action of vancomycin is quite different from that of the aminoglycosides, many clinicians have questioned the need to measure peak concentrations. Vancomycin, like beta-lactam antibiotics, works best if the concentration at the site of activity is maintained above MIC throughout the dose interval (so called time-dependent killing). This argues against the need for peak concentration measurement, and suggests that a continuous infusion may be the ideal. Wysocki and coworkers (34),(35) studied in 119 critically ill patients with MRSA infections to compare a continuous infusion of vancomycin (targeted plateau drug serum concentrations of 20 to 25 mg/L) and intermittent infusions of vancomycin (targeted trough drug serum concentrations of 10 to 15 mg/L). The efficacy and tolerance were comparable. Continuous infusion may be a cost-effective alternative to intermittent infusion of vancomycin**.** In practice, a continuous infusion is rarely administered, and spaced dosing at 6 or 12 hour intervals is more common. Efficacy can usually be assumed if the trough concentration is above MIC of the infection organism (1). Researchers recommend keeping the peak value 5 to 8 times the MIC and the trough value 1 to 2 times the MIC, which for most bacteria is < 5 mg/L. Vancomycin regimens that are based on empiric pharmacokinetics (using a patient's age, weight, and renal function) or adjusted based on serum levels have been shown to be equally effective in treating Gram-positive infections. Zimmernan and coworkers (36) studied in 273 patients receiving vancomycin and found that patients whose trough concentrations were $\geq$ 10 mg/L were likely to become afebrile and had a normal white blood cell count within 72 hours.

It is likely, although unproven, that toxicity is related to total vancomycin exposure. It would seem logical to monitor some index of vancomycin accumulation, such as a trough concentration. Variability of vancomycin concentration in renal failure, renal replacement therapy and sepsis strengthen the case for monitoring in

these conditions. Similarly, in the intensive care situation where drugs with important hemodynamic effects are co-administered, therapeutic drug monitoring is strongly recommended (1).

A greater problem is encountered when one attempts to predict serum vancomycin concentration and/or adjust vancomycin dosage regimens based on reported concentrations in a particular patient. Vancomycin has a large and variable clearance and volume of distribution and exhibits multicompartmental pharmacokinetics best described by 1- to 2- to 3- compartment model. This creates a problem in therapeutic drug monitoring. The serum vancomycin concentration in relation to the time of administration is so variable that one is never certain if the sample is obtained too early (e.g., during the distribution phase), at the peak concentration, or after the peak concentration. The literature regarding this problem is controversial and inconsistent.

Dosing nomograms for vancomycin have been developed in order to achieve serum vancomycin concentration within the reported therapeutic range. These include the Mollering, Matzke, and Lake and Peterson nomograms, as well as the Sawchuk-Zeske and Bayesian methods, and traditional pharmacokinetic equations. These methods have not all been evaluated in large number of patients. However, when evaluated, they have achieved good-to-mixed resulted, due largely to the drug's variable pharmacokinetics. Conceivably, there have been better results obtained with some of these newer methods, but there seems to be little or no reason to use them as most patients probably do not require TDM. A single trough concentration should be adequate in monitoring, as this may be related to clinical efficacy (2).

6.3.2 Who should receive vancomycin therapeutic drug monitoring?

In general, routine monitoring of serum vancomycin concentration does not seem to make sense. However, there are a number of clinical setting in which following vancomycin levels in serum on other body fluids may be prudent (23, 37, 38).

1. *Patients receiving vancomycin/ aminoglycosides combinations*. Although it is not clear that monitoring serum vancomycin concentrations will prevent nephrotoxicity, increasing trough serum levels of vancomycin may be a

sensitive indicator of nephrotoxicity and may provide an early warning to the clinician that the doses of both vanomycin and the aminoglycosides should be adjusted.

2. *Anephric patients undergoing hemodialysis and receiving infrequent doses of vancomycin for serious systemic infection (especially if the newer high-flux dialysis membranes are being used).* For such patients it may be reasonable to monitor a serum trough concentration occasionally to make certain that serum vancomycin concentrations are adequate (or present). The infrequent dosing could lead to prolonged periods of subtherapeutic serum concentration if a dosing error occurs or if the removal of vancomycin is enhanced by the new, more efficient dialysis membrane.
3. *Patients receiving higher-than-usual doses of vancomycin*. The emergence of penicillin-resistant pneumococci has led to increased interest in the use of vancomycin for treating meningitis due to these organisms. Treatment failures have been reported in some cases, perhaps because of the fact that standard doses are inadequate for meningitis. Given the relative lack of toxicity, it may be reasonable to try higher dose of vancomycin. If this is done, monitoring serum concentrations seems prudent.
4. *Patients with endocarditis, IV drug abusers, and patients with sepsis or burned*. These patients tend to have such large volumes of distribution and increased drug clearances that obtaining a vancomycin trough concentration and adjusting the dosage regimen accordingly would be recommended.
5. *Patients with rapidly changing renal function.* Monitoring serum concentration may be reasonable for such patients (even though the dosage could be determined on the basis of nomograms), because it may sometimes be easier to monitor serum levels than attempt repeatedly to correct dosage on the basis of nomograms or other formulae.

6.3.3 Sampling time recommendations

Drug levels that are utilized to make pharmacokinetic dosage adjustments must be correctly and accurately obtained. Failure to do so can result in dangerous and

inappropriate adjustments in drug therapy (39). Justification for monitoring peak concentration measurements with vancomycin is lacking. However, if vancomycin peak concentrations are obtained, there are several issue that must be remembered. Vancomycin pharmacokinetics is described by 1-, 2- and 3- compartment models. To get accurate serum levels to best pharmacokinetic predictions upon, one must be certain that the distribution phase is complete before the peak serum level is drawn. If not, the elimination half-life will be underestimated. This has led to inconsistencies in the timing of peak concentrations related to the distribution phase. There are many suggested times to obtain peak values ranging from 15 minutes to 2 hours post infusion. For example, 1-hour post infusion was recommended in Table 2.5 and Table 2.6. Many studies have taken the peak levels 2 hours following an infusion. There are two practical issues to discuss. Firstly, if a trough is obtained within 30 minutes of the next dose it can be assumed that it was obtained immediately before the next dose. The fall in concentration of the trough over that 30 minute period will in almost all cases be undetectable. Secondly, it is common in practice to measure trough and peak around the administration of a dose. If steady state (at least 5 half-lifes after the initiation of therapy) has been achieved, then the pre-dose trough can be extrapolated to a post-dose trough. Care must be made in performing pharmacokinetic calculations based on the extrapolated trough. This approach will decrease the number of errors associated with sample collection, but can increase pharmacokinetic calculation errors if care is not exercised. The frequency of monitoring is also important. Generally, the clinical situation and patient specific factors should guide frequency of sampling (40, 41).

Andres and coworkers (42) assessed the performance of a one-compartment Bayesian forecasting method for estimating vancomycin 2 hours after infusion (C2h) and mean vancomycin concentration in steady-state (Cav,ss) on the basis of a single trough sample (Cmin), in different conditions (steady state, patient renal function, and age), and according to clinical significance. Vancomycin serum concentrations (n = 108) were analyzed by fluorescence polarization immunoassay, from 79 adult patients. The predictive performance of the Bayesian method was determined by calculating the mean prediction error (ME), the mean absolute error (MAE) and the root squared prediction error (RMSE). A linear regression analysis was earned out between

estimated and observed concentrations. The predicted C2h was not significantly different from the observed, and the least biased (ME = -1.08) and most precise (MAE = 3.81) predictions were from patients with normal renal function and steady-state conditions. In this population, the concordance in dosage recommendations with the data pair results was 75% of patients. The best correlation between observed and predicted concentrations was found for Cav,ss ($r = 0.94$; $p < 0.00005$). Predictions of the Cav,ss were more precise (ME = -0.54) and accurate (MAE = 1.74) than the C2h predictions. Therefore, vancomycin can be monitored by one time determining it's level in steady state for most patients with normal renal function.

Table 2.5 Sampling time recommendation of vancomycin (40)

Vancomycin serum levels	Recommendation
1. Serious or life-threatening infections	Trough only
2. Patients receiving aminoglycoside or amphotericin B combination therapy	Trough only
3. Anephric patients undergoing hemodialysis and receiving infrequent doses of vancomycin for serious systemic infections	Trough only
4. Patients receiving higher than usual doses of vancomycin	Initial peak and trough Once therapeutic, do not repeat levels if fluid status and renal function are stable
5. Patients with rapidly changing renal function*	Random trough only
6. Morbidly obese patients	Trough only
7. Patients receiving prolonged (>14 days) vancomycin therapy	Trough only
8. Patients with endocarditis, osteomyelitis, meningitis	Peak and trough

*Rapidly changing renal function = 50% increase/decrease or 0.5 mg/dL increase/decrease in Scr over 24-48 hours.

Table 2.6 Time to obtain vancomycin concentration (40)

	Time to obtain
Trough concentration	½ hour before infusion
Peak concentration	1 hour after end of infusion

Launay and cowoker (5) studied the pharmacokinetics of vancomycin in patients undergoing hemodialysis with high flux membranes and recommended that determination of vancomycin trough levels in these patients should be performed before the hemodialysis session. To determine if supplemental doses of vancomycin are needed, postdialysis serum concentration should be measured after the rebound period (3-6 hours) in patients receiving hemodialysis with a “high-flux” filter.

Continuous renal replacement therapy increases total body clearance of vancomycin. However, quantification of vancomycin removal is difficult to estimate, and it is thus recommended that plasma levels of the drug be monitored. When a continuous technique is used, there is no rebound in vancomycin plasma concentration. Total body clearance of vancomycin is almost constant, and determination of trough levels may be performed at any time while continuous hemodialysis is being performed. However, if dialysis is stopped and if vancomycin treatment must be continued, then the plasma concentration of vancomycin 4–6 hours after stopping hemodialysis should be determined before any readministration of the drug (Table 2.7).

Table 2.7 Vancomycin dosage and administration in patients on hemodialysis (5)

Vancomycin dosage and administration in patients on hemodialysis			
Dialysis	**Membrane**	**Initial dose**	**Maintenance doses**
Chronic hemodialysis	High flux	1 g	Vancomycin maintenance doses range from 500 mg to 1 g. Maintenance doses should be administered according to plasma vancomycin concentration, as determined from blood samples drawn before a session.
Continuous hemodialysis	High flux	1 g	Vancomycin maintenance doses range from 500 mg to 1 g. Maintenance doses should be administered according to plasma vancomycin concentration, as determined from blood samples that may be drawn at any time during continuous hemodialysis. When the dialysis technique is discontinued and if vancomycin treatment must be continued, then the following maintenance dose should be administered according to plasma vancomycin concentration, as determined from a blood sample drawn at least 6 hours after the end of dialysis.

6.3.4 Therapeutic range

Many putative “therapeutic range” are illusionary. This is the case with vancomycin, at least for peak concentrations. Ranges for peak concentrations of 20-40 mg/L have been widely quoted, but with little supportive evidence. The original report of Geraci and coworkers (43, 44) suggested that peaks greater than 50 mg/L should be avoided based on two cases of ototoxicity at concentrations greater than 80 mg/L. Repetitive citation of this paper in the literature has resulted in the “establishment” of the peak concentration strategy. One of the problems with peak concentration measurement is that the range is meaningless unless the timing of sampling is also stated. A peak concentration of 40 mg/L has no entirely different meaning if the sample was taken just after the end of the infusion than if taken 1 or 2 hours later. A survey of Australasian hospitals (45) indicated that peaks were sampled from immediately postinfusion to 3 hours later and yet was all considered with reference to the same therapeutic range of 20-40 mg/L.

A stronger but incomplete case can be made for trough concentration monitoring. The given range of 5-10 mg/L has reasonable literature support and reflects the need for the concentration of antibiotics to be above the MIC of the organism for the duration of the dose interval. Concentrations below the MIC have been associated with therapeutic failure. The MIC of vancomycin is approximately 1.5 mg/L for many susceptible organisms. The protein binding of vancomycin is approximately 50% which would argue that the minimum total concentration should be at least 3 mg/L. Trough concentrations above 10 mg/L have been associated with an increased risk of nephrotoxicity. It should be noted that nephrotoxicity with vancomycin alone is not common, usually around 5%, and is usually reversible. Therefore, a range of 5-10 mg/L for trough concentration appears to have some validity.

More recently, however, this target is being re-evaluated due to increasing vancomycin MICs and the growing number of vancomyin therapeutic failures. Some investigators have shown that MICs of vancomycin for *Staphylococcus* sp. have not been increasing in recent years. Rather, perhaps "underdosing" of vancomycin is not new and has been associated with failures for decades. Independent on the reason, many clinicians are now targeting higher troughs for vancomycin (from 15 to 20 mg/L), especially when treating more deep-seated infections (i.e., meningitis, endocarditis, osteomyelitis), in which vancomycin penetration may also be an issue (39).

In 2005, the publication of two new sets of treatment guidelines gave clinicians published target vancomycin monitoring parameters for the first time. These recommendations are based on expert opinion, however, and remain somewhat controversial. The recent pneumonia guidelines (46), a joint publication form the American Thoracic Society (ATS) and the Infectious Disease Society of America (IDSA), advocate targeting higher vancomycin trough concentration. Vancomycin is a large molecule, and has been known for sometime that penetration into the lung and other infection sites may be difficult. Therefore, increasing the target trough serum concentrations may result in higher pulmonary drug concentrations. The recommended target vancomycin trough in these guidelines is 15 to 20 mg/L. However, there are no specific data to say that troughs more than 15 mg/L are associated with improved outcomes over trough levels more than 5 or 10 mg/L.

Similarly, the American Heart Association in conjunction with the IDSA revised treatment recommendations for endocarditis in June 2005 (47). The recent published endocarditis guidelines also recommend specific target concentrations for vancomycin. Because many clinicians consider the vegetations involved in endocarditis to be relatively difficult to penetrate, the traditional target troughs were 15 to 20 mg/L for this infection. As with the pneumonia guidelines, these targets reflect the opinion of the expert panel in the absence of data to document the ideal target. As endocarditis typically presents with positive blood cultures and the location of the infection is actually inside the vascular system, the target trough of 10 to 15 mg/L is likely reasonable. Endocarditis is also treated for a relatively long time depending on the cause and type of infection. Therefore, intravenous antibiotics, including vancomycin, may be continued for two to six weeks. In this situation, the targeting of vancomycin troughs of 10 to 15 mg/L may help reduce the incidence of vancomycin toxicity.

The incidence of peak concentration monitoring in these guidelines is intriguing. The expert panel recommended a target peak concentration of 30 to 45 mg/L. Most clinicians rely solely on trough concentration monitoring given the predictable intrapatient kinetics of this agent and the lack of strong association for efficacy or toxiticy with peak concentrations. There are specific instances in which measurement of vancomycin peak concentrations has historically been considered clinically important. These include infections located in sites that are difficult to penetrate and include central nervous system (CNS) infection (48), bone and joint infections and pneumonia. However, the clinical relevance or correlation of improved outcomes and specific peak concentrations has not been proven.

Sakoulas and coworkers (49) evaluated microbiological properties of methicillin-resistant *Staphylococcus aureus* (MRSA) during prolonged vancomycin therapy. Despite the lack of development of detectable resistance, MRSA exposed to vancomycin for prolonged periods may begin to develop vancomycin tolerance and decrease autolysis. In addition, suppression of *agr* (accessory gene regulator function) appears to end after vancomycin is stopped. Whether these changes are prerequisites for attenuated vancomycin efficacy and the development of glycopeptide resistance warrants further study. The development of vancomycin resistance may be more

difficult under conditions where vancomycin serum concentrations are maintained >10 mg/L.

Hidayat and coworkers (50) performed a prospective cohort study in adult patients infected with MRSA to determine the distribution of vancomycin MIC and treatment outcomes with vancomycin doses targeting an unbound trough of at least 4 times the MIC from August 1, 2004, through June 30, 2005. There were 95 patients in the study, 51 (54%) were infected with high-MIC strains and had pneumonia (77%) and/or bacteremia. An initial response rate of 74% was achieved if the target trough was attained irrespective of MIC. However, despite achieving the target trough, the high-MIC group had lower end-of-treatment responses (24/39 (62%) vs. 34/40 (85%); $p = 0.02$) and higher infection-related mortality (11/51 (24%) vs. 4/44 (10%); $p = 0.16$) compared with the low-MIC group. High MIC ($p = 0.03$) and Acute Physiology and Chronic Health Evaluation II score ($p = 0.009$) were independent predictors of poor response in multivariate analysis. Nephrotoxicity occurred only in the high-trough group (11/63 (12%)), significantly predicted by concomitant therapy with other nephrotoxic agents.

In this study, vancomycin therapy was given in doses to attain an unbound trough target of at least 4 times the MIC of the infecting strain. They found that patients who achieved target trough levels within 72 hours of therapy had a 20% higher response rate than those who did not. However, despite favorable initial responses for patients who attained target trough levels, response rates assessed at the end of therapy were significantly lower for patients infected with strains having an MIC of 2 μg/mL compared with 1 μg/mL or less (62% vs. 85%). Both high vancomycin MIC (2 μg/mL) and severity of underlying illness were found to be independent predictors of poor treatment response to vancomycin, with risks of 6.02 and 3.14, respectively, after controlling for potential confounders in a multivariate analysis. Vancomycin failure rates of 22%, 27%, and 51% were observed for patients infected with MRSA strains that had MICs of 0.5, 1.0, and 2.0 μg/mL, respectively. In this study, high MIC was a significant predictor of end-of-therapy vancomycin failure despite the achievement of target trough levels. Initial eradication of susceptible strains, leaving subpopulations of hVISA as the predominant population, may have accounted for the persistence of infection and therefore “late” failure in patients. Of

interest, in a subgroup of nephrotoxicity attributable to vancomycin was observed in a 12% incidence compared with none in the high and low-trough groups, respectively. Duration of therapy increases the risk of nephrotoxicity from 6% to 21% for patients receiving high-dose therapy when treatment extends beyond 1 week and up to 30% for those receiving more than 2 weeks of treatment. Vancomycin therapy with concomitant nephrotoxic agents is the single independent predictor of nephrotoxicity in a multivariate analysis controlling for age, duration of therapy, and trough levels achieved (<15 vs. ≥15 mg/L).

6.3.5 Literature supporting therapeutic drug monitoring

Karam and coworkers (51) found no differences with respect to cure, improvement, failure and nephrotoxicity when patients who were dosed according to nomogram were compared to patients who were monitored using traditional pharmacokinetic equations.

Welty and coworkers (52) found that patients receiving vancomycin who were managed through a therapeutic drug monitoring (TDM) service and patients managed empirically (non-TDM) had the incidence of vancomycin related renal insufficiency 7% and 24%, respectively. Also, TDM patients received an average of 5 grams less of vancomycin than non-TDM patients. The duration of therapy was an average of 2 days less in the TDM group. Mean length of stay was 38.0 days for the TDM group and 44.5 days for the non-TDM group.

Winter and coworkers (53) studied the effects of pharmacokinetic consultation by a pharmacist on the quality of drug therapy. Patients were included in the study if they had received either an aminoglycosides or theophylline preparation. Data were collected retrospectively for three time periods: three months before, four months during and three months after a period of intervention by a pharmacist with special responsibilities for pharmacokinetic monitoring of patients on medical team. Serum drug concentration determination (SDCDs) in the pharmacist intervention phase, 54% were appropriate, compared with 16% before intervention, and 21% in the post intervention phase. However, pharmacist intervention did not affect the number of adverse drug reactions or medical specialty consultations or average length of stay.

Benkert and coworkers (54) performed a retrospective chart review of patients treated with vancomycin to evaluate dose adjustments based on monitoring peak and trough levels versus trough alone. Forty-nine patients were monitored with peak and trough serum vancomycin concentrations, while 37 patients were monitored with trough level only. Patients in both groups received a mean daily vancomycin dose of about 1500 mg. The mean duration of therapy was not significantly different between the groups. A regression analysis revealed the trough concentration as the only significant factor predicting a change in the dose. The availability of peak concentrations did not increase the number of dose adjustment.

Bond and coworkers (55) evaluated the association between pharmacist-managed aminoglycosides or vancomycin therapy for hospitalized Medicare patients and major healthcare outcomes. Data for hospitals with pharmacist-managed aminoglycosides or vancomycin therapy were obtained from the 1995 National Clinical Pharmacy Services Study database. The questionnaires were mailed to directors of pharmacy at 3,701 acute care, general medical-surgical, and acute care pediatric hospitals listed in the American Hospital Association Abridged Guide to the Healthcare Field and 1,109 (30%) were returned. Five hundreds and twenty-seven hospitals (47.5%) had pharmacist-managed aminoglycosides or vancomycin programs. In the hospitals that did not have pharmacist-managed aminoglycosides or vancomycin therapy, death rates were 6.71% higher, length of stay was 12.28% longer, total Medicare charges were 6.30% higher, drug charges were 8.15% higher, laboratory charges were 7.80% higher, hearing loss was 46.42% higher, renal impairment was 33.95% higher and the death rate in patients who developed complications was 10.15% higher than in the hospitals with pharmacists managing these drugs.

Sieradzan and Fuller and coworkers (56) evaluated a procedure to improve inter-department communication and documentation of antibiotic serum sampling data for pharmacokinetic evaluation. A prospective audit by the Pharmacokinetic Service revealed that approximately 40% of all antibiotic serum levels were improperly drawn resulting in unsuitable specimens and erroneous serum concentrations or lacked sufficient data for pharmacokinetic analysis. A lack of communication and documentation between phlebotomist and nursing personnel was found to be the most significant source of potential error in serum sampling. Once the protocol for serum

sampling was revised, less than 5% of antibiotics serum levels were found to be unsuitable for evaluation and interpretation. A continuous audit for procedure compliance identifies any source of potential sampling error and provides a means to improve the overall quality of a pharmacokinetic service.

Fernández de Gatta and coworkers (57) evaluated the cost-effectiveness of vancomycin serum concentration monitoring in patients with hematologic malignancies. A prospective randomized study in 70 immunocompromised febrile patients with hematologic malignancies who were randomly assigned to either a vancomycin therapeutic drug monitoring group (TDM group; n = 37) or to a control group (n = 33). Intervention in the TDM group involved patient follow-up by a clinical pharmacist to obtain and pharmacokinetically interpret serum vancomycin concentrations for dosage individualization. There were no significant differences between the TDM and control groups in the outcome measures, except for the incidence of nephrotoxicity: the rates of minor nephrotoxicity were 33.3% and 13.5% in the control and TDM groups, respectively. The corresponding figures for moderate nephrotoxicity were 9.1% and 0%. Logistic regression analysis confirmed that TDM independently reduced the incidence of nephrotoxicity in this patient population. On the basis of this reduced nephrotoxicity, an incremental cost of $435 per case of nephrotoxicity prevented was found for vancomycin serum concentration monitoring. The TDM for vancomycin therapy in this high-risk population has been shown to be a cost-effective procedure.

Iwamoto and coworkers (58) retrospectively investigated efficacy of TDM of vancomycin in 184 patients with MRSA infection. The incidence of nephrotoxicity was compared between the patients who received TDM practice (TDM group; n = 73) and did not (non-TDM group; n = 111). Creatinine clearance (CrCL) values decreased significantly after the vancomycin therapy in the non-TDM group ($p = 0.05$). The patients with MRSA bacteremia or pneumonia were classified into two groups according to peak concentrations of vancomycin: above 25 mg/L (Group A: n = 29) and below (Group B: n = 24). Mean duration of vancomycin therapy (14.1 days) in Group A was significantly shorter than that (27 days) in Group B. Mean cumulative total vancomycin doses (13.3 g) in Group A was significantly less than that (25.0 g) in Group B. These results indicated that monitoring peak concentration was essential to

obtain better clinical effects for vancomycin therapy, and the peak concentration above 25 mg/L was more effective.

Crowley and coworkers (59) conducted three prospective audits to assess the impact of vancomycin TDM on administration of vancomycin. After the first audit, a number of changes in the TDM process was undertaken. After review of the second audit, a senior pharmacist coordinated ward-based pharmacists in assisting staff to interpret levels, and TDM interpretative charts were designed for drug charts. Following the third audit, feedback to hospital management and a plan for ongoing education were undertaken. There was a significant reduction in the number of vancomycin doses held inappropriately in the third audit [10% (78/782) of prescribed doses] when compared to the first audit [16% (161/1007) of doses] ($p = 0.01$). Of doses that were held inappropriately, there was a significant decrease in doses held for no apparent reason in third audit [16% (27/170) of prescribed doses] when compared to first audit [25% (69/282) of doses] ($p = 0.05$). The interventions resulted in a 37.5% reduction in inappropriately held vancomycin doses over a one-year period; 10% of doses were still being held inappropriately. This study highlights the difficulties in identifying barriers to change and changing healthcare worker behaviors.

Therapeutic drug monitoring at Ramathibodi Hospital

Preliminary study in 2006 at Ramathibodi Hospital, a university teaching hospital, Pharmacy Department provided pharmaceutical care service for patients in medical wards, surgical wards, orthopedic wards, OB-GYN wards, EENT wards and pediatric wards. Pharmaceutical care that was provided include patients monitoring, discharge counseling, pharmacokinetic consultation, ADR and drug interaction monitoring and drug information service. Focus on pharmacokinetic consultation, clinical pharmacist had been consulted for vancomycin, aminoglycosides, phenytoin and warfarin. However, not every patient was consulted.

On reviewing in-patient medical charts of 26 adult patients who received vancomycin from January to March 2006, clinical pharmacist found that 13 patients did not receive vancomycin serum level monitoring. Of these 13 patients, 3 patients (23.1%) had indication for vancomycin serum level monitoring. It was found further that 2 patients (15.4%) of the group receiving vancomycin serum level monitoring had

appropriate serum drug concentration monitoring. The majority of inappropriateness in serum drug concentration monitoring is inappropriate sampling time e.g. drawing serum level before steady state, drawing peak concentration before finishing distribution phase and drawing serum level that is not useful to interpret e.g. immediately after finishing hemodialysis. Other inappropriateness are inappropriate documentation e.g. serum level order without sampling time and inappropriate interpretation. The drug level monitoring is thus costly with less benefit.

These problems were reported in other studies and reduced by clinical pharmacist intervention with therapeutic drug monitoring (52, 55). This study was therefore conducted to develop the pharmacy service of serum vancomycin concentration monitoring (SVCM). It was expected to increase appropriateness of serum sampling time and concentration interpretation of drug like vancomycin and successively promote the service of SVCM conducted by clinical pharmacist.

CHAPTER III
METHODOLOGY

1. Definition of term

Serum vancomycin concentration monitoring (SVCM) was defined as the process of determination of vancomycin concentration in serum of patients in order to ascertain the administered dose will result in serum concentration within therapeutic concentration.

Physician's acceptance was defined as physician accepts the pharmacist's intervention and change in vancomycin dosing according to the pharmacist's recommendation.

2. Study design

The study was a quasi-experimental design.

3. Ethic approval

The study was approved by the Human Research Ethics Committee of Faculty of Medicine, Ramathibodi Hospital, Mahidol University on December 19, 2006.

4. Scope of the study

The 2-phase study was conducted at a total duration of 90 days (2x45 days), and limited to the use of vancomycin in medical and surgical wards. In the first phase or pre-intervention period, a retrospective study was conducted in which the in-patient charts of patients who received vancomycin were reviewed. The second phase or intervention period, a prospective study was conducted in which clinical condition and in-patient charts of patients who received vancomycin were reviewed daily and if SVCM were needed, patient care were then intervened by on criteria as proposed in Figure 3.4 and Figure 3.5.

5. Study population

Study population were all adult patients in medical and surgical wards who received vancomycin during 1st November 2006 and 15th December 2006 (pre-intervention period) and during 15th January 2007 and 28th February 2007 (intervention period). For those who refused to participate in the study and did not sign the informed consent were excluded from the study.

6. Period of study

Between 1st November 2006 and 30th April 2007

7. Study location

Seven medical wards and 7 surgical wards, Ramathibodi Hospital

8. Study work flow

8.1 Development of study tools

8.1.1 Data collection form

The data collection form was developed as shown in appendix A and used to collect data of both phases.

8.1.2 Intervention tools

8.1.2.1 Vancomycin education sheet

The vancomycin education sheet (Figure 3.1) was developed based on literature review and used as a nonverbal media for intervention. The sheet told characteristics of patient who should be ordered for SVCM, and when was the time for blood sampling.

8.1.2.2 Recommendation of SVCM

Template of pharmacist's note of recommendation (Figure 3.2) was developed and used by pharmacist. The note included recommendation of sampling time, and interpretation and dosage adjustment.

8.1.2.3 The administration and sampling time record form

The tabular form of administration and sampling time was developed as shown in Figure 3.3 and used by nurse. The note provided space for recording of real time at start and end of vancomycin infusion, and real time

for blood sampling (peak, trough, and random concentration).

8.1.3 Equation used for in the process of recommendation

8.1.3.1 Equation for recommendation of sampling time

Pharmacokinetic parameters proposed by Sawchuck-Zaske (60) and Ambrose (61) were used to calculate half-life of vancomycin which further used for recommendation of sampling time. From our previous experience (unpublished data), we used the equation from Sawchuck-Zeske in case of hemodialysis patients but the Ambrose equation in those patients with impaired renal function (but not on hemodialysis).

8.1.3.2 Equation for recommendation of dosage adaptation

Equation of Sawchuck-Zaske (60) was used for recommendation of new dosage regimen to bring serum vancomycin concentration into therapeutic concentration. (appendix B).

8.1.4 Criteria for the assessment of appropriateness of SVCM

Audit criteria for serum drug concentration determination adopted by Winter, Herfindal and Bernstein (53) (Figure 3.4) was used to assess for the appropriate of SVCM, after addition of dosage and therapeutic concentration of vancomycin to criteria. The assessment path was developed and demonstrated in Figure 3.5.

8.2 Conduct of intervention

8.2.1 Organize a meeting with physicians and nurses to inform about SVCM.

After the end of pre-intervention period and before the beginning of intervention period, protocol and procedure of SVCM (what is it?, how it works?, what benefit it gives?, etc.) as well as the missing information learnt from the pre-intervention period were discussed with physician and nurses.

8.2.2 Interventions with physicians

Two types of intervention were conducted as followed:-

a) Vancomycin education sheet (Figure 3.1) was inserted into each patient chart of those who received vancomycin.

b) Pharmacist discussed with physicians or wrote a note in the patient chart if vancomycin dosing or blood sampling seems to be

inappropriate. This conduct was a basis of on-service intervention.

8.2.3 Interventions with nurses.

Pharmacist discussed with nurses or wrote a note in the patient chart to inform them to record the exact time of vancomycin dosing and blood sampling. This conduct was a basis of on-service intervention.

8.3 Work flow and data collection

8.3.1 Pre-intervention period

Study work flow of the pre-intervention period was depicted in Figure 3.6 and included the followings:-

a) Identify patients who received vancomycin in the study wards during 1st November 2006 and 15th December 2006 from computerized record.
b) Search for patient charts.
c) Review medical history of these patients and collect data of vancomycin dosing, SVCM, clinical findings before and during vancomycin treatment, and outcome of treatment at discharge. All data were recorded into data collection form (appendix A).
d) Assess for the appropriateness of SVCM.

8.3.2 Intervention period

Study work flow of the intervention period was depicted in Figure 3.7 and included the followings:-

a) Identify patients who received vancomycin in the study wards during 15th January 2007 and 28th February 2007 from computerized record.
b) Insert vancomycin education sheet (Figure 3.1) into each in-patient chart of those identified patients. Physicians (residents) in each ward were reminded about the service of SVCM.
c) Daily and prospectively review in-patient charts of these patients and assess data of dosing, SVCM, and clinical finding and outcome.
d) For those patients who should receive SVCM but did not receive, pharmacist discussed with physician, verbally or nonverbally. The patients were further observed until the end of vancomycin dosing. If they received SVCM, the SVCM could be conducted by either

physician or pharmacist.

e) For those patients who received SVCM and pharmacist was consulted, pharmacist wrote down the exact time of blood sampling in pharmacist's note in the in-patient charts. Pharmacist then talked to nurses about the importance of recording exact time of vancomycin administration and time of blood withdrawal. Nurse recordred the exact time of each activity including the administration time and the blood withdrawal time, into the administration and sampling time recording form. When the result of vancomycin concentration returned from laboratory, pharmacist interpreted the result with the aid of equation (appendix B) and suggested dose maintaining or adaptation. These interpretation and suggestions were written down in the pharmacist's note.

f) For those patients who received SVCM but pharmacist was not consulted, patients were still observed until the end of vancomycin dosing. The serum level was interpreted. If the dose had to be adjusted, pharmacist then informed physician verbally and nonverbally. The suggestions were finally written down in the pharmacist's note.

g) All other cases including patients who should not receive SVCM but received, the data was collected as such until vancomycin was discontinued.

h) All data were recorded into data collection form and assessed the appropriateness of SVCM.

8.4 Vancomycin concentration determination

Vancomycin concentrations were all determined from central laboratory of Ramathibodi Hospital by automated immunoassay systems; fluorescence polarization immunoassay (FPIA) (TDx; Abbott Laboratories, Chicago, IL, U.S.A.).

9. Acceptance criteria for appropriate SVCM (Figure 3.4)

SVCM was considered appropriate if the following aspects were met:-

- All procedures of SVCM were documented and all documents were in patient charts (medication record, resident progress note, staff note, nurse note, administration and sampling time recording form).
- Sampling time was respect to dose and steady state, and
- Interpretation of serum vancomycin concentration was aimed to reach optimal therapeutic range.

All of appropriate SVCM were category 4, 5, 6, 8, 10, 11.

Missing of any of the above aspects, SVCM was considered inappropriate. (Category 1, 2, 3, 7, 9, 12)

10. Data presentation and analysis

Demographic data including gender, age, weight, clinical status, underlying disease, length of stay and concomitant nephrotoxic drug were presented and analyzed by descriptive statistics.

Vancomycin data including indication, dose and time of vancomycin administration, sampling time, serum vancomycin concentration, and dosage adjustment data were presented and analyzed by descriptive statistics.

Drug therapy data including microbiology data, and serum creatinine were presented and analyzed by descriptive statistics.

Data of pre-intervention period and intervention period were compared with the appropriate statistical test and significance level was set at $p \leq 0.05$.

Categorical data including appropriateness of serum drug concentration and frequency of drug level within therapeutic range between 2 groups were compared by chi-square (χ^2) test.

Continuous data including length of stay, total dose of vancomycin, duration of vancomycin usage, average daily dose, and number of dead patients were compared by Student t-test.

Serum Vancomycin Concentration Monitoring (SVCM)

ผู้ป่วยของท่านได้รับยา vancomycin ซึ่งขนาดยาที่เหมาะสมขึ้นอยู่กับชนิดของเชื้อ ตำแหน่งที่ติดเชื้อและสภาวะการทำงานของไต และควรให้ยาในเวลาที่เหมาะสมคือ IV infusion อย่างน้อย 1 ชั่วโมงเพื่อป้องกันการเกิด Red man syndrome นอกจากนั้น vancomycin ยังมีอาการข้างเคียงอื่นๆ เช่น พิษต่อหูและพิษต่อไตซึ่งจะพบได้มากขึ้นถ้าใช้ vancomycin ร่วมกับยาที่มีพิษต่อไต

การตรวจวัดระดับยาในเลือดของยา vancomycin สามารถช่วยเพิ่มประสิทธิภาพในการรักษา ลดโอกาสเกิดพิษต่อไต ลดระยะเวลาการใช้ยา ลดโอกาสเกิดภาวะแทรกซ้อน ลดระยะเวลาในการอยู่โรงพยาบาลและลดอัตราการเสียชีวิตได้ ซึ่งการตรวจวัดระดับยาในเลือดไม่จำเป็นต้องทำในผู้ป่วยทุกรายแต่ผู้ป่วยที่อาจได้รับประโยชน์จากการตรวจวัดระดับยาในเลือด ได้แก่

1. ผู้ป่วยที่มีการทำงานของไตเปลี่ยนแปลงอย่างรวดเร็ว
2. ผู้ป่วยที่ทำ dialysis
3. ผู้ป่วยที่มีปริมาตรการกระจายของยา (volumes of distribution) เปลี่ยนแปลงมาก เช่น morbid obesity, significant edema, burns
4. ผู้ป่วยที่ได้รับ vancomycin ร่วมกับยาที่มีพิษต่อไต เช่น aminoglycosides, amphotericin B, IV contrast media, cyclosporin, tacrolimus
5. ผู้ป่วย CNS infection, endocarditis, osteomyelitis ที่ได้รับ vancomycin

ขณะนี้งานเภสัชกรรมคลินิกได้ให้บริการติดตามตรวจวัดระดับยาในเลือดของยา vancomycin โดยเภสัชกรจะช่วยดำเนินการในเรื่องเวลาที่เหมาะสมในการเจาะเลือดเพื่อตรวจวัดระดับยาในเลือด แปลผลและเสนอการปรับขนาดยาหากจำเป็น โดยได้รับความร่วมมือจากแพทย์และพยาบาล

เวลาที่เหมาะสมในการเจาะเลือดจะแตกต่างกันในผู้ป่วยแต่ละรายดังนี้

1. ผู้ป่วยที่มีการติดเชื้อในบริเวณที่ยาเข้าได้น้อยเช่น CNS infection, endocarditis, osteomyelitis ให้เจาะเลือดวัดระดับยาสูงสุดและระดับยาต่ำสุดหลังจากได้รับยาไปแล้ว 3-4 doses
2. ผู้ป่วยที่ทำ dialysis ให้เจาะเลือดวัดระดับยาหลังจากที่ได้รับยา dose แรก 4-7 วันและรอผลของระดับยาก่อนพิจารณาให้ยา dose ต่อไป
3. ผู้ป่วยที่มีการทำงานของไตผิดปกติหรือได้รับยาที่มีพิษต่อไตร่วมด้วยแนะนำให้เจาะเลือดวัดระดับยาต่ำสุดหลังจากได้รับยาไปแล้ว 3-4 doses

โดยทั่วไปจะเจาะเลือดวัดระดับยาสูงสุดที่เวลา 1 ชั่วโมงหลังจากให้ยาเสร็จและระดับยาต่ำสุดก่อนได้รับยาครั้งต่อไป ครึ่งชั่วโมงซึ่ง **การระบุเวลาที่ถูกต้องในการเจาะเลือดมีความสำคัญอย่างยิ่ง** เนื่องจากมีผลต่อการปรับขนาดยาในผู้ป่วย ทำให้ผู้ป่วยได้รับยาในขนาดที่ถูกต้อง และไม่เกิดความเป็นพิษจากยา

หากผู้ป่วยของท่านมีความจำเป็นต้องได้รับการตรวจวัดระดับยาในเลือดและท่านต้องการให้ดำเนินการในเรื่องเวลาที่เหมาะสมในการเจาะเลือด การแปลผล และการปรับขนาดยา

กรุณาติดต่อที่งานเภสัชกรรมคลินิก โทร. 1270

Figure 3.1 Education sheet

Pharmacist's note for serum vancomycin concentration monitoring

S, O: ผู้ป่วย ชาย/หญิง อายุ…….. ปี admit ……..… (date)
Diagnosis: ……..……..

ได้รับ vancomycin สำหรับ [ ] empirical therapy [ ] documented therapy
Dose……Start …….. with the first dose at ……(time).

Sampling time recommendation note

A:

1. เนื่องจากผู้ป่วยติดเชื้อที่……ซึ่งเป็นบริเวณที่ยาเข้าได้น้อย ต้องการยาในขนาดสูง แนะนำให้เจาะเลือดวัดระดับยาต่ำสุดก่อนให้ยา (trough level) และระดับยาสูงสุดหลังให้ยา (peak level) ในวันที่……..... เวลา…….. เพื่อปรับขนาดยาให้เหมาะสมกับผู้ป่วย
2. เนื่องจากผู้ป่วยได้รับ vancomycin ร่วมกับยาที่มี nephrotoxic คือ……โดย Scr ของผู้ป่วยมีแนวโน้มเพิ่มขึ้น ระดับยา vancomycin จากการคำนวณด้วย population pharmacokinetic มีค่าสูงกว่า therapeutic range แนะนำให้เจาะ vancomycin level ในวันที่……..เวลา…..... เพื่อปรับขนาดยาให้เหมาะสมกับผู้ป่วย

P: แนะนำให้เจาะระดับยาต่ำสุดในเลือดก่อนให้ยา (trough level)/หรือระดับยาสูงสุดหลังให้ยา (peak level) ในวันที่……...เวลา …….. ร่วมกับ monitor BUN/Scr

Interpretation and dosage adjustment note

1. ถ้าผู้ป่วย on hemodialysis

A: Patient on [] low flux/ [] high flux hemodialysis ทุกวัน ……..….
แนะนำให้เจาะ vancomycin level หลังจากได้รับยาวันแรกประมาณ 4-7 วัน คือในวันที่…….
เวลา…….. และรอผลระดับยาในเลือดก่อนพิจารณาให้ยา dose ต่อไป

P: เจาะ vancomycin level หลังจากได้รับยาdoseแรกประมาณ 4-7 วัน คือในวันที่……....เวลา……...

a. ถ้าระดับยาในเลือด ≤ 15 mg/L สามารถให้ยา dose ต่อไปได้ในขนาด ……..……
b. ถ้าระดับยาในเลือด > 15 mg/L ขอ Hold ยา dose ต่อไปและเภสัชกรจะมาคำนวณขนาดยาและเวลาที่เหมาะสมต่อไป

2. ถ้าระดับยาต่ำกว่า therapeutic ranage

A: vancomycin level ในวันที่……..….เวลา…….…….…… = …….…..... mg/L
ซึ่งเป็นค่าที่ *ต่ำกว่า* therapeutic range (peak = 25-40 mg/L, trough = 5-15 mg/L)
จากการคำนวณ pharmacokinetic parameter ได้ t1/2 ……..…hr, Vd……. L, Ke……. hr^{-1}
เนื่องจากผู้ป่วยติดเชื้อที่ซึ่งเป็นบริเวณที่ยาเข้าได้น้อยต้องการ trough level ~ 15-20 mg/L แนะนำให้เพิ่มขนาดยา vancomycin จาก…...……. เป็น ……..

P: เพิ่มขนาดยา vancomycin จาก……..……..……..……...monitor Scr อย่างน้อยสัปดาห์ละสองครั้งและเจาะระดับยาซ้ำอีกครั้งในวันที่…… เวลา……...และเภสัชกรจะมาคำนวณขนาดยาที่เหมาะสมต่อไป

3. ถ้าระดับยาสูงกว่า therapeutic range

A: vancomycin level ในวันที่ ……เวลา……..=……..mg/L
ซึ่งเป็นค่าที่ *สูงกว่า* therapeutic range (peak = 25-40 mg/L, trough = 5-15 mg/L)
จากการคำนวณ pharmacokinetic parameter ; T1/2 ….mg/L , Vd..…L, Ke … hr^{-1}
แนะนำให้ hold vancomycin dose ต่อไปอีก ….day เพื่อให้ระดับยาลดลงเหลือ ~ 15 mg/L

P: hold vancomycin dose ต่อไปอีก ……day และเจาะระดับยาอีกซ้ำครั้ง
ในวันที่ ……เวลา……..…และเภสัชกรจะมาคำนวณขนาดยาที่เหมาะสมต่อไป

Thank you for the consult. Pharmacist will continue to follow.

Signature, (Tel 1270)

Figure 3.2 Pharmacist's note of recommendation

แบบบันทึกเวลาการให้ยาและเวลาเจาะเลือดเพื่อวัดระดับยา vancomycin

(เฉพาะวันที่มีคำสั่งการรักษาจากแพทย์)

ชื่อ..... HN……..…...Ward……..….. Bed……..….

ว/ด/ป	ขนาดยา (ให้.....mg ทุก.....ชม)	ระดับยาต่ำสุด เวลาเจาะเลือด ก่อนให้ยา (ครึ่งชั่วโมง)	เวลาที่เริ่มให้ยา	เวลาที่ยาหมด	ระดับยาสูงสุด เวลาเจาะเลือด หลังให้ยาหมด (1 ชม.)	เวลาเจาะเลือดแบบสุ่ม

****ขอขอบพระคุณในความร่วมมือ****

Figure 3.3 Administration and sampling time record form

Audit criteria for serum vancomycin concentration determination

1. Time of sampling

Time of sampling indicated on laboratory report: **proceed to 2**

Time of sampling not indicated on laboratory report:

Time of sampling **not indicated** in medical record (orders, progress notes, nurses' note, medication administration record):

audit category = 1

Time of sampling indicated in medical record:

Documentation of sampling time is acceptable: **proceed to 2**

Criteria

Exact time of sampling indicated, or

Sampling time indicated within a one-hour interval for patients receiving drug

Caution: Frequently the progress notes indicate a time of sampling that is in fact the time the determination was received by the laboratory.

Documentation of sampling time is not acceptable:

audit category = 1

2. Appropriateness of sampling time

A. Time of sampling with respect to dose:

Sample obtained at correct time with respect to dose: **proceed to B**.

Criteria: Peak: 1 hour after end of 1-hour infusion

Trough: within 30 min before next dose

Sample not obtained at correct time with respect to dose:

Note in medical record to defend nonstandard sampling time: **proceed to 3**.

No note in medical record to defend nonstandard sampling time: ***audit category = 2***

B. Time of sampling with respect to steady state:

Sample obtained at steady state: **proceed to 3**

Criteria: No change in dose, interval or rate of administration within 24 hours before time of sampling.

Sample obtained before steady state:

Note in medical record to defend sampling before steady state or sampling in patient with ESRD: **proceed to 3**

No note in medical record to defend sampling before steady state: ***audit category = 3.***

3. Serum drug concentration results

Therapeutic:

No change in drug regimen: then, ***audit category = 4.***

Change in drug regimen:

Results of repeated serum drug concentration in therapeutic range: ***audit category = 5***

Results of repeated serum drug concentration not in therapeutic range:

Appropriately defended in medical record:

audit category = 6

Assay result is suspected to be in error and new sample is ordered to be obtained within 24 hours:

audit category = 7

Vancomycin: **Peak concentration: 25-40 mg/L**

Trough concentration: 5-15 mg/L

Example of acceptable defense:

Concentration low: appropriate minimum inhibitory concentration

Concentration high: immunocompromised patient, resistant organism, questions results as laboratory error and rechecks result within 24 hours, CNS infection, osteomyelitis, pneumonia may have higher trough concentration (15-20 mg/L)

Nontherapeutic:

No change in drug regimen:

Defense in medical record: ***audit category = 8***

No defense in medical record: ***audit category = 9***

Change in drug regimen:

Results of repeated serum drug concentration in therapeutic range: ***audit category = 10***

Results of repeated serum drug concentration no in therapeutic range:

Defense in medical record:

audit category = 11

No defense in medical record:

audit category = 12

Appropriate: **Category 4, 5, 6, 8, 10, 11**
Inappropriate: Category 1, 2, 3, 7, 9, 12

Figure 3.4 Serum vancomycin concentration monitoring assessment criteria (detail)

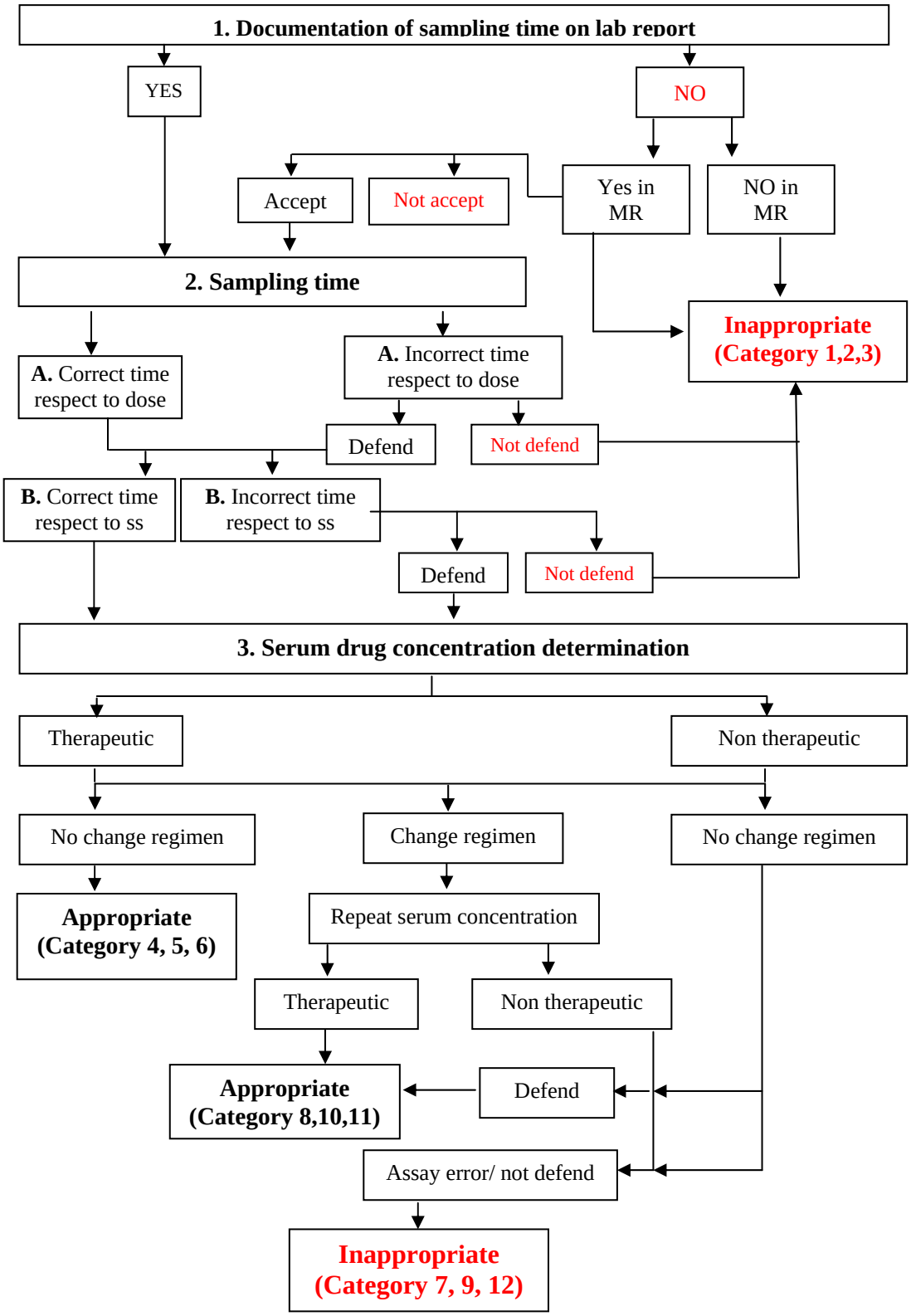

Figure 3.5 Serum vancomycin concentration monitoring assessment criteria (flow)
MR: medical record, ss: steady state

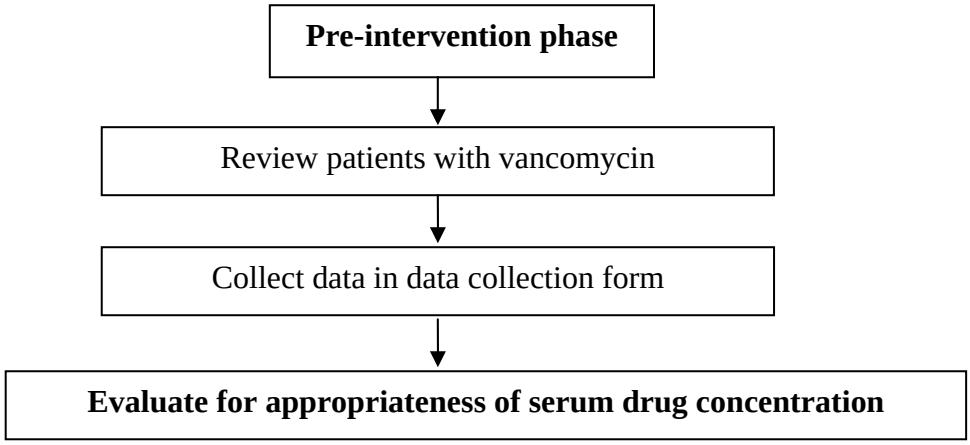

Figure 3.6 Work flow in the pre-intervention period

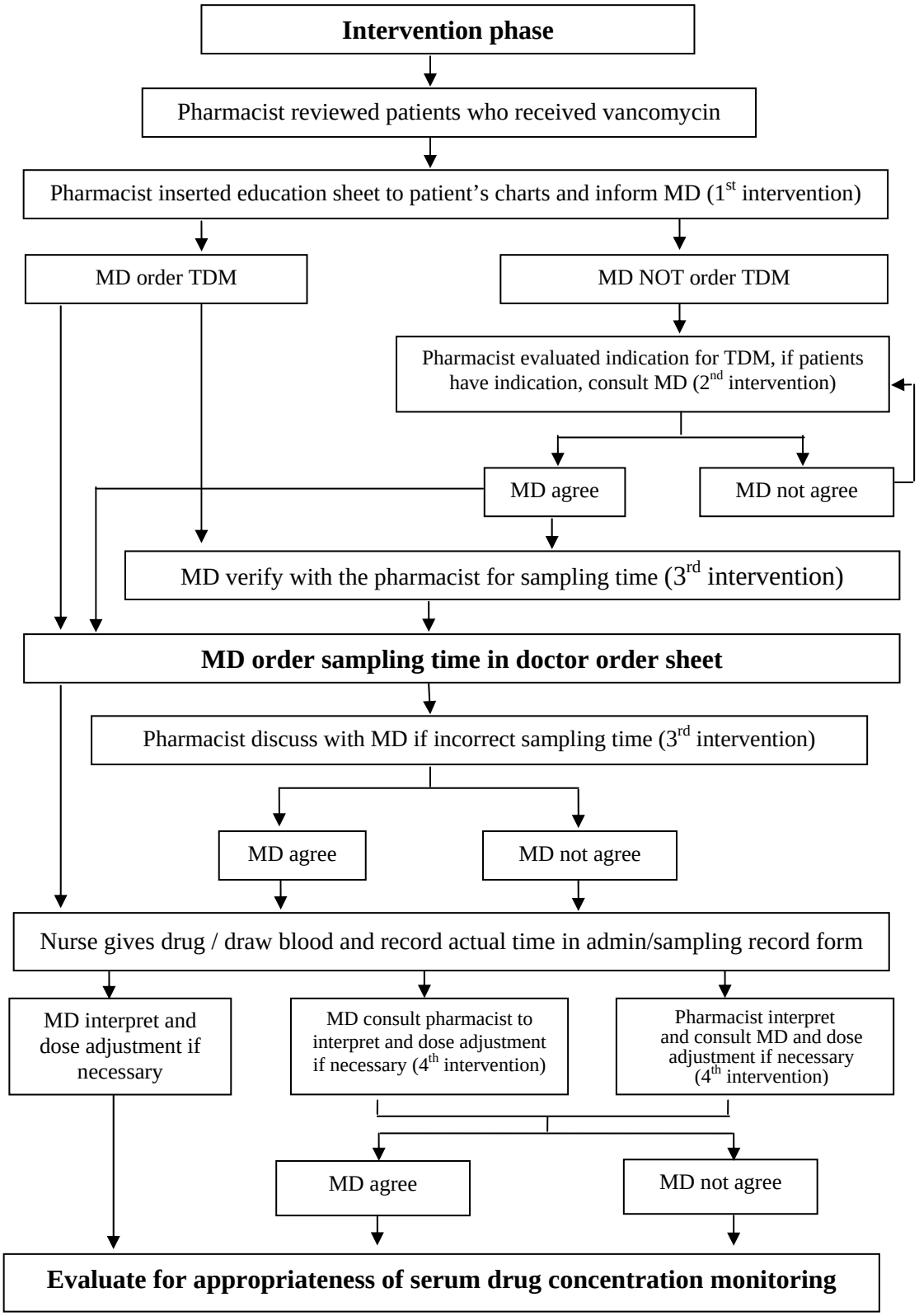

Figure 3.7 Serum Vancomycin Concentration Monitoring and work flow in the intervention period

CHAPTER IV
RESULTS

This study was performed with the following objectives; (a) to assess the appropriateness of serum sampling time and interpretation of serum vancomycin concentration, (b) to determine the frequency of having vancomycin concentration in therapeutic range and (c) to compare data obtaining in the intervention period to those from the pre-intervention period. It was found that 95 patients in the selected ward received vancomycin during pre-intervention period (1st November 2006 - 15th December 2006) and 106 patients during intervention period (15th January 2007 - 28th February 2007). Only 24 patients (25.3%) and 28 patients (26.4%) in the pre-intervention group and the intervention phase, respectively were in the process of serum vancomycin concentration monitoring conducted by pharmacist. All data of the 2 periods were presented in the following aspects:-

1. Development of SVCM service
2. Patient characteristics
3. Characteristics of vancomycin regimen
4. Appropriateness of serum vancomycin concentration assessment
5. Frequency of having vancomycin level in therapeutic range assessment
6. Determination of pharmacokinetic parameter of vancomycin
7. Pharmacist interventions and physician's acceptance

1. Development of SVCM service

Our study had developed SVCM at Ramathibodi Hospital, as followed.

1. Education sheet which told physician about characteristics of patient who should be ordered for SVCM, when is the time for blood sampling and what is therapeutic range was developed. This education sheet was used as the first intervention from pharmacist in the intervention phase, and was inserted into in-patient chart who received vancomycin.

2. Intervention by pharmacist was conducted to physician by verbal communication and writing down as pharmacist's note into the in-patient chart, if the patient needed SVCM. Nurse was also intervened by pharmacist. Verbal and nonverbal communication were used to let her know when was the time for blood sampling in relation to vancomycin administration.

3. Administration and sampling time recording form was developed. Nurse wrote down exact time when she administered vancomycin to patient and drew blood sample from patient for SVCM.

2. Patient characteristics

There were 24 patients (8 males and 16 females) in the pre-intervention groups and 28 patients (13 males and 15 females) in the intervention group. Average ages of patients in between the two groups were significantly different ($p< 0.05$) and patients in the pre-intervention group were older (67.8 $\pm$ 15.6 years vs. 56.0 $\pm$ 18.2 years) with the range of 39-93 years vs. 18-91 years. The average weight and the length of hospital stay were not significantly different between the two groups (Table 4.1). On average, patients had more than one underlying disease, reason for admission and episodes of vancomycin usage. Microbial culture was positive in almost all patients (95.8% vs. 96.4%, pre-intervention vs. intervention period). Concomitant nephrotoxic drugs were administered in 25% of the pre-intervention group and 46.4% of the intervention group. There were 9 patients (37.5%) in the pre-intervention group and 9 patients (32.1%) in the intervention group who received dialysis. All of dialysis types were hemodialysis. Sepsis and acute renal failure were the most common diagnosis of patients in both groups (Table 4.2).

Table 4.1 Patient characteristics

Characteristic	Pre-intervention group (n=24)	Intervention group (n=28)	P-Value
Age (yrs)			
- Mean ± SD	67.8 ± 15.6	56.0 ± 18.2	0.015[a]
- Median	68	52.5	
- Range	39 – 91	18 – 93	
Gender			
- Male	8 (33.3%)	13 (46.4%)	0.403[b]
- Female	16 (66.7%)	15 (53.6%)	
Ward			
- Medicine	16 (66.7%)	21(75.0%)	0.508[b]
- Surgery	8 (33.3%)	7 (25.0%)	
Weight (kg)			
- Mean ± SD	50.9 ± 8.3	55.4 ± 13.0	0.140[a]
- Median	57.5	50	
- Range	37 - 90.1	34.5 – 65	
Length of stay (days)			
- Mean ± SD	59.0 ± 64.7	38.5 ± 27.8	0.159[a]
- Median	35	34.5	
- Range	7 – 293	6 – 126	
Number of underlying disease (mean ± SD)	2.0 ± 1.2	1.6 ± 1.1	0.271[a]
Number of diagnosis (mean ± SD)	1.9 ± 0.8	2.2 ± 0.9	0.272[a]
Number of episode of vancomycin usage (mean ± SD)	1.1 ± 0.3	1.3 ± 0.4	0.118[a]
Microbial culture			
- Negative	1 (4.2%)	1 (3.6%)	0.991[b]
- Positive	23 (95.8%)	27 (96.4%)	
Concomitant nephrotoxic drug			
- No	18 (75.0%)	15 (53.6%)	0.152[b]
- Yes	6 (25.0%)	13 (46.4%)	
Being on renal hemodialysis			
- No	15 (62.5%)	19 (67.9%)	0.774[b]
- Yes	9 (37.5%)	9 (32.1%)	

[a]Student's t-test

[b]Chi-square test

Table 4.2 Reason for admission

Diagnosis	Number of episodes	
	Pre-intervention group	**Intervention group**
Sepsis	9 (19.6%)	10 (16.4%)
Acute renal failure	9 (19.6%)	8 (13.1%)
Urinary tract infection	7 (15.2%)	5 (8.2%)
Cerebral hemorrhage s/p craniotomy	0	5 (8.2%)
Pneumonia	4 (8.7%)	3 (4.9%)
End stage renal disease	2 (4.3%)	3 (4.9%)
Febrile neutropenia	1 (2.2%)	3 (4.9%)
Infective endocarditis	1 (2.2%)	3 (4.9%)
Cellulitis	3 (6.5%)	1 (1.6%)
Infected vascular graft	2 (4.3%)	1 (1.6%)
Septic shock	1 (2.2%)	2 (3.3%)
Acute cholecystitis	2 (4.3%)	0
Acute cholangitis	0	2 (3.3%)
SLE	0	2 (3.3%)
Meningitis	1 (2.2%)	0
Osteomyelitis	0	1 (1.6%)
Others	4 (8.7%)	12 (19.8%)

Table 4.3 Indication of vancomycin

Indication	Number of episodes	
	Pre-intervention group	**Intervention group**
Sepsis	10 (38.5%)	8 (24.2%)
Catheter related infection	5 (19.2%)	4 (12.1%)
Urinary tract infection	4 (15.4%)	3 (9.1%)
Infected vascular graft	3 (11.5%)	1 (3.0%)
Bacteremia	1 (3.9%)	3 (9.1%)
Empirical therapy in febrile neutropenia	0	3 (9.1%)
Infective endocarditis	0	3 (9.1%)
Infected bed sore	1	2 (6.1%)
Acute cholangitis	0	2 (6.1%)
Others	3 (11.5%)	4 (12.1%)

The common indication of vancomycin in the pre-intervention group was similar to the intervention group. Sepsis, catheter-related infection and urinary tract infection were top three infection causes (Table 4.3).

Samples for microbial culture in both groups were blood, urine, sputum, wound, CSF, ascites, bile and pleural fluid, respectively. Microbes most frequently found from the culture were methicillin-resistant *Staphylococcus aureus* (MRSA) and *Enterococcus* spp. (Table 4.4).

Table 4.4 Number (%) of microbial culture

Site	Pathogen	Number of culture	
		Pre-intervention group	**Intervention group**
Blood culture	Number of sample	14	15
	Staphylococcus aureus (MRSA)	3 (21.4%)	3 (20.0%)
	Staphylococcus epidermidis	0	4 (26.7%)
	Coagulase-negative staphylococci	2 (14.3%)	3 (20.0%)
	Staphylococcus hemolyticus	2 (14.3%)	2 (13.3%)
	Staphylococcus hominis	3 (21.4%)	0
	Enterococcus spp.	1 (7.1%)	1 (6.7%)
Urine culture	Number of sample	5	5
	Enterococcus spp.	4 (80.0%)	3 (60.0%)
	Staphylococcus epidermidis	0	1 (20.0%)
	Coagulase-negative staphylococci	0	1 (20.0%)
	Staphylococcus aureus (MRSA)	1 (20.0%)	0
Sputum culture	Number of sample	2	4
	Staphylococcus aureus (MRSA)	1 (50.0%)	2 (50.0%)
	Staphylococcus aureus (MSSA)	1 (50.0%)	0
	Coagulase-negative staphylococci	0	1 (25.0%)
	Viridians streptococci	0	1 (25.0%)
Wound culture	Number of sample	3	1
	Coagulase-negative staphylococci	2 (66.7%)	0
	Staphylococcus aureus (MRSA)	0	1
	Enterococcus spp.	1 (33.3%)	0
Tissue culture	*Staphylococcus aureus* (MRSA)	0	2 (100.0%)
CSF culture	*Staphylococcus aureus* (MRSA)	0	1 (100.0%)
	Enterococcus spp.	1 (100.0%)	0
Bile culture	*Enterococcus* spp.	1 (100.0%)	2 (100.0%)
Ascites culture	*Enterococcus* spp.	1 (100.0%)	0
Pleural culture	*Staphylococcus aureus* (MRSA)	0	1 (100.0%)

2. Characteristics of vancomycin regimen

Duration of vancomycin use, total vancomycin dose, average vancomycin daily dose and number of SVCM per patient in the intervention group was not significantly different from the pre-intervention group.

The average daily dose of vancomycin was categorized according to hemodialysis group and non-hemodialysis group and it was found that hemodialysis group used lower dose of total vancomycin dose and average daily dose than non-hemodialysis group. Although no statistically significant difference in duration of vancomycin use, total vancomycin dose, average vancomycin dose per day and number of SVCM per patient were observed, the intervention group had higher value in all respect as shown in Table 4.5.

However, 11 patients (45.8%) in the pre-intervention group and 4 patients (14.3%) in the intervention group died, respectively. This difference was significant, $p = 0.012$ (Table 4.5).

Table 4.5 Detail of vancomycin usage

Outcome	Pre-intervention group (n=24)	Intervention group (n=28)	P-Value
Duration of vancomycin use(day)			
- Mean ± SD	15.7± 13.8	17.8 ± 14.6	0.607[a]
- Median	10	12.5	
- Range	1 – 49	4 – 62	
Total vancomycin dose (g)			
- Mean ± SD	11.7 ± 17.4	15.9 ±15.7	0.360[a]
- Median	6	10	
- Range	1 – 68	1 – 58	
Average daily dose (g/day)			
- Mean ± SD	0.8 ± 0.7	1.0 ± 0.9	0.437[a]
- Median	0.6	0.6	
- Range	0.1 – 2.0	0.1 – 3.5	
- *HD[b] patients*			
- Mean ± SD	0.3 ± 0.1	0.3 ± 0.1	0.858[a]
- Median	0.3	0.3	
- Range	0.1 – 0.4	0.1 – 0.5	
- *Non-HD[b] patients*			
- Mean ± SD	1.1 ± 0.6	1.3 ± 0.9	0.490[a]
- Median	1.0	1.0	
- Range	0.3 – 2.0	0.3 – 3.5	
Average daily dose (g/kg/day)			
- Mean ± SD	0.02 ± 0.01	0.02 ± 0.01	0.382[a]
- Median	0.01	0.01	
- Range	0 – 0.05	0 – 0.05	
Number of dead patients	11 (45.8%)	4 (14.3%)	0.012[c]
Number of SVCM /patient	2.6 ± 3.2	3.0 ± 2.2	0.727[a]

[a] Student's t-test

[b] HD: Hemodialysis

[c] Chi-square test

The incidence of nephrotoxicity was evaluated in the studied patients who did not receive hemodialysis, 15 patients in the pre-intervention group and 19 patients in the intervention group. Nephrotoxicity was defined as a rise in serum creatinine concentration of grater than 0.5 mg/dL during vancomycin therapy. It was found that there were 3 patients (20.0%) in the pre-intervention group and 3 patients (15.8%) in the intervention group developed nephrotoxicity from vancomycin. All of these nephrotoxicity were assessed to be due to vancomycin. However, there was no significant difference between the pre-intervention group and the intervention group, as shown in Table 4.6.

Table 4.6 Nephrotoxicity assessment in no hemodialysis patients compared between the pre-intervention group and the intervention group

Nephrotoxicity	**Pre-intervention group** (n=15)	**Intervention group** (n=19)	**P-Value**
Total nephrotoxicity (n)	3 (20.0%)	3 (15.8%)	1.000[a]
Concomitant nephrotoxic drug			
- Aminoglycosides	1 (16.7%)	8 (61.4%)	
- Furosemide	3 (49.9%)	3 (23.2%)	
- Amphotericin B	1 (16.7%)	1 (7.7%)	
- Cyclosporine A	0	1 (7.7%)	
- Tacrolimus	1 (16.7%)	0	

[a] Chi-square test

3. Appropriateness of serum vancomycin concentration assessment

Only 24 patients in the pre-intervention group and 28 patients in the intervention group had SVCM. The appropriateness of SVCM was assessed based on the use of the serum drug concentration determination adopted from Winter, Herfindal and Bernstein, with slight modification.

In the pre-intervention group, 63 times of SVCM was conducted in 24 patients whereas the monitoring in the intervention group was 85 times in 28 patients. However, 7 data of SVCM in the pre-intervention group and 10 data of SVCM in the intervention group were not complete as there were no repeated order of serum vancomycin concentration after dosage changes by pharmacist or physician. Therefore, data of SVCM could be assessed in 56 times of SVCM in the pre-intervention group and 75 times of SVCM in the intervention group. It was found that appropriateness was 0.75 times of inappropriateness in the pre-intervention group but 3 times in the intervention group. The higher percentage of appropriateness in the intervention group was significantly; as compared to the pre-intervention group (65.9% vs. 38.1%, intervention group vs. pre-intervention group) as shown in Table 4.7.

Table 4.7 Appropriateness of serum vancomycin concentration

SVCM	Pre-intervention group	Intervention group	P-Value
Inappropriate (n)	32 (50.8%)	19 (22.3%)	<0.001 [a]
Appropriate (n)	24 (38.1%)	56 (65.9%)	

[a] Chi-square test (2x2 table)

Types of inappropriate serum vancomycin concentration monitoring were shown in Table 4.8. There were 3 major types of inappropriate serum vancomycin concentration monitoring.

1. Inappropriate documentation
2. Inappropriate sampling time
3. Inappropriate interpretation of serum vancomycin concentration

Table 4.8 Types of inappropriate serum vancomycin concentration monitoring

Type of inappropriate SVCM	Pre-intervention group	Intervention group
Documentation	15 (46.9%)	3 (15.8%)
Sampling time	13 (40.6%)	15 (79.0%)
- Blood drawn before reaching steady state	5	7
- Blood drawn for peak level in distribution phase	1	3
- Blood drawn for trough level at wrong time	3	5
- Blood drawn after dialysis	4	0
Interpretation of SVC (not defend)	4 (12.5%)	1 (5.2%)

The major type of inappropriate SVCM in the pre-intervention group was inappropriate documentation 15 times (46.9%), followed by inappropriate sampling time. However, the inappropriate documentation was less pronounced than the inappropriate sampling time in the intervention group, i.e., 15.8% and 79% respectively. The inappropriate sampling time consisted of obtaining blood for peak level in distribution phase, before reaching steady state, for trough level at wrong time, and blood drawn after dialysis. All of these inappropriate sampling time except the last one were found in both groups.

4. Frequency of having vancomycin serum concentration in therapeutic range assessment

Twenty eight patients in the intervention group received 85 times of SVCM conducted by pharmacist. Of these, 34 times were trough concentrations, 22 times were peak concentrations and 29 times were random concentrations. Pre-intervention group (n=24) had serum vancomycin concentration determination fewer than the intervention group. They had 63 times of SVCM which 14 times were trough concentrations, 5 times were peak concentrations and 44 times were random concentrations.

Most of the serum concentration measured in the pre-intervention group was the random concentration (69.9 %) while in the intervention group was the trough concentration (40.0%).

Significant difference was not found for mean trough concentration of the pre-intervention group and the intervention group (pre-intervention group; 13.1 ± 6.8 mg/L vs. intervention group; 17.4 ± 7.6 mg/L, p = 0.075). Similarly, mean of peak vancomycin concentration of the intervention group was higher than those of the pre-intervention group, but not significant (pre-intervention group; 30.9 ± 14.7 mg/L vs. intervention group; 40.8 ± 12.8 mg/L) as shown in Table.4.9.

There was no significant difference of random concentration between the 2 groups. The purpose of these random concentrations was mainly due to the need to know level before giving the next dose in acute renal failure (Table 4.10).

Table 4.9 Mean of measured serum vancomycin concentration

Measured serum vancomycin concentration	Pre-intervention group	Intervention group	P-Value
Trough concentration (mg/L)			
- n	14 (22.2%)	34 (40.0%)	
- Mean ± SD	13.1 ± 6.8	17.4 ± 7.6	0.075[a]
- Median	12.3	16.4	
- Range	2.9 – 25.5	2.3 – 32.8	
Peak concentration (mg/L)			
- n	5 (7.9%)	22 (25.9%)	
- Mean ± SD	30.9 ± 14.7	40.8 ± 12.8	0.140[a]
- Median	27.2	40.1	
- Range	16.8 – 47.7	21.9 – 67.1	
Random concentration (mg/L)			
- n	44 (69.9%)	29 (34.1%)	
- Mean ± SD	15.7 ± 11.0	19.4 ± 9.3	0.130[a]
- Median	12.6	19.2	
- Range	2.0 – 46.1	2.0 – 38.	

[a] Student's t-test

Table 4.10 Reason for random concentration in the intervention group

Causes of random concentration[a]	Frequency
1. Check level in patient with acute renal failure to determine dosage and time for the next dose of vancomycin	10
2. Recheck level after holding dose to determine the next dose	7
3. Check level in hemodialysis patients to determine the next dose and appropriate dosing interval	8
4. Order for trough level but blood was drawn before true trough	4

[a] Random concentration was vancomycin serum concentration that was dertermined not respect to dose in time of administration such as concentration in patient with hemodialysis, concentration after hold vancomycin dosage

The frequency of trough concentration determination which was in therapeutic range was not significantly different between the 2 groups. The pre-intervention group had 11 (78.6%) trough concentrations that were within therapeutic range whereas the intervention group had 22 (64.7%). Similarly, the frequency of peak concentration within therapeutic range was 3 (60%) in the pre-intervention group and 13 (59.1%) in the intervention group, as shown in Table 4.11.

Table 4.11 The details of frequency of peak and trough concentration in therapeutic range

	Pre-intervention group	**Intervention group**	**P-Value**
Trough concentration	14	34	
(Therapeutic range 5-15 mg/L)			
- Within therapeutic range	11 (78.6%)	22 (64.7%)	0.498[a]
- Out of therapeutic range	3 (21.4%)	12 (35.3%)	
Peak concentration	5	22	
(Therapeutic range 20-40 mg/L)			
- Within therapeutic range	3 (60.0%)	13 (59.1%)	1.000[a]
- Out of therapeutic range	2 (40.0%)	9 (40.9%)	

[a] Chi-square test

5. Determination of pharmacokinetic parameters of vancomycin

Pharmacokinetic parameters of vancomycin were derived from data obtained in the intervention period. The results were categorized into hemodialysis group and non-hemodialysis group (appendix D). Value of Ke and $T_{1/2}$ were different between the two populations (Table 4.12).

Table 4.12 Pharmacokinetic parameters of vancomycin in the intervention group

Pharmacokinetic parameter	Hemodialysis group*	Non - hemodialysis group	p-Value
Ke[a] (hr^{-1})			
- Mean ± SD	0.0098 ± 0.0038	0.0646 ± 0.072	0.017[d]
- Median	0.0090	0.049	
- Range	0.0055 – 0.0174	0.0096 - 0.3300	
Vd[b] (L)			
- Mean ± SD	35.12 ± 7.12	34.04 ± 10.98	0.729 [d]
- Median	36.68	31.19	
- Range	25.52 - 48.00	20.43 – 69.23	
$T_{1/2}$[c](hr)			
- Mean ± SD	80.49 ± 28.50	23.34 ± 19.31	< 0.0001 [d]
- Median	77.00	18.76	
- Range	39.85 - 127.00	2.09 - 74.09	

[a]Ke: Elimination rate constant

[b]Vd: Volume of distribution

[c]$T_{1/2}$: Half-life

[d]Student's t-test

*Blood withdrawal not during hemodialysis

6. Pharmacist's interventions and physician's acceptance

In total, pharmacist provided 103 interventions to physicians. Interventions were performed as direct communication and pharmacist's note. There were 98 interventions including recommending physicians to order SVCM at appropriate sampling time and giving advices in the interpretation and recommendation for proper dosage. The rest were the intervention generated by physicians; physicians consulted pharmacist to recommend appropriate sampling time and physicians consulted pharmacist to interpret and recommend proper dosage.

The most common interventions were related to recommendation of SVCM, interpretation of serum vancomycin concentration and recommendation for proper dosage, as shown in Table 4.13.

Table 4.13 Pharmacist's intervention

Pharmacist intervention	Frequency
1. Pharmacist recommended physicians to order SVCM	36 (35.0%)
• SVCM in acute renal failure	5
• SVCM of suspected low dose	2
• SVCM of suspected high dose	7
• SVCM after changed dose to check level	10
• SVCM after hold dose to check level before giving the next dose	12
2. Pharmacist recommended physicians to order appropriate sampling time	3 (2.9%)
3. Pharmacist counseled physicians in the interpretation and recommendation proper dosage	59 (57.3%)
4. Physicians consulted pharmacist for appropriate sampling time	2 (1.9%)
5. Physicians consulted pharmacist to interpret and recommend proper dosage	3 (2.9%)
Total	**103**

The major type of pharmacist interpretation of SVCM and dosage adjustment was to decrease dose of vancomycin (50.8%), followed by hold dose of vancomycin (23.7%), as shown in Table 4.14.

Table 4.14 Pharmacist interpretation of SVCM and dosage adjustment

Type of intervention	Frequency
Hold dose	14 (23.7%)
Increase dose	12 (20.3%)
Decrease dose	30 (50.8%)
Same dose per day	3 (5.2%)
- Adjust dose - Adjust dosing interval	
Total	59 (100%)

Of 103 interventions, 98 (95.1%) were accepted and 5 interventions (4.9%) were not accepted by physicians. Detail of pharmacist's interventions that physician did not accept were shown in Table 4.15.

Table 4.15 Physician's acceptance

Physician acceptance	Frequency
1. Accepted intervention	98 (95.1%)
2. Not accepted intervention • Hold 1st SVCM in acute renal failure patient • Interpret level and recommend 750 mg IV[a] q[b] 24 hr but the nephrologist suggested 750 mg IV q 12 hr, then the patient had acute renal failure and the dose was changed to 1 g IV q 24 hr • Interpret level and recommend to hold dose for 1 day before giving 1 g IV q 5 day • Suggest physician for random concentraion check after holding dose but he stopped all antibiotics and provided supportive care • Consult physician for random concentration check in CKD[c] patient after the first dose instead of ordering for both peak and trough concentration	5 (4.9%)

[a]IV: intravenous
[b]q: every
[c]CKD: chronic kidney disease.

CHAPTER V
DISCUSSION

The present study was performed to evaluate the appropriateness of serum vancomycin concentration monitoring and determine the frequency of serum vancomycin concentration within the therapeutic range during the pre-intervention and the intervention period. There was only one study in United States (53) that was conducted to evaluate and compare the appropriateness of serum drug concentration monitoring (SDCM) of aminoglycosides and theophylline. There was also a study that performed to evaluate the impact of vancomycin therapeutic drug monitoring on patient care (52). No such study was found in Thailand, our study thus was the first one in Thailand to evaluate the appropriateness of SVCM.

In Ramathibodi Hospital, the majority of vancomycin usage was in medical wards and surgical wards as compared to other wards. The results thus could represent overall usage of vancomycin in adult patients of Ramathibodi Hospital. However, the present study was unable to be extrapolated to pediatric patients as pharmacokinetic characteristics of the two groups were different.

Concerning of the development of SVCM at Ramathibodi Hospital, we found that education sheet contained too long information. This might explain why 12.9% of SVCM data were unable to be assessed. Therefore, further improvement to make it simple would be our next step. The administration and sampling time record form caused no problem to nurse. However, inappropriate time of blood sampling was still occur. Its causes await further determination. Apart from that, the co-operation within multidisciplinary patient care team needs further management for good quality of SVCM.

We discussed our results in terms of patient characteristics, characteristics of vancomycin regimen, appropriateness of serum vancomycin concentration monitoring, frequency of having vancomycin level in therapeutic range, pharmacokinetic analysis of vancomycin, pharmacist interventions, and physician’s acceptance, as followed:

1. Patient characteristics

The intervention group had average age of 56.0 ± 18.2 years (mean ± SD). This was significantly lower than the pre-intervention group whose average age was 67.8 ± 15.6 years; ($p = 0.015$). As the age range was 18-93 years and 39-91 years in the intervention group and the pre-intervention group, respectively. The 18 years old patient was omitted in the first analysis because it was extremely young relative to others. The obtained average age of intervention group was then 57.4 ± 16.9 years, which was still significantly lower than the pre-intervention group ($p = 0.027$). Therefore, age factor might have effect upon results of vancomycin usage. We found no statistically significant difference in other characteristics such as, gender, ward, weight, length of stay, number of underlying disease, number of diagnosis, and number of episode of vancomycin usage. Our patients' characteristics were similar to several previous studies (51, 52). However, a study by Karam and coworkers (51) reported the longer length of stay in non-pharmacist group than pharmacist group. Although there was a clinically significant, but no statistically significant difference in length of stay, this parameter was not an accurate measure for evaluating the impact of vancomyin concentration monitoring in that study and most patients were admitted to hospital for a disease other than infection. In contrast to the study of Karam and coworkers, our study included all patients who were admitted in selected wards and received vancomycin with or without renal replacement therapy. Inspite of the different type of patients, our result remained similar to that study. Welty and coworkers (52) studied outcome of vancomycin therapy in patients managed through a TDM service, and excluded patients who had estimated creatinine clearance less than 20 mL/min meanwhile Iwamoto and coworkers (58) performed a study in patients who had underwent surgical operation during vancomycin therapy or had more than 1.5 mg/dL of baseline Scr concentration. The criteria to include patients into these 2 studies were different and also different from our study. Nevertheless, length of stay of the pre-intervention and the intervention group in our study and in those 2 studies were in the same trend.

Sepsis was the most common indication for vancomycin in both groups. However, the intervention group had 3 (9.1%) infective endocarditis patients, while the pre-intervention group had no patient with infective endocarditis. The difference might result in different dose and duration of vancomycin usage.

2. Characteristics of vancomycin regimen

Duration of vancomycin usage in the intervention group was longer than the pre-intervention group, although not significant (17.8 ± 14.6 days vs. 15.7 ± 13.8 days; p = 0.607). The longer duration might be influenced by 3 patients of the intervention group who received vancomycin for the treatment of infective endocarditis which required long duration of treatment (4-6 weeks) (47). The result was contrast to previous study by Welty and coworkers (52), which found more patients in the TDM group who were prescribed vancomycin empirically, and shorter duration of therapy; day of therapy for the TDM and the non-TDM groups was 11.3 days and 13.4 days, respectively.

The average daily dose of vancomycin was higher in the intervention group (1.0 ± 0.9 g/day vs. 0.8 ± 0.7 g/day; p = 0.437). However, the difference was not significant. This might result from the difference in average age, body weight, and indication of vancomycin. When average daily dose was calculated per kilogram body weight, the result still showed no significant difference between the two groups (the average daily dose in the intervention group and the pre-intervention group as 0.0185 ± 0.0144 g/kg/day and 0.0152 ± 0.0126 g/kg/day; p = 0.382, respectively). This could indicate that body weight was not the important factor of average daily dose in our study. Subgroup analysis of average daily dose of vancomycin in hemodialysis patients revealed no significant difference in either the pre-intervention group or the intervention group (0.3 ± 0.1 g/day vs. 0.3 ± 0.1 g/day; p = 0.858). But the difference, though non-significant, were found between the average daily dose in the non-hemodialysis patients of the pre-intervention group and the intervention group (1.1 ± 0.6 g/day vs. 1.3 ± 0.9 g/day; p = 0.490). The higher dose found in the intervention group could be from the new therapeutic range suggested by IDSA and ATS in the year 2004 and 2005, which increased trough concentration of vancomycin to 15-20

mg/L in some kinds of infection such as meningitis (48) and pneumonia (46). Too few number of patients in the intervention group who were in need of higher trough concentration might explain why significant difference was not found

With the vancomycin regimen used during the 2 study phases, there were incidences of dead patients and nephrotoxicity. Percentage of dead patients in the pre-intervention group were three times higher than those in the intervention group; 11 patients (45.8%) vs. 4 patients (14.3%), $p = 0.012$. All of them died from other causes which were not related to vancomycin given to them. Thus, the difference in incidence of dead patients resulted from the better vancomycin regimen in the intervention phase, as one might expect, awaits further verification.

The incidence of vancomycin induced nephrotoxicity has been reported to occur in a range of 5 to 25% (52, 62, 63). Similar results have been confirmed in the present study. The incidence of nephrotoxicity was evaluated in the studied patients who did not receive hemodialysis to see whether vancomycin induced nephrotoxicity or not. There was an increase in the baseline Scr above 0.5 mg/dL in 3 of 19 patients of the intervention group (15.8%) versus 3 of the 15 patients of the pre-intervention group (20.0%); $p = 0.753$. This indicated that SVCM by pharmacist did not increase the incidence of nephrotoxicity from vancomycin. But there were still incidence of nephrotoxicity in the intervention group. On seriously review, we found a higher percentage of patients in the intervention group receiving concomitant nephrotoxic drug such as aminoglycoside. These drugs might contribute nephrotoxicity to our patients and might additionally affect to vancomycin-induced nephrotoxicity still seen in the intervention group.

Although pharmacist conducted SVCM seriously during the intervention period, but there was no statistically significant difference in the number of SVCM per patient between the 2 phases (2.6 ± 3.2 times vs. 3.0 ± 2.2 times; the pre-intervention group vs. the intervention group; $p = 0.727$). The results thus were not biased by the frequency. However we expected to see the better results as a consequence from better quality of SVCM.

3. Appropriateness of serum vancomycin concentration assessment

The appropriateness of SVCM, based on the use of serum drug concentration determination adopted from Winter and coworkers (53) was used in the pre-intervention and the intervention group. This criteria as it was only one criteria that assessed appropriateness of serum drug concentration, through each step of serum drug concentration monitoring, while other studies (59, 64) provided only definition of appropriateness of serum drug concentration. Therefore Winter and coworker criteria would be fit to our study as we expected to know causes of inappropriate SVCM in order to improve it. To make use of Winter criteria, we changed 3 points in the process of assessment. These were sampling time of vancomycin, therapeutic range of vancomycin, and defend criteria.

The significant reduction in the number of inappropriate serum vancomycin concentration was found in the intervention group as compared to the pre-intervention group; 32 times (50.8%) in the pre-intervention group to 19 times (22.3%) in the intervention group. The major type of inappropriate SVCM in the pre-intervention group was the inappropriate documentation such as no record of exact time of vancomycin administration and time of blood sampling in either medical's or nurse's note. In the intervention group, pharmacist had opportunity to talk to nurses in medical department and surgical department about the importance of recording exact time of vancomycin administration and time of blood sampling and the need of receiving corporation of multidisciplinary team in the use of vancomycin administration and sampling time record form. The inappropriate documentation was not surprised to be reduced from 15 times (46.9%) in the pre-intervention group to 3 times (15.8%) in the intervention group. These results indicated that multidisciplinary team work could reduce the inappropriate documentation of SVCM.

The inappropriate sampling time was comparable in the pre-intervention group and the intervention group. One explanation might be because pharmacist was available during working hours while many of the serum vancomycin samples were drawn between 6 p.m. and 6 a.m., the time period that pharmacist was off-service. Hence the influence of the pharmacist was not as strong as it could be when the pharmacist was available around the clock. Although instruction of appropriate

sampling time has been given, some nurses were still unable to follow such protocol. The co-operation within patient care team should be further improved.

A case of inappropriate sampling time that pharmacist could intervene before it occurred was the order to draw blood sample for SVCM immediately after finishing the hemodialysis session. This level would then be misinterpreted, if it was used, as the vancomycin concentration would dramatically decrease during hemodialysis and then increase 3-6 hours post dialysis. Pharmacist eventually providing information of disadvantage and low benefit of post hemodialysis level to physician and the intervention was accepted.

Winter and coworkers (53) studied the impact of decentralized pharmacokinetics consultation service on the appropriateness of serum drug concentration of aminoglycosides and theophylline. The service was provided by clinical pharmacist and the following functions were include: participation in daily ward rounds, monitoring medication use, providing inservice education to physicians and nurses, discussing with physicians about those patients who would benefit from serum drug concentration monitoring, discussing with physicians about the optimum times for obtaining blood samples, and scheduling the appropriate time for obtaining each sample or, if timing was critical or not compatible with normal morning phlebotomy rounds, obtaining the sample at the appropriate time, discussing with physician when reports of serum drug concentration returned with the emphasis on the care with potential problems, and providing a written note or report documenting the relationship between maintenance dose and the drug concentration at steady state. The results revealed that pharmacist could decrease the number of inappropriate serum aminoglycoside and theophylline concentration and increase the number of appropriateness in making therapeutic decision. Our study showed similar results, although we did not participate in daily ward round.

Crowley and coworkers (59) conducted three prospective audits to assess the impact of vancomycin therapeutic drug monitoring (TDM) on administration of vancomycin. After the first audit, a number of changes in the TDM process were undertaken. After the second audit, a senior pharmacist coordinated ward-based pharmacists in assisting staff to interpret levels, and TDM interpretative charts were designed for drug charts. Finally, after the third audit, feedback to hospital

management and a plan for ongoing education was undertaken. They found a significant reduction in the number of vancomycin doses held inappropriately in the third audit [10% (78/782) of prescribed doses] when comparing to the first audit [16% (161/1007) of doses] ($p = 0.01$). Of doses that were held inappropriately, there was a significant decrease in doses held for no apparent reason in the third audit [16% (27/170) of prescribed doses] when comparing to the first audit [25% (69/282) of doses] ($p = 0.05$).

Ratanajamit and coworkers (64) retrospectively studied the appropriateness of TDM for lithium in Thailand. They found only 36.3% of appropriate TDM for lithium according to the indication, sampling time and subsequent dose adjustment. The findings indicated the need for strategies to improve the utilization of TDM for lithium. Previous studies (65, 66) reported that the TDM service could be improved by educating hospital staff involved in TDM service, including nursing staff, laboratory personnel, physicians and pharmacists. The pharmacy-based clinical pharmacokinetic service was also able to improve the appropriateness of physician utilization of serum drug levels (67).

Although our study provided education of serum vancomycin concentration monitoring to multidisciplinary team and had pharmacist involved in patient care team, there was still inappropriateness of SVCM. On discussion with the patient care team, we found that physicians and nurses had unclear communication concerning about time for sampling, and resulting in too early or too late blood drawn by nurses. Further management to improve the appropriateness of SVCM in our hospital should consist of providing education to physicians (staff and resident), medical students and nurses. Secondly, guidelines should be set up for monitoring serum vancomycin concentration in which physicians should consult pharmacist for appropriate sampling time, and interpret the result of vancomycin concentration with or without dosage adaptations and note into medical chart. Thirdly, adding guideline for monitoring serum vancomycin concentration into medication order computer program in Ramathibodi Hospital, which physician can read information and check appropriateness before ordering SVCM. Finally, setting up practice criteria to the central laboratory that the blood samples were not analyzed if the labels on sample tubes contained incomplete information, such as sampling time.

4. Frequency of having vancomycin serum concentration in therapeutic range assessment

Random concentration in our study was defined as vancomycin serum concentration that was drawn not respect to dose, such as those in patient with hemodialysis, or after holding vancomycin dosage. Cause of random concentration in the pre-intervention group was not evaluated because it was retrospective nature of the study that such information was seldom available in medical records. But in the intervention period, pharmacist could recommend the appropriate sampling time with respect to dose and steady state. Therefore, it was not surprised that the frequency of random concentration in the intervention group was lower than that in the pre-intervention group (34.1% vs. 69.9%). Nevertheless, random concentration may be essential for determining the next dose of vancomycin, especially in hemodialysis patient that random concentration was needed for determining the appropriate dosing interval. The result thus suggested that the random concentration should have standard instruction for use. For example, in the hemodialysis patients should give 1 gram of vancomycin stat and then vancomycin concentration monitoring at 2-3 days after the first dose.

Both peak and trough concentration in the intervention group was higher than those in the pre-intervention group, but no statistically significant difference was seen (trough concentrations: 17.4 $\pm$ 7.6 mg/L vs. 13.1 $\pm$ 6.8 mg/L and peak concentrations: 40.8 $\pm$ 12.8 mg/L vs. 31.0 $\pm$ 14.7 mg/L; the intervention group vs. the pre-intervention group). Peak and trough concentration in the intervention group were both high and out of the therapeutic range. This might result from the different indication of vancomycin between the intervention group and the pre-intervention group. The important indications of vancomycin use in the intervention group consisted of 3 cases of infective endocarditis, 3 cases of meningitis, and 2 cases of acute cholangitis which caused by Methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterococcus* species and *Staphylococcus epidermidis*. Because each site of infection in the intervention group was more deep-seated infections (i.e., meningitis, endocarditis, cholangitis) in which vancomycin penetration may also be an issue and the recent recommendations for treating these infections based on expert opinion was changing target peak and

trough concentration to 30-45 mg/L and 15-20 mg/L, respectively. We decided to increase dose of vancomycin to reach higher peak and trough level, even it was only expert opinion recommendation. Moreover, after we increased dose to reach higher trough concentration, we also monitored renal function together with vancomycin concentration and no declining in renal function was found. Although some authors (2, 21, 52, 57, 68) suggested that the trough concentration above 15 mg/L was considered to be associated with an increased incidence of nephrotoxicity. In our study the incidence of nephrotoxicity from vancomycin was similar between the intervention group (higher trough concentration) and the pre-intervention group (lower trough concentration).

In spite of the higher peak and trough concentration in the intervention group compared to the pre-intervention group, though non-significant, the frequency of peak and trough concentration within the therapeutic range remained similar between the 2 groups.

The result of our study was similar to the study of Karam and coworkers (51), which assessed outcome of vancomycin to minimize vancomycin monitoring and dosing adjustment. They found no difference between nomogram and pharmacokinetic dosing of vancomycin with respect to cure, improvement, failure, or days to eradication, or with respect to nephrotoxicity and total drug cost/ patient. There were 94% of patients that had trough concentration in the target range of 5-20 mg/L.

Our study did not evaluate the clinical outcome of vancomycin, because there were many factors that affected the clinical outcome of patients, so we could not conclude that higher peak and trough concentration associated with the improvement of clinical outcome or toxic effect. Therefore, the evaluation of the clinical outcome of vancomycin to find out that pharmacist’s participation in SVCM can improve clinical outcome would be further investigated.

5. Determination of pharmacokinetic parameter of vancomycin

The retrospective study by Fernandez and coworkers (69) analyzed pharmacokinetic parameter of vancomycin in ICU patients by using data of serum vancomycin concentration obtained in routine monitoring. Then, pharmacokinetic and pharmacodynamic analysis was performed by Monte Carlo simulation. They found higher Vd and different vancomycin clearance - creatinine clearance relationship, as compared to non-ICU patients.

Our data was analyzed for pharmacokinetic parameters and patients were divided into 2 groups; those who were on hemodialysis and the other were not on hemodialysis. Elimination rate constant, Ke (hr^{-1}) of the hemodialysis group (n = 9 patients) was significantly lower than the non-hemodialysis group (n = 19 patients); (0.0098 $\pm$ 0.0038 vs. 0.0646 $\pm$ 0.0720, hemodialysis group vs. non-hemodialysis group, p = 0.017). Half-life, $T_{1/2}$ (hrs) of hemodialysis group was significantly longer than the non-hemodialysis group (80.5 $\pm$ 28.5 vs. 23.3 $\pm$ 19.3, hemodialysis group vs. non-hemodialysis group, p < 0.0001). Volume of distribution, Vd (L) in both groups was not significantly different (35.12 $\pm$ 7.12 L vs. 34.04 $\pm$ 10.98 L, hemodialysis group vs. non-hemodialysis group, p = 0.729). Further studies that interest to identify pharmacokinetic parameters and dosage of vancomycin in Thai patients should be conducted and included more patients.

6. Pharmacist's intervention and physician's acceptance

Twenty-six patients (92.9%) in 28 patients received interventions from pharmacist. A total of 103 interventions were provided to physician by direct communication and pharmacist's note. The majority of interventions were pharmacist counseled physician in the interpretation and recommendation for the proper dosage of vancomycin. Types of recommendation conducted in successive frequency were as followed: the decrease dose of vancomycin (50.8%), the holding dose of vancomycin (23.7%), and the increase dose of vancomycin (20.3%).

Of 103 interventions, 5 interventions (4.9%) were not accepted by physician. The first case was a patient with acute renal failure, and SVCM was ordered with no

relation to dose and steady state. Pharmacist recommended to hold that SVCM and wait for 2 days before ordering a new SVCM. But at that time, pharmacist could not contact physician, so she wrote down her recommendation in the pharmacist's note. The note of recommendation was not read, the order for SVCM was not changed, and blood was drawn according to the first order. On returning of laboratory report, high serum vancomycin concentration was found. The concentration could not be used to interpret therapeutic efficacy or determine timing for next dose. This SVCM was thus performed without benefit. The second case was a patient with impaired renal function, and vancomycin dose was recommended. Pharmacist had recommended dosing at 750 mg IV every 24 hours but nephrologist suggested 750 mg IV every 12 hours. Finally, primary physician decided to increase dose as nephrologist suggestion. After the third dose of 750 mg IV every 12 hours, patient developed acute renal failure. High trough concentration was found, and nephrologist told resident to follow pharmacist recommendation. At this time, pharmacist recommended to change the dose to 1 g IV every 24 hours and further conducted proper SVCM. The third case was a patient with end stage renal disease. Pharmacist recommended to hold vancomycin for 1 day because too high concentration was found. Physician agreed with pharmacist's recommendation. But before physician wrote his order to hold dose, patient was transferred to other ward on that night. The physician from the second ward did not see the pharmacist's note of holding dose, and therefore vancomycin was still given on that night. In the next morning, pharmacist followed-up this case and further conducted proper SVCM. High trough concentration (out of therapeutic range) was found but no further nephrotoxic effect. The fourth case was a patient that pharmacist recommended random SVCM after holding dose. But the patient was terminally ill and physician decided to stop all antibiotics and gave only supportive care till end of life. The last case was a patient with chronic kidney disease and physician ordered blood sample for both peak and trough concentration after the first dose. Pharmacist suggested to have blood sampling for random concentration instead, and explained that the concentrations derived were not usable; the trough and peak concentration derived from 2 consecutive dosing were not in steady state and were unable to be calculated for pharmacokinetic parameters. However, physician insisted to have 2 blood samples; one at peak and the other at trough. On returning of

laboratory report, 2 concentrations were reported but they were not used for further determination. Patient was followed-up and no problems caused by vancomycin were observed.

The above scenarios demonstrated problems in communication within patient care team. We thought that if the recommendation was more frequent, took longer time, or provided simple procedure, the problems would be reduced. However, this expectation needs elucidation.

CHAPTER VI
CONCLUSIONS

This study was performed to evaluate the appropriateness of SVCM and determine the frequency of serum vancomycin concentration in therapeutic range during the pre-intervention and the intervention period (1st November 2006 - 15th December 2006 and 15th January 2007 - 28th February 2007, respectively). The results were concluded as followed:-

1. Twenty four patients (25.3%) of the pre-intervention group received SVCM and twenty eight patients (26.4%) of the intervention group received SVCM.
2. Average age in the pre-intervention and the intervention group were 67.8 $\pm$ 15.6 years and 56.0 $\pm$ 18.2 years, respectively, and the difference was statistically significant.
3. Average weight in the pre-intervention and the intervention group were 50.9 $\pm$ 8.3 kg and 55.4 $\pm$ 13.0 kg, respectively, but the difference was not statistically significant.
4. Sepsis was the major indication of vancomycin usage in both groups.
5. Average daily dose of vancomycin were 0.8 $\pm$ 0.7 g and 1.0 $\pm$ 0.9 g in the pre-intervention group and in the intervention group, respectively, but the difference was not statistically significant.
6. The incidence of nephrotoxicity induced by vancomycin was lower but not statistically significant in the intervention group than the pre-intervention group (15.8 % vs. 20%; intervention group vs. pre-intervention group).
7. The appropriateness of SVCM was significantly increased from 38.1% in the pre-intervention group to 65.9% in the intervention group ($p < 0.001$) whereas the inappropriateness of SVCM was significantly decreased from 50.8% in the pre-intervention group to 22.3% in the intervention group ($p < 0.001$).

8. The intervention group had higher peak concentration than the pre-intervention group, but no statistically significant difference was found (30.9 ± 14.7 mg/L vs. 40.8 ± 12.8 mg/L.; the pre-intervention group vs. the intervention group.)
9. The intervention group had higher trough concentration than the pre-intervention group, but no statitically significant difference was found (trough concentrations: 13.1 ± 6.8 mg/L vs. 17.4 ± 7.6 mg/L; the pre-intervention group vs. the intervention group)
10. The frequencies of peak concentration within the therapeutic range (peak concentration 20-40 mg/L) were comparable between the pre-intervention group and the intervention group (60.0% vs. 59.1%; the pre-intervention group and the intervention group).
11. The frequencies of trough concentration within the therapeutic range (trough concentration 5-15 mg/L) were comparable between the pre-intervention group and the intervention group (78.6% vs. 64.7%; the pre-intervention group and the intervention group).
12. Pharmacist's interventions were accepted by physician at the frequency of 95.1%.

Limitation of the study

1. The study was limited to adult patients in medical wards and surgical wards.
2. The intervention was limited to those patients who were already prescribed with vancomycin, insead of intervention during ward round before the drug was prescribed.
3. No evaluation of the clinical efficacy of vancomycin in terms of treating infection was included in the study.
4. Neither cost-effectiveness nor cost of SVCM was included in the study.

Recommendations for further study:

1. Pediatric patients should be studied as pharmacokinetic parameters were different from adults.
2. Clinical efficacy of vancomycin in terms of treating infection and cost-effectiveness as well as cost of SVCM by pharmacist should be studied.
3. More data of vancomycin concentration and its relevant information should be collected and may be used to calculate for pharmacokinetic parameters of Thai patients via population pharmacokinetic theory.

Recommendations for Ramathibodi Hospital:

1. Continuing education program for SVCM to physicians, medical students and nursing staffs should be provided so that the SVCM will be conducted appropriately and beneficial.
2. More pharmacists are needed to run SVCM, and may expand to TDM work for all wards so that patients will receive the best practice from multidisciplinary team.
3. Develop guideline of SVCM for Ramathibodi Hospital by incorporation of multidisciplinary team.
4. Adding guideline of SVCM into medication ordering computer program for the ease of physician to order.
5. Setting up practice criteria to the central laboratory that the blood samples will be not analyzed if the labels on sample tubes contain incomplete information, such as sampling time.

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APPENDIX

APPENDIX A

Data collection form

Consultation: Yes/No	Consultation date:……..…
Consultation for: ○ Recommend sampling time	
○ Interpretation and dosage adjustment	

Name……..... Age…..…..yrs HN…...….....Ward: ……. Bed…….
Gender: Male/Female Ht …....cm TBW ……kg IBW…...…..kg Adm. date ……..... D/C date ……
CC: ……..……..……...
PI: ……..…….…….....
……...……..……...…..
Allergy: □ 1 No □ 2 Yes ……
PMH: □ 1 Cardiovascular disease □ 4 CNS disease
□ 2 Diabetes mellitus □ 5 Others …….
□ 3 Renal disease
PE: V/S : BT ……..… ^{O}C PR ..... /min RR …….. /min BP……mmHg
……..…..
……..…..
Diagnosis/Impression:
……
……..……
➢ Indication of vancomycin
……
……
➢ Vital sign

Date															
BT (^{O}C)															
PR /min															
RR /min															
BP (mmHg)															
Weight (kg)															
Input (ml)															
Output (ml)															

- Laboratory test

Urinalysis		Date					
Test	Normal range						
WBC /HPF	0-5						
RBC /HPF	0-2						
Cast /LPF	0-1						
Epithelial cell /HPF	5-10						
Bacteria	Neg						

Blood Chemistry		Date												
Test	Normal range													
Alb mg/L	35-42													
BUN mg/dL	7-20													
SCr mg/dL	0.5-1.5													
CrCL mL/min														
Hemodialysis type and duration														

Hematology		Date					
Test	Normal range						
WBC (/mcL)	4000-11000						
Platelets $x10^3$/mm	150-440						
ANC $x10^3$/mm	1.8-7.7						
N / L / M / E / B %	40-74 / 19-48 / 3.4-9 0-7 / 0-1.5						

Culture and sensitivity					
Date	Site	C/S results	Sensitive	Resistant	MIC
		□ MRSA □ Enterococci □ others……	□vancomycin □……..	□ampi/oxacillin □……	
		□ MRSA □ Enterococci □ others……	□vancomycin □……..	□ampi/oxacillin □……	
		□ MRSA □ Enterococci □ others……	□vancomycin □……..	□ampi/oxacillin □……	

Vancomycin profile

Date													
Dosage regimen													
Infusion time (hr)													
Admin times													
Sampling time □ Not record □ Record in [○ lab report ○ medical chart ○ nurse's note ○ blood tube ○ others…..]													
Peak	Order												
	Drawn												
Trough	Order												
	Drawn												
Vancomycin level													
Peak level (mg/L)													
Trough level (mg/L)													
Spot level (mg/L)													

Other medication regimen	Date											

Calculation

Population PK of vancomycin:

Sawchuck-Zaske method (60); K = 0.00082 (CrCL(ml/min)) + 0.00255 , Vd = 0.7 L/Kg, T1/2 = 0.693/K

K……..hr^{-1}, Vd……..L, T1/2 ……. hr

Predicted level: Peak = …… mg/L Trough = …….mg/L

Ambrose method (61); K = 0.06 x CrCL(ml/min) / Vd, Vd = 0.17(age) + 0.22 (wt) + 15, T1/2 = 0.693/K

K……..hr^{-1}, Vd……..L, T1/2 ……. hr

Predicted level: Peak = …… mg/L Trough = …….mg/L

Sampling time:

……..…

……..

Drug level:

Peak: Date……. Time……..…… level….....mg/L

Trough: Date…….…… Time…….. level….....mg/L

Conc

Date

……

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Recommendation:

Dosage adjustment:

……..…….

……

……

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……

Type of Intervention:
□ 1. Pharmacist intervene MD to recommend SVCM ○ Accept ○ Not accept; Reason……..……
□ 2. Pharmacist intervene MD to recommend appropriate sampling time ○ Accept ○ Not accept; Reason:……..…
□ 3. Pharmacist intervene MD to interpret and recommend proper dosage ○ Accept ○ Not accept; Reason:…….……..…..
□ 4. MD consult pharmacist to recommend appropriate sampling time ○ Accept ○ Not accept; Reason:……....
□ 5. MD consult pharmacist to interpret and recommend proper dosage ○ Accept ○ Not accept; Reason:…….……...

Intervention
……
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Serum vancomycin concentration determination

□ 1. Appropriate serum drug concentration

□ 2. Inappropriate serum drug concentration

Reason:……
……
……
……

APPENDIX B

Vancomycin Dosage Adjustment (60)

1. Calculate Creatinine Clearance (CrCL): (ml/min)
    a. Estimated CrCL using Crockoft and Gault method:

$$\frac{140\text{-age} \times \text{IBW} \times 0.85 \text{ (females only)}}{72 \times \text{Serum creatinine (mg/dL)}}$$

    b. Determine dosing weight (DW)
    c. Dosing weight should be actual body weight
2. Population pharmacokinetic calculation
    - Volume of Distribution (Vd)
        - Normal range=0.5-0.9 L/Kg
        - Average=0.7 L/Kg
    - Elimination Rate Constant (Ke) from population pharmacokinetic
        - Sawchuck-Zaske method (60);

        Ke = 0.00082 (CrCL (ml/min)) + 0.00255

        Vd = 0.7 L/Kg
        - Ambrose method (61);

        Ke = 0.06 x CrCL (ml/min) / Vd

        Vd = 0.17(age) + 0.22 (wt) + 15

Symbol	Meaning
(D)	Dose (mg)
(t')	Infusion duration (hr)
(T)	Dosing interval (hr)
(t)	Time since infusion completion (hr)
(t ")	Time since completion of infusion when C_1 drawn (hr)
(Vd)	Volume of distribution (L)

3. Patient's pharmacokinetic calculation

Calculate Ke

$$Ke = \frac{\ln C_1 - \ln C_2}{t_1 - t_2}$$

Calculate $T_{1/2}$

(Normally dosing interval should be 1-2 $T_{1/2}$)

$$T_{1/2} = \frac{0.693}{Ke}$$

Calculate true peak (Cmax) and trough (Cmin) level

$$Cmax = \frac{C_1}{e^{-Ke(t'')}}$$

$$Cmin = Cmax\ (e^{-Ke(T-t')})$$

Calculate Vd

$$Vd = \frac{Dose\ (mg) \times (1-e^{-Ke(t')})}{t' \times Ke\ (Cmax - Cmin\ e^{-Ke(t')})}$$

Calculate New Dose

$$Dose = \frac{Cmax_{(desired)} \times Ke \times Vd \times (1-e^{-Ke(T)}) \times t'}{1-e^{-Ke(t')}}$$

Calculate new peak and trough

$$Cmax_{(new)} = \frac{Dose(mg) \times (1-e^{-Ke(t')})}{t' \times Ke \times Vd \times (1-e^{-ke(T)})}$$

$$Cmin_{(new)} = Cmax\ (e^{-Ke(T-t')})$$

If a change is made, check a peak and trough level at 3-5 half-life later

APPENDIX C

เอกสารชี้แจงข้อมูล/คำแนะนำแก่ผู้เข้าร่วมการวิจัย

(Patient/Participant Information Sheet)

ชื่อโครงการ โครงการพัฒนาระบบการติดตามตรวจวัดระดับยาในเลือดของยา vancomycin ในโรงพยาบาลรามาธิบดี

ชื่อ นางสาว พาขวัญ ปุณณุปูรต

สถานที่วิจัย หอผู้ป่วยอายุรกรรม หอผู้ป่วยศัลยกรรมและหอผู้ป่วยออร์โธปิดิกส์ โรงพยาบาลรามาธิบดี

แพทย์ผู้ดูแลผู้เข้าร่วมงานวิจัย ผู้ช่วยศาสตราจารย์ นายแพทย์กำธร มาลาธรรม

รองศาสตราจารย์ นายแพทย์วินัย วนานุกูล

โครงการวิจัยนี้ทำขึ้นเพื่อพัฒนาระบบการติดตามตรวจวัดระดับยาในเลือดของยา vancomycin โดยมีเภสัชกรเข้าร่วมให้บริการตรวจวัดระดับยาในเลือด เพื่อช่วยเพิ่มประสิทธิภาพในการรักษา ลดโอกาสเกิดพิษต่อไต รวมทั้งอาจช่วยลดค่าใช้จ่ายด้านห้องปฏิบัติการ ลดระยะเวลาการใช้ยา ลดโอกาสในการเกิดภาวะแทรกซ้อน ลดระยะเวลาในการอยู่โรงพยาบาลและลดอัตราการเสียชีวิต

ท่านได้รับเชิญให้เข้าร่วมการวิจัยนี้เนื่องจากในขณะที่ท่านอยู่โรงพยาบาลและพบการติดเชื้อที่จำเป็นต้องได้รับยาแวนโคมัยซิน (vancomycin) ซึ่งเป็นยาฆ่าเชื้อแบคทีเรียที่มีประสิทธิภาพแต่มีอาการข้างเคียงที่สำคัญคือเป็นพิษต่อไต การเข้าร่วมในโครงการวิจัยนี้ท่านจะได้รับการตรวจวัดระดับยาในเลือด (Therapeutic drug monitoring; TDM) ของยาแวนโคมัยซิน ติดตามผลการรักษา ปรับขนาดยาตามความจำเป็นและเหมาะสมตลอดเวลาที่ท่านได้รับยาแวนโคมัยซิน

ผลดีที่เกิดจากการเข้าร่วมโครงการวิจัยนี้คือ ท่านเป็นผู้มีส่วนร่วมในการพัฒนาระบบการดูแลผู้ป่วยที่ได้รับยาแวนโคมัยซิน

ผลเสียที่เกิดจากการเข้าร่วมโครงการวิจัยนี้คือ การเจ็บตัวเนื่องจากได้รับการเจาะเลือด

สิ่งที่ท่านจะต้องปฏิบัติคือปฏิบัติตามวิธีการรักษาตามความเห็นของแพทย์ผู้รักษา

หากท่านไม่เข้าร่วมในโครงการวิจัยนี้ ท่านก็จะได้รับการรักษาโรคของท่านตามวิธีการที่เป็นมาตรฐาน คือ ได้รับการรักษาตามความเห็นของแพทย์ผู้รักษา

หากเกิดผลข้างเคียงที่ไม่พึงประสงค์จากการวิจัย ท่านจะได้รับการดูแลตามมาตรฐานการรักษาของโรงพยาบาลรามาธิบดี ผู้วิจัยที่จะสามารถติดต่อได้หากท่านมีข้อข้องใจที่จะสอบถามเกี่ยวข้องกับการวิจัย หรือเมื่อมีผลข้างเคียงจากการรักษาคือ รองศาสตราจารย์บุษบา จินดาวิจักษณ์ โทร 08-1934-2424 เภสัชกรหญิง พาขวัญ ปุณณุปูรต โทร 08-1752-6801 ผู้ช่วยศาสตราจารย์ นายแพทย์กำธร มาลาธรรมโทร 02-2011581 และรองศาสตราจารย์ นายแพทย์วินัย วนานุกูล โทร 02-2011610, 02-2011628

การวิจัยนี้ไม่มีค่าตอบแทนและท่านจะต้องรับผิดชอบค่ายาและค่าตรวจทางห้องปฏิบัติการซึ่งเกี่ยวข้องกับการรักษา และทางผู้วิจัยจะเป็นผู้รับผิดชอบค่าใช้จ่ายซึ่งไม่เกี่ยวข้องกับการรักษาโดยตรง ซึ่งหากมีข้อมูลเพิ่มเติมทั้งด้านประโยชน์และโทษที่เกี่ยวข้องกับการวิจัยนี้ ผู้วิจัยจะแจ้งให้ทราบโดยรวดเร็วไม่ปิดบัง

ข้อมูลส่วนตัวของท่านจะถูกเก็บรักษาไว้ ไม่เปิดเผยต่อสาธารณะเป็นรายบุคคล แต่จะรายงานผลการวิจัยเป็นข้อมูลส่วนรวม ข้อมูลของผู้เข้าร่วมการวิจัยเป็นรายบุคคลอาจมีคณะบุคคลบางกลุ่มเข้ามาตรวจสอบได้ เช่น ผู้ให้ทุนวิจัย, สถาบัน หรือองค์กรของรัฐที่มีหน้าที่ตรวจสอบ, คณะกรรมการจริยธรรมฯ เป็นต้น

ท่านมีสิทธิ์ถอนตัวออกจากโครงการวิจัยเมื่อใดก็ได้ โดยไม่ต้องแจ้งให้ทราบล่วงหน้า และการไม่เข้าร่วมการวิจัยหรือถอนตัวออกจากโครงการวิจัยนี้จะไม่มีผลกระทบต่อการบริการและการรักษาที่สมควรจะได้รับแต่ประการใด

ข้าพเจ้าได้อ่านรายละเอียดในเอกสารนี้ครบถ้วนแล้ว

ลงชื่อ...../วันที่.....

(.....)

ถ้าท่านมีปัญหาข้องใจหรือรู้สึกกังวลใจกับการเข้าร่วมในโครงการวิจัยนี้ ท่านสามารถติดต่อกับประธานกรรมการ

หนังสือยินยอมโดยได้รับการบอกกล่าวและเต็มใจ

(Informed Consent Form)

ชื่อโครงการ โครงการพัฒนาระบบการติดตามตรวจวัดระดับยาในเลือดของยา Vancomycin ในโรงพยาบาลรามาธิบดี

ชื่อผู้วิจัย นางสาว พาขวัญ ปุณณุปูรต

*ชื่อผู้เข้าร่วมการวิจัย .....

อายุ ..... เลขที่เวชระเบียน .....

คำยินยอมของผู้เข้าร่วมการวิจัย

ข้าพเจ้า นาย/นาง/นางสาว ..... ได้ทราบรายละเอียดของโครงการวิจัยตลอดจนประโยชน์ และข้อเสี่ยงที่จะเกิดขึ้นต่อข้าพเจ้าจากผู้วิจัยแล้วอย่างชัดเจน ไม่มีสิ่งใดปิดบังซ่อนเร้นและยินยอมให้ทำการวิจัยในโครงการที่มีชื่อข้างต้น และข้าพเจ้ารู้ว่าถ้ามีปัญหาหรือข้อสงสัยเกิดขึ้น ข้าพเจ้าสามารถสอบถามผู้วิจัยได้ และข้าพเจ้าสามารถไม่เข้าร่วมโครงการวิจัยนี้เมื่อใดก็ได้ โดยไม่มีผลกระทบต่อการรักษาที่ข้าพเจ้าพึงได้รับ นอกจากนี้ผู้วิจัยจะเก็บข้อมูลเฉพาะเกี่ยวกับตัวข้าพเจ้าเป็นความลับและจะเปิดเผยได้เฉพาะในรูปที่เป็นสรุปผลการวิจัย การเปิดเผยข้อมูลเกี่ยวกับตัวข้าพเจ้าต่อหน่วยงานต่างๆที่เกี่ยวข้องกระทำได้เฉพาะกรณีจำเป็นด้วยเหตุผลทางวิชาการเท่านั้น

ลงชื่อ.....(ผู้เข้าร่วมการวิจัย)

.....(พยาน)

.....(พยาน)

วันที่ .....

คำอธิบายของแพทย์หรือผู้วิจัย

ข้าพเจ้าได้อธิบายรายละเอียดของโครงการ ตลอดจนประโยชน์ของการวิจัย รวมทั้งข้อเสี่ยงที่อาจจะเกิดขึ้นแก่ผู้เข้าร่วมการวิจัยทราบแล้วอย่างชัดเจนโดยไม่มีสิ่งใดปิดบังซ่อนเร้น

ลงชื่อ..... (แพทย์หรือผู้วิจัย)

วันที่.....

หมายเหตุ : กรณีผู้เข้าร่วมการวิจัยไม่สามารถอ่านหนังสือได้ ให้ผู้วิจัยอ่านข้อความในหนังสือยินยอมฯ นี้ให้แก่ผู้เข้าร่วมการวิจัยฟังจนเข้าใจดีแล้ว และให้ผู้เข้าร่วมการวิจัยลงนามหรือพิมพ์ลายนิ้วหัวแม่มือรับทราบในการให้ความยินยอมดังกล่าวข้างต้นไว้ด้วย

* ผู้เข้าร่วมการวิจัย หมายถึง ผู้ยินยอมตนให้ทำวิจัย

หนังสือยินยอมโดยได้รับการบอกกล่าวและเต็มใจ

สำหรับผู้เข้าร่วมการวิจัยที่ไม่สามารถแสดงความยินยอมได้ด้วยตนเอง

ชื่อโครงการ โครงการพัฒนาระบบการติดตามตรวจวัดระดับยาในเลือดของยา Vancomycin ในโรงพยาบาลรามาธิบดี

ชื่อผู้วิจัย นางสาว พาขวัญ ปุณณปูรต

*ชื่อผู้เข้าร่วมการวิจัย .....

อายุ ..... เลขที่เวชระเบียน .....

คำยินยอมของผู้มีอำนาจกระทำการแทนผู้เข้าร่วมการวิจัย

ข้าพเจ้า นาย/นาง/นางสาว ..... ซึ่งเป็นผู้มีอำนาจกระทำการแทน นาย/นาง/นางสาว/ด.ช./ด.ญ. ..... ในฐานะ .....ได้ทราบรายละเอียดของโครงการการวิจัย ตลอดจนประโยชน์ และข้อเสี่ยงที่จะเกิดขึ้นต่อผู้เข้าร่วมการวิจัยจากผู้วิจัยแล้วอย่างชัดเจนไม่สิ่งใดปิดบังซ่อนเร้นและยินยอมให้ทำการวิจัยในโครงการที่มีชื่อข้างต้น และข้าพเจ้ารู้ว่าถ้ามีปัญหาหรือข้อสงสัยเกิดขึ้นข้าพเจ้าสามารถสอบถามผู้วิจัยได้ และข้าพเจ้าสามารถไม่ให้ผู้เข้าร่วมการวิจัยเข้าร่วมโครงการวิจัยนี้เมื่อใดก็ได้ โดยไม่มีผลกระทบต่อการรักษาที่ผู้เข้าร่วมการวิจัยได้รับ นอกจากนี้ผู้วิจัยจะเก็บข้อมูลเฉพาะเกี่ยวกับตัวผู้เข้าร่วมการวิจัยเป็นความลับและจะเปิดเผยได้เฉพาะในรูปที่เป็นสรุปผลการวิจัย การเปิดเผยข้อมูลเกี่ยวกับตัวผู้เข้าร่วมการวิจัยต่อหน่วยงานต่างๆที่เกี่ยวข้อง กระทำได้เฉพาะกรณีจำเป็นด้วยเหตุผลทางวิชาการเท่านั้น

ลงชื่อ.....(ผู้มีอำนาจกระทำการแทน)

.....(พยาน)

.....(พยาน)

วันที่ .....

คำอธิบายของแพทย์หรือผู้ทำวิจัย

ข้าพเจ้าได้อธิบายรายละเอียดของโครงการ ตลอดจนประโยชน์ของการวิจัย รวมทั้งข้อเสี่ยงที่อาจจะเกิดขึ้นแก่ผู้เข้าร่วมการวิจัยให้ผู้มีอำนาจกระทำการแทนทราบแล้วอย่างชัดเจนโดยไม่มีสิ่งใดปิดบังซ่อนเร้น

ลงชื่อ.....(แพทย์หรือผู้วิจัย)

วันที่.....

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*ผู้เข้าร่วมการวิจัย หมายถึง ผู้ยินยอมตนให้ทำวิจัย

APPENDIX D

Pharmacokinetic parameters of vancomycin in the intervention group

No	Gender (M/F)	Age (year)	Weight (kg)	Ke (hr^{-1})	Vd (L)	$T_{1/2}$ (hr)
Hemodialysis patients						
1	M	18	45.0	0.0138	25.52	50.22
				0.0090	25.52	77.00
				0.0135	25.52	51.32
2	M	50	50.0	0.0174	37.60	39.85
3	F	81	50.0	0.0066	33.75	105.00
4	M	34	54.0	0.0082	38.89	84.50
				0.0059	38.89	118.00
5	M	52	64.8	0.0055	48.00	127.00
6	F	38	40.7	0.0096	40.20	72.19
7	F	73	42.9	0.0073	36.68	94.93
8	F	42	52.6	0.0106	35.70	65.39
9	F	52	45.1	0.0108	31.57	64.47
Mean				0.0098	34.82	79.16

No	Gender (M/F)	Age (year)	Weight (kg)	Ke (hr^{-1})	Vd (L)	$T_{1/2}$ (hr)
Non hemodialysis patients						
1	M	68	50.0	0.0096	37.50	72.19
2	F	56	55.6	0.1026	50.52	6.75
3	F	50	46.7	0.0218	33.62	31.78
4	F	88	34.5	0.0134	25.88	51.72
5	F	57	45.5	0.0650	24.28	10.66
				0.0370	29.67	18.73
				0.0240	29.67	28.40
				0.0260	29.67	26.65
				0.0308	29.67	22.50
				0.0370	29.67	18.79
6	F	93	40.5	0.0350	39.61	19.80
7	F	53	44.0	0.0120	33.00	57.66
8	F	42	46.0	0.0660	22.22	10.47
				0.0499	32.70	13.86
				0.0480	25.31	14.44
				0.0496	25.31	13.97
9	M	60	65.0	0.1123	31.19	6.30
				0.0775	39.50	8.24
10	M	22	65.0	0.2500	20.43	2.78
				0.3300	40.43	2.09
11	F	77	60.0	0.0165	69.23	40.86
12	F	74	50.0	0.0648	38.58	10.69
13	M	74	50.0	0.0360	51.47	19.52
14	M	45	55.0	0.0500	21.43	13.87
15	M	51	51.6	0.0573	40.50	12.09
16	F	42	40.0	0.0568	38.44	12.20
17	M	65	64.4	0.1000	40.22	6.92
18	M	62	56.3	0.1170	47.57	5.92
19	F	50	58.0	0.1077	33.25	6.43
		Mean		0.0691	34.85	19.53

BIOGRAPHY

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