Optimizing antimicrobial dosages using therapeutic drug monitoring within the Intensive Care Unit of Dr George Mukhari Academic Hospital

A mini-dissertation submitted by

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DECLARATION

I declare that the mini-dissertation hereby submitted to the Sefako Makgatho Health Sciences University, for the degree of Master of Pharmacy, in the Faculty of Health Sciences, School of Health Care Sciences, has not previously been submitted by me for a degree at this or any other university; that it is my work in design and execution, and that all material contained herein has been duly acknowledged.

__________________________________  __________________
Surname, Initials (Title)                  Date
TABLE OF CONTENTS

ACKNOWLEDGEMENTS ........................................................................................................... v
LIST OF FIGURES ................................................................................................................ vi
LIST OF TABLES ................................................................................................................... vii
LIST OF APPENDICES ........................................................................................................ viii
ABBREVIATIONS AND ACRONYMS .................................................................................. ix
ABSTRACT ............................................................................................................................ x

CHAPTER 1 INTRODUCTION ................................................................................................. 1

1.1 BACKGROUND AND RATIONALE FOR THE STUDY .................................................. 1
1.2 AIM OF THE STUDY ......................................................................................................... 2
1.3 OBJECTIVES OF THE STUDY ......................................................................................... 2
1.4 CONCLUSION .................................................................................................................. 3

CHAPTER 2 LITERATURE REVIEW ......................................................................................... 4

2.1 INTRODUCTION ............................................................................................................. 4
2.2 THERAPEUTIC DRUG MONITORING IN SEVERE INFECTIONS ................................. 4
2.3 PHARMACOKINETIC MODELS USED IN THE THERAPEUTIC DRUG MONITORING OF AMINOGLYCOSIDES AND VANCOMYCIN .............................................. 5
2.4 PHARMACOKINETIC CHANGES IN THE CRITICALLY ILL PATIENT .............................. 6
2.5 HYPOALBUMINAEMIA .................................................................................................... 6
2.6 SEVERE INFECTIONS ..................................................................................................... 7
2.7 RENAL FUNCTION QUANTIFICATION .......................................................................... 7
2.8 AMINOGLYCOSIDES ..................................................................................................... 8
2.9 AMINOGLYCOSIDE PHARMACOKINETIC AND PHARMACODYNAMIC PROFILE ................................................................. 9
2.10 TOXICITIES ASSOCIATED WITH AMINOGLYCOSIDE THERAPY .......................... 10
2.11 GRAM NEGATIVE INFECTIONS ................................................................................... 11
2.12 VANCOMYCIN ............................................................................................................. 11
2.13 VANCOMYCIN PHARMACOKINETIC AND PHARMACODYNAMIC PROFILE .... 12
2.14 ADVERSE EVENTS ASSOCIATED WITH VANCOMYCIN THERAPY ....................... 13
2.15 MRSA AND MSSA ....................................................................................................... 14
2.16 MRSA IN SOUTH AFRICA .......................................................................................... 15
CHAPTER 3 METHOD .................................................................................. 16

3.1 INTRODUCTION .............................................................................. 16
3.2 STUDY DESIGN .............................................................................. 16
3.3 STUDY SITE .................................................................................... 16
3.4 STUDY POPULATION ...................................................................... 16
3.5 SAMPLE SELECTION ....................................................................... 17
3.6 SAMPLING METHOD ....................................................................... 17
3.7 DATA COLLECTION .......................................................................... 18
3.8 DATA COLLECTION INSTRUMENTS ................................................. 18
3.9 THERAPEUTIC DRUG MONITORING ............................................. 18
3.10 ADMINISTRATION OF MEDICATION ............................................. 18
3.11 DRAWING AND HANDLING OF SPECIMENS ................................ 18
3.12 ANALYTICAL TECHNIQUES ............................................................. 19
3.13 ASSAY METHODOLOGY ................................................................. 20
3.14 CALCULATION OF PHARMACOKINETIC PARAMETERS ................. 20
3.15 RENAL FUNCTION QUANTIFICATION .......................................... 22
3.16 DATA COLLECTION PERIOD ............................................................ 23
3.17 DATA ENTRY AND ANALYSIS ......................................................... 23
3.18 ETHICAL CONSIDERATIONS ........................................................... 23
3.19 SUMMARY ..................................................................................... 24

CHAPTER 4 RESULTS AND DISCUSSION ..................................................... 25

4.1 DEMOGRAPHICS ............................................................................. 25
4.2 WEIGHT .......................................................................................... 26
4.3 DIAGNOSES, ANTIBIOTIC USED AND INDICATION .................... 27
4.4 ANTIBIOTIC REGIMENS ................................................................. 29
4.5 PHARMACOKINETIC AND PHARMACODYNAMIC PARAMETERS FOR ALL PARTICIPANTS ................................................................. 30
4.6 AMINOGLYCOSIDES ...................................................................... 30
4.6.1 AMINOGLYCOSIDE HALF-LIFE .................................................. 31
4.6.2 AMINOGLYCOSIDE VOLUME OF DISTRIBUTION ........................................... 32
4.7 AMIKACIN PEAK AND TROUGH SERUM CONCENTRATIONS .................... 32
4.7.1 GENTAMICIN PEAK AND TROUGH SERUM CONCENTRATIONS......... 33
4.8 PARTICIPANTS WHO RECEIVED DIALYSIS ............................................. 34
4.8.1 ELIMINATION HALF-LIFE ................................................................. 35
4.8.2 VOLUME OF DISTRIBUTION .............................................................. 36
4.8.3 PEAK AND TROUGH AMINOGLYCOSIDE CONCENTRATION .......... 36
4.9 VANCOMYCIN ...................................................................................... 38
4.9.1 VANCOMYCIN PEAK AND TROUGH SERUM CONCENTRATIONS: ...... 38
4.9.2 VANCOMYCIN AREA UNDER THE CURVE: .................................... 40
4.9.3 VANCOMYCIN VOLUME OF DISTRIBUTION: ............................. 40
4.9.4 ELIMINATION HALF-LIFE ................................................................. 41
4.10 RENAL FUNCTION QUANTIFICATION ...................................................... 41
4.11 AMINOGLYCOSIDES .......................................................................... 41
4.12 RENAL FUNCTION QUANTIFICATION IN VANCOMYCIN PARTICIPANTS ..... 46
4.13 AUGMENTED RENAL CLEARANCE IN PARTICIPANTS RECEIVING VANCOMYCIN ................................................................. 47
4.14 ADVERSE EVENTS .............................................................................. 49
4.15 PATIENT CASE STUDIES ...................................................................... 50

CHAPTER 5 SUMMARY OF RESULTS, CONCLUSION AND RECOMMENDATIONS .... 56
5.1 INTRODUCTION .................................................................................... 56
5.2 LIMITATIONS OF THE STUDY .............................................................. 56
5.3 UNAVALIABILITY OF AMIKACIN, GENTAMICIN AND VANCOMYCIN REAGENTS ................................................................. 56
5.4 UNWILLINGNESS FROM ICU STAFF .................................................... 56
5.5 PATIENT WEIGHT ESTIMATES .............................................................. 56
5.6 SMALL SAMPLE SIZE ........................................................................ 56
5.7 WORK ENVIRONMENT ....................................................................... 57
5.8 CHANGE OF STUDY PROTOCOL ........................................................ 57
5.9 LABORATORY ERRORS ...................................................................... 57
5.10 INEXPERIENCE .................................................................................. 57
ACKNOWLEDGEMENTS

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LIST OF FIGURES

Figure 2.1: The linear relationship between AG elimination rate constant and CrCl (Bauer, 2014) ................................................................. 10

Figure 3.1: Flow diagram illustrating the steps involved in the data collection process. .... 17

Figure 4.1: Participants excluded from results .......................................................... 25

Figure 4.2: Aminoglycoside volume of distribution .................................................. 32

Figure 4.3: Peak and trough amikacin serum concentrations ................................... 33

Figure 4.4: Peak and trough gentamicin serum concentrations ................................ 34

Figure 4.5: Volume of distribution for aminoglycosides in patients receiving dialysis. .... 36

Figure 4.6: Peak and trough vancomycin serum concentrations ............................. 38

Figure 4.7: Calculated area under the curve ............................................................. 40

Figure 4.8: CrCl by different methods for aminoglycoside participants .................... 42

Figure 4.9: Participant CrCl estimations ................................................................. 43

Figure 4.10: CrCl through different methods ............................................................ 44

Figure 4.11: CrCl through different methods ............................................................ 46

Figure 4.12: CrCL calculated through the Cockcroft-Gault formula compared to the vancomycin derived $k_{el}$ CrCl ........................................... 48

Figure 4.13: Amikacin elimination during intermittent dialysis (participant 3) ............. 50

Figure 4.14: Vancomycin serum concentration after dosage adjustment ................. 51

Figure 4.15: Gentamicin serum concentration throughout treatment course (participant 9) ................................................................................. 52
LIST OF TABLES

Table 4.1 Participant demographic information: ................................................................. 26
Table 4.2: Participant amikacin treatment regimen background ........................................... 27
Table 4.3: Participant gentamicin treatment regimen background ......................................... 28
Table 4.4: Participant vancomycin treatment regimen background ....................................... 28
Table 4.5: Summary of participant amikacin pharmacokinetic parameters ............................ 30
Table 4.6 Summary of participant gentamicin pharmacokinetic parameters: ....................... 31
Table 4.7: Participant amikacin pharmacokinetic parameters .............................................. 35
Table 4.8 Participant gentamicin pharmacokinetic parameters .......................................... 35
Table 4.9: Participant vancomycin pharmacokinetic parameters ........................................... 38
Table 4.10 Renal function measurements in amikacin participants ....................................... 41
Table 4.11 Renal function measurements in gentamicin participants ................................... 42
Table 4.12: Pearson correlation analysis aminoglycosides .................................................... 43
Table 4.13: Pearson correlation analysis in impaired renal function ...................................... 44
Table 4.14: Correlation of CrCl calculation methods .............................................................. 45
Table 4.15: Renal function estimates in vancomycin participants .......................................... 46
Table 4.16: Correlation of CrCl calculation methods vancomycin ......................................... 47
Table 4.17: Correlation of CrCl calculation methods .............................................................. 48
LIST OF APPENDICES

Appendix 1: Consent forms ........................................................................................................................................... 67
Appendix 2: Patient demographics capturing sheet ........................................................................................................... 69
Appendix 3: Data collection Form ...................................................................................................................................... 70
Appendix 4: SMUREC clearance certificate ....................................................................................................................... 71
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>AG</td>
<td>Aminoglycoside</td>
</tr>
<tr>
<td>AG’s</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>CGE</td>
<td>Cockroft-Gault equation</td>
</tr>
<tr>
<td>CrCl</td>
<td>Creatinine Clearance</td>
</tr>
<tr>
<td>DGMAH</td>
<td>Dr George Mukhari Academic Hospital</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated glomerular filtration rate</td>
</tr>
<tr>
<td>EUCAST</td>
<td>European Committee on Antimicrobial Testing</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>MIC</td>
<td>Minimum Inhibitory Concentration</td>
</tr>
<tr>
<td>MRSA</td>
<td>Methicillin Resistant <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>MSSA</td>
<td>Methicillin Sensitive <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>SCR</td>
<td>Serum creatinine concentration</td>
</tr>
<tr>
<td>TDM</td>
<td>Therapeutic drug monitoring</td>
</tr>
<tr>
<td>VRE</td>
<td>Vancomycin Resistant <em>Enterococcus</em></td>
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ABSTRACT

Introduction: Vancomycin and aminoglycosides are regularly prescribed antibiotics and are of vital importance within the critically ill population. Current vancomycin and aminoglycoside (AG) dosing practices within Dr George Mukhari Academic Hospital can be considered arbitrary. Vancomycin and aminoglycoside pharmacokinetics differ greatly between individual patients, especially within the critically ill population, yet these patients often receive standard dosages. Optimal PK/PD parameters have been defined for the aminoglycosides and vancomycin. The aminoglycosides require a peak serum concentration of 8-10 x MIC for optimal bactericidal activity while vancomycin requires an AUC: MIC ratio of 400, which positively correlates with a trough level between 15-20 μg/ml.

Objectives: The objectives of the study were to evaluate whether current vancomycin and aminoglycoside dosing practices achieve optimal serum concentrations, to monitor for the occurrence of any adverse events during vancomycin or AG therapy, to optimise vancomycin and AG dosages by using PK/PD parameters and to develop treatment guidelines for the optimization of vancomycin/AG therapy based on the data generated from the use of therapeutic drug monitoring.

Method: The study was conducted in the general ICU of Dr George Mukhari Academic Hospital, Pretoria, Gauteng Province. The ICU consists of 22 beds, of which two are isolation rooms, and six are cardiac ICU. The study was a descriptive interventional study done by conducting therapeutic drug monitoring on patients who received amikacin gentamicin or vancomycin, using single compartment pharmacokinetic equations, from September 2015 to July 2016.

Results: During the nine month study period a total of 20 patients were enrolled, seven patients received vancomycin, six received gentamicin and seven received amikacin. Participants receiving amikacin had a mean; true peak of 51.8±8.9 μg/ml; true trough of 6.1±5.44 μg/ml; half-life of 6.6±3.6 hours, Vd of 0.28±0.04 L/kg and a total clearance of 4.86±1.86 L/hr. Those receiving gentamicin had a mean true peak of 10.18±2.92 μg/ml, true trough of 0.58±0.69, half-life of 5.8±3.66 hours, Vd of 0.35±0.14 L/kg and a total clearance of 4.29±1.4 L/hour. Those receiving vancomycin had a mean true peak of 43.89±15.98 μg/ml; true trough of 7.45±3.6 μg/ml; elimination half-life of 3.46±0.75 hours; a Vd of 0.42±0.24 L/kg and a total clearance of 4.44±1 L/hr. No drug-related adverse events occurred. Four patients receiving aminoglycosides had severe renal failure and were receiving dialysis.
**Conclusion:** Patients within the ICU had deranged PK parameters. Without therapeutic drug monitoring many abnormalities would not have been identified. SCr used within the Cockcroft-Gault equation and the MDRD eGFR could not accurately equate drug elimination rates in all patients. Current dosing strategies do not accommodate aminoglycoside and vancomycin optimal pharmacodynamic parameters. Routine TDM and MIC monitoring is required to optimise amikacin, gentamicin and vancomycin dosage within the ICU of DGMAH.
CHAPTER 1

Introduction

Chapter 1 provides an overview of the study and will include the background and rationale for initiating the study, problem statement, research questions, purpose and importance of the study.

1.1 BACKGROUND AND RATIONALE FOR THE STUDY

Aminoglycosides (AG) and vancomycin are vital antibiotics needed to treat various resistant infections worldwide. Vancomycin is vital in the treatment of methicillin resistant *Staphylococcus aureus* (MRSA), methicillin resistant *Staphylococcus epidermidis* (MRSE) and resistant enterococci infections. AG’s are vital against a wide array of resistant gram negative infections, especially those with extended spectrum beta-lactamase producing capabilities (Vandecasteele, De Vriese and Tacconelli, 2012; Duszynska, Taccone, Hurkacz, Kowalska-Krochmal, Wiela-Hojeńska. and Kübler, 2013).

Both the AG’s and vancomycin display severe inter individual differences with regards to their pharmacokinetic parameters, especially in septic patients (Rybak, Lomaestro, Rotschafer, Moellinger, Craig, Billeter, Dalovisio, Levine; 2009; Duszynska, *et al.*, 2013; Roberts and Lipman, 2009). These altered pharmacokinetic parameters in different patients often lead to sub-optimal dosing.

Dosing vancomycin to achieve an area under the concentration-time curve (AUC) to the minimum inhibitory concentration (MIC) ratio (AUC: MIC) of 400:1, was found to deliver optimal therapeutic outcomes (Gawronski, Goff, Brown, Khadem, Bauer; 2013). Dosing an AG to achieve a serum peak concentration of 8-10 times the organism’s MIC, delivers optimal therapeutic outcomes (Roberts and Lipman, 2009). The AUC: MIC ratio and the Cmax x MIC are pharmacodynamic (PD) markers that have been proven to provide the best clinical outcomes.

It was found that out of the 4656 ICU patients who received vancomycin, only 980 (21 %) patients received the correct dosages, 3143 patients where under dosed and 318 patients where overdosed within the emergency departments of various hospitals within the USA (Fuller, Mohr, Skrupky, Mueller and McCammon, 2013).
Chapter 1: Introduction

A study done by Duszynska, *et al*, (2013) concluded that only 83% of septic patients receiving AG therapy, needed further dosage adjustments after an initial loading dose to achieve the optimal serum concentrations.

Optimal use of anti-microbial therapy has become an increasingly pressing concern in South Africa, since antimicrobial resistance is becoming increasingly more prevalent (Mendelson, Whitelaw and Nicol, 2012).

In the intensive care unit (ICU) of Dr George Mukhari Academic hospital (DGMAH), vancomycin and the AG’s are often prescribed to patients, but serum concentrations of these drugs are seldom monitored. Thus, it is not always known if the patient’s antimicrobial therapy is optimal. This is an area of concern since there is considerable morbidity and mortality associated with systemic infections (McKay and Bamford, 2015).

By using data generated through the use of therapeutic drug monitoring (TDM), patient pharmacokinetic parameters can be estimated for each patient receiving vancomycin and the AG’s within the ICU setting of DGMAH. These population specific pharmacokinetic (PK) parameters can then assist in the optimization of vancomycin and AG treatment guidelines to accommodate each drugs PD profile which has been found to be most efficacious.

1.2 **AIM OF THE STUDY**

To optimize aminoglycosides and vancomycin dosing, in the ICU setting of DGMAH, through the use of therapeutic drug monitoring.

1.3 **OBJECTIVES OF THE STUDY**

The objectives of the study were as follows:

- To evaluate whether current vancomycin and aminoglycoside dosing practices are inline, in terms of what is considered to be optimal serum concentrations for these drugs
- To monitor for the occurrence of any adverse events, during vancomycin or AG therapy
- To use PK/PD parameters to optimise the vancomycin and AG dosages
- To develop treatment guidelines for the optimization of vancomycin and AG therapy based on the data generated from the use of therapeutic drug monitoring
1.4 CONCLUSION

Conducting TDM and understanding patient PK parameters is a clinical skill that is underdeveloped in Africa. South Africa is ahead of the continent in terms of TDM, since there are TDM sites where antibiotic, ARV and Immunosuppressant serum concentrations are monitored (Nwobodo, 2014). Although South Africa has developed facilities that can conduct TDM, many of these facilities do not include a thorough interpretation of the serum concentrations. At DGMAH therapeutic drug monitoring of gentamicin, amikacin and vancomycin is conducted through the Pharmacology Department. The results they obtain are relayed to the physician, without interpretation bearing the patient’s diseased state in mind. Before the commencement of this study, there have been no relevant studies used to ascertain whether or not AG and vancomycin are dosed to achieve optimal serum concentrations according to patients’ pharmacodynamics within the ICU of DGMAH.
2.1 INTRODUCTION

The following chapter is a review of literature pertaining to the following topics:

Therapeutic drug monitoring in severe infections, pharmacokinetic models used in the therapeutic drug monitoring of aminoglycosides and vancomycin, pharmacokinetic changes in the critically ill patient, hypoalbuminaemia, severe infections, renal function quantification, aminoglycosides, aminoglycoside pharmacokinetic and pharmacodynamic profile, toxicities associated with aminoglycoside therapy, gram negative infections, vancomycin, vancomycin pharmacokinetic and pharmacodynamic profile, adverse events associated with vancomycin therapy, MRSA and MSSA, MRSA in South Africa. Ending with a chapter conclusion and a summary of the discussed literature.

2.2 THERAPEUTIC DRUG MONITORING IN SEVERE INFECTIONS

Therapeutic drug monitoring (TDM) is the measuring of serum concentrations of certain drugs at scheduled intervals to evaluate the concentration of the drug in the patient’s bloodstream (Nwobodo, 2014). Knowledge of the serum concentrations provides the information necessary to optimise dosage regimens and is not done for all drugs but only for those with narrow therapeutic ranges, pharmacokinetic variability where target concentrations are difficult to monitor and also in drugs that cause known adverse effects at high concentrations. (Fuchs, Csajka, Thoma, Buclin and Widmer, 2012) Antimicrobial dosage optimization through TDM is an aspect of antimicrobial stewardship (Kullar, Davis, Levine and Rybak, 2011; Van Lent, Mathôt, Geus, van Hout and Vinks, 1999). As part of antimicrobial stewardship, TDM acts as a tool, which guides the healthcare team toward dose/regimen optimization according to the optimal drug PK/PD parameters, found to deliver the best clinical outcomes (Kullar, et al, 2011; Rybak, et al, 2009; van Lent-Evers, et al, 1999). Antimicrobial treatment regimens are based largely on population pharmacokinetic profiles. In the critically ill population where there may be large deviations from these averages, many of these antimicrobial dosage regimens may be considered arbitrary at best in treating patients with severe infections. (Roberts, et al, 2014) Without knowing a patient's pharmacokinetic parameters it is difficult to dose him/her appropriately.

Sub-therapeutic antibiotic exposure is a contributing cause of mortality within the critically ill patient population suffering severe systemic infections. This inadequate dosing of various
antibiotics is largely due to the various underlining disease states affecting the patient's pharmacokinetic parameters for many drugs (Wong, Sime, Lipman and Roberts, 2014).

TDM has demonstrated a definite benefit in optimizing dosages for aminoglycosides in clinical practice (Lacy, Nicolau, Nightingale and Quintiliani, 1998). To date much controversy still surrounds the TDM of many antibiotics, with few clinical outcome studies available to, beyond any doubt, support the use thereof (Wong, et al, 2014). Optimizing antibiotic usage through TDM use can potentially aid the healthcare team in: decreasing anti-microbial resistance, decreasing drug toxicity and improving clinical outcomes (Wong, et al, 2014).

2.3 PHARMACOKINETIC MODELS USED IN THE THERAPEUTIC DRUG MONITORING OF AMINOGLYCOSIDES AND VANCOMYCIN

With the therapeutic monitoring of vancomycin various methods have been formulized to estimate the serum vancomycin concentration. These methods, referred to as nomograms are based pharmacokinetic parameters from certain populations. Zokufa, et al, (1989) examined five methods (Matzke, Moellering, Nielsen, Lake-Peterson, and the manufacturer's provided formula) for dosing vancomycin to achieve desired peak and trough serum concentrations. He found that none of the methods delivered accurate results within his study population (Zokufa, Rodvold, Blum, Riff, Fischer, Crossley and Rotschafer, 1989). Another study comparing the accuracy of seven nomograms for estimating vancomycin serum concentration also concluded that the results varied widely between the different nomograms (Murphy, Gillespie and Bateman, 2006).

Both one-compartment and two-compartment pharmacokinetic equations have been used to calculate vancomycin pharmacokinetic parameters in patients. In the case of vancomycin which follows a two compartment model, during the distribution phase, one can use single compartment pharmacokinetic equations to calculate pharmacokinetic parameters if the peak serum concentration was sampled after the distribution phase (one hour after the infusion has ended) (Rxkinetics.com, 2016).

Various nomograms have been created to predict AG serum concentrations in patients, these nomograms have also been based on population pharmacokinetic averages (Tsubaki and Chandler, 1994). When comparing these different nomograms in terms of their accuracy different studies found that the individualized method which Sawchuk and Zaske created for establishing multiple infusion regimens based on individually calculated pharmacokinetic parameters delivered the most accurate predictive results in terms of the AG serum concentration estimation (Lesar, 1982; Tsubaki and Chandler, 1994).
Monte Carlo simulations have also been used to predict drug serum concentration in patients using population pharmacokinetic parameters for various antibiotics. These include serum concentration simulations for aminoglycosides and vancomycin (Roberts, Kirkpatrick and Lipman, 2010; Sarubbi and Hull, 1976)

2.4 PHARMACOKINETIC CHANGES IN THE CRITICALLY ILL PATIENT

Dosing of antibacterial agents in the critical ill, remains an area shrouded in unresolved issues. This is mainly due to various antimicrobials having deranged pharmacokinetic parameters in the critically ill, thus influencing also their therapeutic effectiveness (Ulldemolins, et al, 2011). In the typical ICU patient, changes in volume of distribution (Vd) and clearance (CL) of antibiotics have been noted, which may affect the antibiotic concentration at the target site, thus influencing the PD effect of the antibiotic (Roberts and Lipman, 2009). Some of these PK/PD changes, such as alterations in the volume of distribution and accelerated or decelerated drug clearance, may be brought upon by a variety of different factors, that may include, but are not limited toward: systemic inflammatory response syndrome (SIRS), fluid resuscitation, the use of inotropes, oedema, and dehydration, all of which can be found within an ICU (Roberts and Lipman; 2009; Ulldemolins, et al, 2011).

2.5 HYPOALBUMINAEMIA

Albumin levels are generally low in the critically ill patients admitted to ICU, this is largely due to: disease driven physiological changes, transcapilary albumin escape due to SIRS, decrease in albumin due to inflammatory processes, insufficient protein intake, hepatic damage (Ulldemolins, et al, 2011). Albumin is an important marker for hydrophilic drugs, due to the fact that it possesses a high osmolarity that attracts water. When albumin is lost, water will move to other tissues that have a higher osmolarity, the extravascular space. This change will increase the volume of distribution for many hydrophilic drugs, as fluid moves to the extravascular space, due to the loss of albumin’s oncotic forces, which kept the fluid within the intravascular space. This decrease in albumin serum concentrations indirectly affects the clinical outcome of drug therapy (Burkhardt, Kumar, Katterwe, Majcher-Peszynska, Drewelow, Derendorf and Welte, 2006).
2.6 SEVERE INFECTIONS

Critically ill patients are at an increased risk for the development of sepsis and septic shock. This is mostly due to their deteriorating physical condition coupled with the use of various invasive devices within the ICU (Blot, 2008).

Severe sepsis and septic shock are always accompanied by varying degrees of organ failure. Septic shock is often accompanied by a refractory hypotension necessitating vasopressor support. This refractory hypotension is largely due to the leaky capillary syndrome, this disease state greatly influences the fluid status of a patient. Leaky capillaries lead to the loss of fluid from the intravascular space toward the interstitial fluid compartments, resulting in oedema. This loss of fluid toward the extra vascular space is driven by the decreased amount of albumin within the vasculature and also the excessive release of histamine within the vasculature. The net result is a decreased oncotic pressure within the vasculature (Blot, Pea and Lipman, 2014). Oedema positively correlates with an increase in volume of distribution for hydrophilic molecules, such as vancomycin, amikacin and gentamicin. Patients who dwell up sepsis often have an increased volume of distribution for these molecules and require a larger dose to achieve the optimal serum concentrations (Blot, Pea and Lipman, 2014).

2.7 RENAL FUNCTION QUANTIFICATION

Vancomycin and the AG’s are both renally cleared antibiotics, thus the renal clearance greatly influences the elimination of these drugs. Equations such as the Cockroft-Gault and Modification of Diet in Renal Disease (MDRD) have never been validated in critically ill patients (Pong, Seto, Abdolell, Trope, Wong, Herridge, Harvey and Kavanagh, 2005).

Using SCr to calculate glomerular filtration has been known to grant a GFR overestimation (Delanaye et al, 2014). SCr generation is dependent on various factors, which include ethnicity, dietary protein intake, age and geographic locations (Stevens, et al, 2006). An important factor in the ICU is the SCr dependency on muscle mass. The muscle mass may be altered at the very start of ICU stay due to illness and disease and may also further be altered as muscle mass atrophies during ICU stay (Delanaye, et al, 2014).

As a result, many researchers agree that, the use of glomerular filtration rate estimations based from the SCr are inaccurate within the critically ill populations, since the production of
creatinine is altered in severely ill populations due to disease states and changes in muscle mass (Delanaye, et al., 2014; Stevens, et al., 2006; Udy, et al., 2010).

A case study by Chaudhry, Mayo and Mooradian in 2005 on a paralyzed African-American patient with HIV, who had extensive atrophy of his skeletal muscles, found that his serum creatinine concentrations became undetectable during the course of the patient’s hospital stay. This case serves to provide insight into the effects that HIV/AIDS and muscular atrophy has on the serum creatinine concentration (Chaudhry, Mayo and Mooradian, 2005). This case places some emphasis on the possible baseline SCr reductions in South Africans, since many individuals suffer from poverty and HIV/AIDS.

If a patient’s kidney function declines, there may arise a need to start renal replacement therapy (RRT) or commonly referred to as dialysis. RRT’s effect on drug therapy greatly depends on the drug, the method of RRT and the equipment being used (Choi, Gomersall, Tian, Joynt and Lipman, 2010). There are five stages of renal failure used to measure kidney failure in clinical practice today, these are based on a patient’s estimated glomerular filtration: Stage one renal failure, ≥90 ml/min; stage 2, 60–89 ml/min; stage 3, 30–59 ml/min; stage 4, 15–29 ml/min; stage 5, <15 ml/min (Avramovic and Stefanovic, 2012).

Another important consideration within the critically ill is the occurrence of augmented renal clearance, defined as a GFR exceeding 130 ml/min (Udy, Putt, Shanmugathasan, Lippman, 2010). The effect that augmented renal clearance has on the elimination rate of various hydrophilic drugs has not extensively been studied. Thus it is unsure whether the augmented renal function would alter the linear relationship that exists between the AG elimination and GFR and so also for the linear relationship between vancomycin and GFR (Udy, et al., 2010).

### 2.8 AMINOGLYCOSIDES

Aminoglycosides were first developed in the 1940’s; these molecules were derived from substances that Streptomyces and Micromonospora produced. Today, close to 70 years later, these are still considered to be effective antibiotics in the fight against serious gram negative infections across the world. (Avent, Rogers, Cheng and Paterson, 2011)

Aminoglycosides are considered bactericidal at high concentrations, in other words they are effective at killing bacteria at higher concentrations. They enter the bacterial cell by means of active transport into the cell cytosol, where they act by inhibiting the 30S ribosomal subunit, thereby disrupting protein synthesis. According to Brunton, Chabner, Knollman (2011) the
aminoglycosides primarily act by binding to the amino-acyl site of 16S ribosomal RNA within the 30S ribosomal subunit, leading to misreading of the genetic code and inhibition of translocation. Aminoglycoside antibiotics target prokaryotic cells rather specifically and exert their antibacterial effects mainly through an inhibition of protein synthesis. Aminoglycosides bind to the A-translational site of the 16S rRNA of the 30S ribosomal subunit and cause misreading from the mRNA. This results in the accumulation of dysfunctional proteins intracellularly and eventual death of the microbe.

This class of antibiotic also displays a post antibiotic effect that endures long after the serum concentrations of the drug has fallen below the MIC (Mandell, Bennett, Dolin, Blaser, and Douglas, 2010). By increasing dosages and extending dosage intervals the post antibiotic effect is maximized since it is directly related to the concentration the antibiotic reached within the blood stream (Bauer, 2014).

2.9 AMINOGLYCOSIDE PHARMACOKINETIC AND PHARMACODYNAMIC PROFILE

The AG’s follow a single-compartment pharmacokinetic model with a half-life which is almost entirely dependent on a patient’s renal GFR, normally ranging between 1.5-3 hours according to population averages. Within the critically ill population group the average half-life was 3.22 hours (Marsot, Guilhamou, Riff, Blin, 2016). Being dependant on a patients kidney function, the half-life of AG’s may also be greatly increased in those who suffer from renal failure since there exists a linear relationship between CrCl and AG elimination rate constant (Bauer, 2014). This relationship can be described through the following equation: 

\[ k_{el} = 0.00293 \times \text{CrCl} + 0.014 \]  

(Bauer, 2014). The half-life would change as the GFR changes.

The volume of distribution of these drugs are normally around 0.3 L/kg in a healthy population, but can greatly vary in different populations especially those with other co-morbidities and underlying disease processes (Roberts and Lipman, 2009; Bauer, 2014). There exists on average a 44% inter individual variability in terms of half-life and volume of distribution in the critically ill population group (Marsot, et al, 2016)

From a PD perspective, these drugs have been found to be most effective when dosed to achieve high peak concentrations. Dosing high enough to achieve 8-10 times the MIC has been advocated in recent literature (Bauer, 2014; Marsot, Guilhamou, Riff, Blin, 2016).
2.10 TOXICITIES ASSOCIATED WITH AMINOGLYCOSIDE THERAPY

The dose limiting side effects of AG’s are nephrotoxicity and ototoxicity (Guthrie; 2008). Selimoglu (2007) stated that aminoglycoside ototoxicity seems to be mediated by the disruption of mitochondrial protein synthesis, the over activation of glutamatergic receptors and the forming of free radicals. The types of ototoxicity that aminoglycosides cause are auditory and vestibular, and the damage is permanent (Bauer, 2014). When comparing gentamicin and amikacin to each other there is no clear difference between these drugs in terms of the occurrence of toxicities (Burton, Shaw, Schentag and Evans, 2008; Turnidge, 2003). Genetic pre-disposition seems to contribute toward the development of AG induced toxicities. The only definite factor with regards to the development of AG toxicities remains length of therapy, with the chances of developing AG induced toxicities increasing with length of therapy (Paterson, Robson and Wagener, 1998).

When intermittent conventional dosing was compared to extended interval dosing, researchers found that extended interval dosing (i.e. once daily) lead to a decreased incidence of nephrotoxicity. This held true even though peak concentrations were much higher with extended interval dosing when compared to conventional intermittent dosing. The adverse effects associated with aminoglycoside use, is thus believed to be due to accumulation of aminoglycosides in body tissue. When a patient receives AG's at extended dosing intervals, there is less accumulation of the drug within various body tissues, due to

Figure 2.1: The linear relationship between AG elimination rate constant and CrCl (Bauer, 2014).
long dose-free intervals, which allows the patient to excrete a larger amount, before being exposed to the next dose. (Bailey, Little, Littenberg, Reichley and Dunagan, 1997)

When extended dosing intervals are used patients generally require much larger dosages to achieve the optimal peak serum concentration. This would lead one to suspect an increased incidence of toxicities due to higher peak serum concentration; this has not been the case. Higher peak concentrations have not lead to increased toxicities but rather reduced their incidence. This is likely due to accumulation of AG’s with conventional dosing, where the extended interval dosing would allow the body a longer time to clear, the drug before administering another dose (Barkley, Kirkpatrick and Begg, 1999).

2.11 GRAM NEGATIVE INFECTIONS

Treatment of drug resistant Gram negative bacteria is problematic in South Africa (Brink, Botha, Poswa, Senekal, Badal, Grolman, Richards, Feldman, Boffard, Veller, Joubert and Pretorius, 2012). The emergence of resistant gram negative infections, is a serious cause of nosocomial related morbidity and mortality. In a study by Brink 2012, susceptibilities for various intra-abdominal infections where reported on from three large hospitals in South Africa, where the following organisms were cultured: Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Proteus mirabilis, Enterobacter cloacae, Klebsiella oxytoca, Acinetobacter baumanii, Citrobacter freundii, Serratia marcescens, Enterobacter aerogenes, Morganella morganii, Citrobacter koseri, Enterobacter, non-speciated. He concluded that next to ertapenem, amikacin was the second most active against the various reported gram negative organisms. This means that amikacin is still a viable option in most cases of gram negative septicaemia, with the exception of Acinetobacter baumanii, which was only susceptible to amikacin in 37% of the reported cases (Brink, et al, 2012).

2.12 VANCOMYCIN

Vancomycin is a glycopeptide antibiotic used in the prophylaxis and treatment of infections caused by gram positive bacteria (Candemir, Aribuca, Ozcan, Gerede Kaya; 2012). Upon vancomycin’s discovery, when it was still referred to as compound 05865, researchers tried inducing resistance into staphylococci in vitro, using penicillin as a control. They found that the staphylococci became 100000 fold more resistant toward penicillin and only 4-8 fold more resistant toward vancomycin upon completion of the trial (Levine, 2006). This corresponds with current resistance patterns toward vancomycin being far less when compared to beta-lactams which has widespread resistance toward its use. It is also postulated that Enterococci only became resistant toward vancomycin due to the extensive
use of vancomycin as an oral treatment for pseudomembranous colitis. Vancomycin resistant *Staphylococcus aureus* is still rare in South Africa (Fortuin-de Smidt, Singh-Moodley, Badat, Quan, Kularatne, Nana, Lekalakala, Govender and Perovic, 2015).

Today vancomycin is widely used as first line therapy for MRSA infections (Fuller, Mohr, Skrupky, Mueller and McCammon; 2013) and is also indicated for the treatment: of *Staphylococcus aureus* (vancomycin susceptible), coagulase negative staphylococci, *Streptococcus pneumoniae*, *Streptococcus spp.*, *Enterococcus spp.* (Vancomycin-susceptible), and *Clostridium spp.* Vancomycin has both time dependant and concentration dependant bactericidal properties (Jeurissen, Sluyts and Rutsaert, 2011). Since the 1980’s vancomycin use has increased 100 fold, this is mostly due to the emergence of MRSA (Levine, 2006). Today vancomycin is still used as the cornerstone antibiotic in the fight against MRSA infections, thus vancomycin usage positively correlates with the rate of MRSA infections (Rosini, Grovola, Levine and Jasani, 2013). Currently vancomycin remains the first line option within the public sector in the fight against many resistant enterococci and MRSA, due to the lack of availability of alternative agents such as linezolid.

### 2.13 VANCOMYCIN PHARMACOKINETIC AND PHARMACODYNAMIC PROFILE

Vancomycin follows a two-compartment pharmacokinetic model, with a half-life ranging from 6 to 12 hours depending on a patient's renal function, since vancomycin is primarily renally cleared (Bauer, 2014; Rybak, Lomaestro, Rotschafer, Moellering, Craig, Billeter, Dalovisio and Levine 2009). The volume of distribution (Vd) varies between different patient populations, although literature defines the volume of distribution of vancomycin as 0.7-1.2 L/kg (Bauer, 2014). Three studies conducted within a critically ill population group found the following volume of distributions ranges: 0.6-1.1 L/kg, 0.53-0.78 L/kg and 0.2-0.56 L/kg (Chaijamorn, Jitsurong, Wiwattanawongsa, Wanakamanee and Dandecha 2011; Shahrami, Najmeddin, Mousavi, Ahmadi, Rouini, Sadeghi and Mojtahedzadeh, 2016; Udy, Covajes, Taccone, Jacobs, Vincent, Lipman, and Roberts, 2013).

Vancomycin exhibits time- and concentration-dependant bactericidal activity (Jeurissen, Sluyts and Rutsaert, 2011). Dosing vancomycin to achieve an AUC:MIC of around 400 units, in MRSA pneumonia was found to reduce the time to bacterial clearance by 2.5 fold, compared to patients who did not receive adequate amounts of vancomycin (Gawronski, Goff, Brown, Khadem and Bauer 2013; Moise-Broder Forrest Mary, Birmingham and Schentag 2006). An AUC of 400 units positively correlated with trough concentrations of 15-20 μg/ml. This method of serum concentration monitoring assumes an MIC of 1 μg/ml (Gawronski, Goff, Brown, Khadem and Bauer 2013).
2.14 ADVERSE EVENTS ASSOCIATED WITH VANCOMYCIN THERAPY

Vancomycin was created in the 1950's and dubbed, “Mississippi Mud”, due to its brown colour. Manufacturers had to devise a new method of synthesising the drug, before clinical trials could commence. Even after producing a purer form of the drug it was still labled as an undesirable drug, due to adverse effects, including: red man syndrome, ototoxicity, infusion related chills, phlebitis and nephrotoxicity. It was later determined that most of these adverse drug reactions were due to the impurities in the vancomycin formulation. In retrospective analysis on patients receiving vancomycin between 1974 and 1981, it was found that: fevers and rash were uncommon at 1-3%, phlebitis was common at 13%, nephrotoxicity incidence was 5%, all of which were reversible (Levine, 2006). The frequency of vancomycin-induced ototoxicity is reported to range from 1-9% for patients receiving vancomycin therapy and the occurrence rate positively correlates with vancomycin peak levels exceeding 40 μg/ml (Rybak, et al, 2009).

Although phlebitis incidence of 13% is a cause for concern, a study published in 2016 by Abolfotouh, Salam, Mustafa and Balkhy found that the general rate of IV induced phlebitis was 17.58% in 359 adults who received IV therapy and that the incidence is linked to the use of peripheral catheters. (Abolfotouh, Salam, Mustafa, White, and Balkhy, 2016)

Since the impure form of vancomycin was associated with a nephrotoxicity for a number of years, vancomycin is today still associated with a high incidence of inducing renal failure. The biggest risk factors for vancomycin induced kidney injury are: doses exceeding 4 g daily, higher trough serum concentrations, extended treatment duration, advanced age, already compromised kidney function before treatment and concurrent use of nephrotoxic agents (Fullmer, McCue and Feng, 2013). Unnecessarily high doses of vancomycin can contribute toward an increase in nephrotoxicity (Bauer, 2014; Bamgbola, 2016). A retrospective analysis done on 159 critically ill patients over a five year course concluded that the overall incidence of vancomycin induced nephrotoxicity was 8.8% and that the biggest risk factor for the development of an acute kidney injury with vancomycin therapy was concurrent treatment with an aminoglycoside, a higher APACHE II score and high vancomycin trough serum concentrations. (Hanrahan, Harlow, Hutchinson, Dulhunty, Lipman, Whitehouse, Roberts, 2015) The inclusion of patients receiving AG’s with vancomycin obscures vancomycin's true incidence of nephrotoxicity. There does not seem to be a definite predictor of vancomycin induced nephrotoxicity.

Nephrotoxicity and ototoxicity is a possibility when patients receive vancomycin therapy. However, by adjusting vancomycin dosage regimens so that potentially toxic serum
concentrations are avoided, drug concentration-related adverse effects can be held to the absolute minimum (Bauer; 2014; Hanrahan, et al, 2015).

In a recent systematic literature review and meta-analysis it was concluded that literature concerning vancomycin nephrotoxicity strongly suggests that there exists a relationship between vancomycin serum concentrations and nephrotoxicity (Bamgbola, 2016; van Hal, Paterson and Lodise, 2012). Drug-induced acute kidney injury can be defined as a 25-30% rise in serum creatinine concentration from baseline values (Tisdale and Miller, 2010).

### 2.15 MRSA AND MSSA

Humans are natural reservoirs for *Staphylococcus aureus* (Franklin, 1998; Huson, Stolp, Van der Poll and Grobusch, 2013; Stoltz 2016,). 20-80% of humans are colonized by *Staphylococcus aureus*, with 10-20% being persistently colonized. Both MSSA and MRSA are consistent colonizers, patients who are colonized by MSSA or MRSA are at an increased risk of acquiring a subsequent infection, with up to 80% nosocomial *Staphylococcus aureus* bacteraemia cases originating from nasal Staphylococcus colonization (Huson, *et al*, 2013; Stoltz, 2016). There is an interplay/balance between various organisms and host immunity concerning colonization risk for staphylococcus aureus colonization and eventual infection (Huson, *et al*, 2013). Risk for infection with current colonizing bacteria is greatly increased in those who are immunocompromised, have undergone surgery and critically ill (Franklin; 1998; Stoltz, 2016). Many patients within South Africa are immunocompromised due to HIV and AIDS, placing them at an increased risk for subsequent infections with opportunistic organisms (Huson, *et al*, 2013; Stoltz, 2016).

Transmission primarily occurs from healthcare workers or other people in contact with a patient who is immune compromised, a healthcare worker or visitor may be a carrier of MSSA or MRSA organisms. When a carrier of MSSA or MRSA comes in contact with an immune compromised patient, chances for subsequent colonization and infection increase (Franklin, 1998; Huson, Stolp, Van der Poll and Grobusch, 2013; Stoltz, 2016). At a recent mini congress Stoltz, 2016, described that patients may be colonized with all pathogens known in the ICU within 2 days of admission. This has serious implications in patients who are immune compromised, especially if there are resistant pathogens present in said unit.

Of those patients who are diagnosed a severe systemic infection or septicaemia only 50% survive while in hospital (Mahmoudi, Mohammadpour, Ahmadi, Nikham, & Mojtahedzadeh, 2013).
2.16 MRSA IN SOUTH AFRICA

In South Africa it was found that HIV and AIDS are risk factors that positively correlate with MRSA infections (Fortuin-de Smidt, et al, 2015). HIV positive patients had a 5-times higher likelihood for an MRSA infection and generally had a higher incidence of MRSA colonization. Within Charolette Maxeke hospital, Steve Biko hospital and Pretoria District hospital, there were 442 cases of Staphylococcus aureus septicaemia over the course of thirteen months. Of these 442 cases 241 cases had isolates that were submitted to the reference laboratory for antimicrobial susceptibility testing. Within those isolates submitted to the reference laboratory they found that 36% (86 cases) of the submitted isolates were indeed MRSA infections (Fortuin-de Smidt, et al, 2015). In this study they also found no resistance for the 241 cases submitted for antimicrobial susceptibility testing toward vancomycin. Of those patients suffering MRSA septicaemia, who did not receive vancomycin, 61% died. MRSA incidence in South Africa is very low. This study was conducted from September 2012 to September 2013.

2.17 CONCLUSION

Optimizing dosages for antimicrobials in an intensive care includes many variables to be considered for every patient. These variables are more evident within an ICU setting treating those critically ill. A holistic approach to antimicrobial therapy cannot achieve the optimal antimicrobial usage for every patient in an intensive care setting. An in depth understanding of the underlying disease burden of each patient is required to adapt antimicrobial regimens to fit said patient individually according to his/her own pharmacokinetic parameters.

2.18 SUMMARY

Chapter 2 reviewed relevant literature and information pertaining to the study and serves as an introduction to the theoretical components and latest information regarding the TDM of vancomycin and AG’s.
Chapter 3: Method

CHAPTER 3
METHOD

3.1 INTRODUCTION
This chapter describes the methodology followed during the course of the study. It discusses the study design, the study site, the study population and sample. It also describes the data collection instruments, data collection process.

3.2 STUDY DESIGN
The study followed a prospective, interventional study design with a quantitative approach. Quantitative aspects included: SCr, CrCl, peak and trough drug serum concentrations, patient demographics, clinical data and pharmacokinetic parameters calculated.

3.3 STUDY SITE
The study was conducted in the general adult ICU of DGMAH, Pretoria Gauteng Province. The ICU consists of 22 beds, of which two are isolation rooms. The researcher worked in the unit and documented data from the patients.

3.4 STUDY POPULATION
The sample population included all the patients within the ICU receiving vancomycin, gentamicin or amikacin during the study period. The ICU has an average patient turnover of 65 patients per month. Initially the sample size was calculated for vancomycin only and assumed that the sample size would be 5% of all patients admitted. During the course of data collection the incidence of vancomycin usage was considerably less within the ICU, more toward two percent of all patients admitted. The research proposal was then, in April 2016, revised to include all the patients receiving aminoglycosides.
3.5 SAMPLE SELECTION

Inclusion criteria

The following inclusion criteria were used:

- Adult patients receiving vancomycin, amikacin or gentamicin treatment intravenously in the ICU of DGMAH.

Exclusion criteria

The following exclusion criteria were used:

- Patients receiving vancomycin orally

3.6 SAMPLING METHOD

Patients receiving vancomycin, gentamicin or amikacin within the ICU were enrolled by the researcher prospectively.

The participants have been enrolled in the following way, refer to Figure 3.1

![Flow diagram illustrating the steps involved in the data collection process](image_url)

**Figure 3.1: Flow diagram illustrating the steps involved in the data collection process**
3.7 DATA COLLECTION

3.8 DATA COLLECTION INSTRUMENTS

Patient pharmacokinetic parameter capturing sheet (Appendix 2), these forms were used to document all the applicable pharmacokinetic parameters for each patient, to adjust dosages and to make recommendations accordingly.

The patient demographic capturing sheet (Appendix 3), this was used to allocate each patient to a number; the number was then used during the course of the study to ensure patient confidentiality.

3.9 THERAPEUTIC DRUG MONITORING

3.10 ADMINISTRATION OF MEDICATION

An initial dosage was determined by the physician, after which the researcher collected blood samples (peak and trough samples). The AG and vancomycin dosages were prepared and infused in an IV solution by the nursing staff, infusion times were noted by the researcher. The researcher was responsible for the AG and vancomycin TDM and calculating the PK parameters. The researcher recorded all the information e.g. dose and exact times of administration on the patient pharmacokinetic capturing form (Appendix 2).

3.11 DRAWING AND HANDLING OF SPECIMENS

Blood specimens were taken as soon as a patient received gentamicin, amikacin or vancomycin. This was most often on the first dosage and in some cases peak and trough serum samples were only collected at a later stage. Specimens for the trough level were drawn as close to the next dose and the peak levels were drawn roughly one hour after administration of a dose. A volume of 0.5 mL blood was drawn from a central venous catheter on two separate occasions (peak and trough) by the treating physician or nurse. After the initial peak and trough blood samples were taken and PK-parameters defined.

The calculations of the PK parameters were cross-checked by supervisors before feedback was provided to the ICU. The researcher recorded all the information e.g. dose and exact times of administration on the participant pharmacokinetic capturing form (Appendix 2).
The blood specimens and completed laboratory request forms were taken to Sefako Makgatho Health Sciences University (SMU) therapeutic drug laboratory at the Department of Pharmacology and Therapeutics. The necessary data was captured on site were after the samples were by the researcher and handed over to the lab technicians stationed in the pharmacology lab. The following information was noted on the pharmacology request form by the researcher:

- Patient name
- Date of birth
- Gender
- Weight
- Hospital file number
- Date and time when the sample was drawn
- Duration of current AG or vancomycin course
- Nature of sample, namely blood sample
- Date and time when last dose of amikacin, gentamicin or vancomycin was last administered
- Route of administration, namely intravenous

In some cases additional sets of peak and trough blood samples were taken after the initial blood samples, to monitor the participant more closely in terms of pharmacokinetic changes the patient experienced during treatment.

3.12 ANALYTICAL TECHNIQUES

The specimens were analysed by using a QMS® Amikacin, QMS® Gentamicin and the QMS® Vancomycin immunoassay reagents kit on the Humor Diagnostic Indiko ® system. The laboratory technicians had to set up the reagents for the Humor Diagnostic Indiko ® system and calibrate it according to the supplier’s recommendations. A representative from Humor Diagnostica was responsible for the maintenance of the system.
3.13 ASSAY METHODOLOGY

The QMS® amikacin, gentamicin and vancomycin assays are intended for the quantitative determination of amikacin in human serum or plasma on automated clinical chemistry analysers. It is a homogenous particle-enhanced turbidimetric immunoassay.

The assay is based on competition between drug in the sample and drug coated onto a microparticle for antibody binding sites of the amikacin antibody reagent. The drug-coated microparticle reagent is rapidly agglutinated in the presence of the anti-drug antibody reagent and in the absence of any competing drug in the sample. The rate of absorbance change is measured photometrically. When a sample containing amikacin, gentamicin or vancomycin is added, the agglutination reaction is partially inhibited, slowing down the rate of absorbance change. A concentration-dependent classic agglutination inhibition curve can be obtained with maximum rate of agglutination at the lowest drug concentration and the lowest agglutination rate at the highest drug concentration.

3.14 CALCULATION OF PHARMACOKINETIC PARAMETERS

The patient’s AG and vancomycin peak and trough serum concentrations analysed by the TDM LAB and results conveyed to the researcher, afterwards it was analysed by the research team through a one compartment open pharmacokinetic model (Herfindal, Gourley and Hart, 1992) and using the Sawchuck-Zaske method (Sawchuk and Zaske, 1976) to calculate the following pharmacokinetic parameters for each participant: $k_{el}$, $t_{1/2}$, $C_{max}$, $C_{min}$, $V_{d}$, CL. The researcher decided to use Sawchuck-Zaske’s single compartment pharmacokinetic equations for determining participant pharmacokinetics above two-compartment models due simplicity above two-compartment models.

The PK parameters were calculated by using the following equations:

The elimination constant ($k_{el}$) was calculated as follows:

$$k_{el} = \frac{\ln \left( \frac{C_1}{C_2} \right)}{(t_2 - t_1)}$$

The elimination half-life was calculated using the following equation:

$$t_{1/2} = \frac{0.693}{k_{el}}$$
The true Cmax was then calculated using:

\[ C_{\text{max}} = \frac{C}{e^{-k_e \cdot t}} \]

True Cmin was calculated using the following formula:

\[ C_{\text{min}} = C \cdot e^{-k_e \cdot t} \]

The total volume of distribution was calculated using the following equation:

\[ Vd = \frac{D}{k_e \cdot T} \cdot \frac{1 - e^{-k_e \cdot T}}{[C_{\text{max}} - (C_{\text{min}} \cdot e^{-k_e \cdot T})]} \]

Where a dosing adjustment was necessary the following formula was used, the participant's PK parameters were substituted into the formula where needed and the desired Cmax was substituted instead of the participant's actual Cmax.

\[ D = C_{\text{max(desired)}} \cdot k_e \cdot V \cdot T \cdot \frac{1 - e^{-k_e \cdot T}}{1 - e^{-k_e \cdot T}} \]

Where dosage adjustments were necessary the dosing interval was also calculated according to the following formula:

\[ \tau = \frac{\ln \left( \frac{C_{\text{max(desired)}}}{C_{\text{min(desired)}}} \right)}{k_e} + T \]

Participant clearance rates were calculated using the following formula:

\[ CL = V \cdot k_e \]

**Pharmacokinetic abbreviations**

C1 = peak concentration; the concentration measured after a new dosage has been administered and the antibiotic infusion had been finished for at least one hour (μg/ml)

C2 = trough concentration, the concentration measured closest to the following dosage (μg/ml)
t1 = the time at which C1 was taken (hours)

t2 = the time at which C2 was taken (hours)

$K_{el}$ = first order elimination rate constant

$t_{1/2}$ = elimination half-life (hours)

$C_{max}$ = theoretical maximum serum concentration; i.e. the concentration at the end of the infusion ($\mu$g/ml)

$C_{min}$ = theoretical minimum serum concentration; i.e. the concentration at the end of the dosing interval

$t$ = the time difference between the two concentrations

$\tau$ = the time between intervals (hours)

It is possible to evaluate the standard regimen through a comparison between the calculated peak and trough serum concentrations and the recommended literature concentrations. The $t_{1/2}$, Vd and CL were calculated to compare the study population with previously studied populations. An adjusted dose was calculated when the peak level and trough serum concentrations did not fall within the optimal ranges.

### 3.15 RENAL FUNCTION QUANTIFICATION

Participant's also had renal function quantified with the following formulas:

- Participant estimated glomerular filtration rate ($eGFR$) was equated using the MDRD formula:

  \[ eGFR = 186 \times \left(\frac{SCr}{88.4}\right)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black}) \]

- Participant creatinine clearance (CrCl) using the Cockroft-Gault equation (CGE):

  \[
  CrCl = \frac{(140-\text{age}) \times \text{Weight}}{0.82 \times \text{Scr}} \times 0.85 \text{ if female}
  \]

- Participant CrCl was also calculated by using the drug elimination rates for AG's and vancomycin using the following formulas:

  For the AG's; \[ k_{el} = 0.00293 \times (CrCl) + 0.014 \]

  For vancomycin; \[ k_{el} = 0.00083 \times (CrCl) + 0.0044 \]
Since these formulas use the creatinine clearance to calculate the Elimination rate constant, they can also inversely be used, to calculate the creatinine clearance from the elimination rate constant. Henceforth creatinine clearances calculated though this method will be referred to \( k_{el} \) derived CrCl. The elimination rate constant, used in the formula, was calculated by using a peak and a trough serum concentration obtained from the participant's blood samples at the appropriate times as stated in the methods. Augmented renal clearance was defined if a creatinine clearance of >130 mL/min was calculated through the MDRD eGFR formula or the Cockroft-Gault equation.

3.16 DATA COLLECTION PERIOD

Started on September 2015 and continued until July 2016

3.17 DATA ENTRY AND ANALYSIS

Data were captured into Microsoft Excel running Windows 7™. The data captured were then analysed by a review team consisting of the researcher and a clinical pharmacist using GraphPad 6™. Results were compared to population estimates of pharmacokinetic parameters for vancomycin, amikacin and gentamicin.

Pharmacokinetic parameters for each of the 20 patients have been calculated and used to evaluate the patient’s dose. When necessary, dosage adjustments were recommended based on these pharmacokinetic parameters. Patient demographic data and the different pharmacokinetic parameters were analysed and described.

3.18 ETHICAL CONSIDERATIONS

The clinical pharmacist was present in the ICU which forms part of the clinical pharmacist’s daily activities in rendering of service. Permission was obtained from the Chief Executive Officer (CEO) of DGMAH and head of department (HOD) of ICU to conduct the study in the ICU. Permission to perform the study was obtained from the School of Health Care Sciences (SREC) and Sefako Makgatho Health Sciences University Research Ethics Committees (SMUREC) before commencement of data collection (SMUREC/H/211/2015: PG). Personal patient information was kept confidential; each patient was assigned a study number which was used during data collection. No electronic copies were kept of patient records. All documented and captured data were locked away in the pharmacy department and will remain there for the required five year period.
3.19 SUMMARY

This chapter described the methods used to conduct this prospective, interventional study.
CHAPTER 4
RESULTS AND DISCUSSION

The findings of the study are presented and discussed in this chapter.

4.1 DEMOGRAPHICS

Figure 4.1 depicts the amount of patients lost during follow-up and the reasons therefore. In total 10 patients were lost. Two participants had peak and trough serum concentrations monitored which could not be repeated by the TDM laboratory. Six participants were lost due to unavailability of TDM reagents needed to measure serum concentrations. Two patients had a single serum concentration measured through TDM but could not have a second measurement taken due to antibiotics being stopped before the second blood sample could be taken. There were a total of 20 participants enrolled.

![Figure 4.1: Participants excluded from results](image_url)

Table 4.1 summarizes participant number, age, gender, weight and which antibiotic was used. The population was divided equally between male and female participants with a mean age of 39.8±2 years. The 20 participants seven received amikacin, six received gentamicin and seven received vancomycin. The average weight was 78.5±16kg.
Table 4.1 Participant demographic information:

<table>
<thead>
<tr>
<th>Participant number</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Weight (kg)</th>
<th>Antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>F</td>
<td>42</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>F</td>
<td>74.2</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>M</td>
<td>90</td>
<td>Amikacin</td>
</tr>
<tr>
<td>4</td>
<td>22</td>
<td>M</td>
<td>75</td>
<td>Vancomycin</td>
</tr>
<tr>
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<td>36</td>
<td>M</td>
<td>55</td>
<td>Gentamicin</td>
</tr>
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<td>M</td>
<td>90</td>
<td>Gentamicin</td>
</tr>
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<td>Gentamicin</td>
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<td>F</td>
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<td>M</td>
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</tr>
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<td>M</td>
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<td>Vancomycin</td>
</tr>
<tr>
<td>12</td>
<td>40</td>
<td>F</td>
<td>60</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>13</td>
<td>22</td>
<td>M</td>
<td>75</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>14</td>
<td>24</td>
<td>M</td>
<td>60</td>
<td>Amikacin</td>
</tr>
<tr>
<td>15</td>
<td>61</td>
<td>F</td>
<td>110</td>
<td>Gentamicin</td>
</tr>
<tr>
<td>16</td>
<td>25</td>
<td>F</td>
<td>90</td>
<td>Gentamicin</td>
</tr>
<tr>
<td>17</td>
<td>18</td>
<td>F</td>
<td>70</td>
<td>Amikacin</td>
</tr>
<tr>
<td>18</td>
<td>40</td>
<td>M</td>
<td>90</td>
<td>Amikacin</td>
</tr>
<tr>
<td>19</td>
<td>67</td>
<td>F</td>
<td>90</td>
<td>Amikacin</td>
</tr>
<tr>
<td>20</td>
<td>64</td>
<td>F</td>
<td>85</td>
<td>Amikacin</td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td>39.8 (±18)</td>
<td></td>
<td>78.5 (±16)</td>
<td></td>
</tr>
</tbody>
</table>

4.2 WEIGHT

Patients admitted to the ICU are not weighed while receiving care, so an estimation of the patient’s weight was made in all cases. Where the dietician had calculated the patient’s weight using a validated formula, that weight was used. Although this was the preferred method, the dietician stationed in the ICU was not always available to provide a more accurate estimation for every patient. The average weight of the patients was 78.5±16kg, with a minimum estimated weight of 42kg and a maximum estimated weight of 110kg.

The inability to weigh patients is not unique to the study site and is a challenge in most ICUs due to the lack of weighing beds and or the severity of patients. It is important that all healthcare workers stationed in an ICU setting are aware that an estimation of weight is seldom accurate and can differ from actual weight by as much as 20kg. This can have an influence on medication dosages and may result in patients being over- or under dosed (Henderson, Robinson & Roland, 2006). Moisey, Mourtzakis, Kozar, Compher and Heyland (2016) compared existing equations to estimate lean body mass within the ICU and found that collectively they had an error range of 7.5-9.9kg. It was concluded that specific equations are needed to measure the lean body mass accurately within the critically ill population (Moisey, et al, 2016).
4.3 **DIAGNOSES, ANTIBIOTIC USED AND INDICATION**

Diagnoses were made by the attending physicians. These diagnoses were written on the patient’s charts and were documented by the researcher. The diagnosis refers to the primary diagnosis the patient was admitted with and often the patient would develop secondary diseases during hospital care for example septicemia. These secondary diagnoses, although often the main health concern, were documented in daily treatment plan of the patient. Table 4.2, 4.3 and 4.4 depict the serum albumin concentrations, diagnosis, dosage, antibiotic indication and cultured organism where applicable for participants who were prescribed amikacin, gentamicin and vancomycin respectively.

Table 4.2: Participant amikacin treatment regimen background

<table>
<thead>
<tr>
<th>Participant number</th>
<th>Diagnoses</th>
<th>Initial dosage (mg)</th>
<th>Dosing interval (hours)</th>
<th>Dose per weight (mg/kg)</th>
<th>Indication/secondary diagnosis</th>
<th>Organism(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Laparotomy stab in neck</td>
<td>1500</td>
<td>24</td>
<td>18.78</td>
<td>Septicaemia</td>
<td>Acinetobacter baumanii, resistant to amikacin sensitive to colistin only</td>
</tr>
<tr>
<td>10</td>
<td>Laparotomy</td>
<td>1000</td>
<td>24</td>
<td>11.1</td>
<td>Prophylaxis</td>
<td>None</td>
</tr>
<tr>
<td>14</td>
<td>Traumatic brain injury</td>
<td>1000</td>
<td>24</td>
<td>16.7</td>
<td>Septicaemia</td>
<td>Klebsiella pneumoniae</td>
</tr>
<tr>
<td>17</td>
<td>Total abdominal hysterectomy</td>
<td>1000</td>
<td>24</td>
<td>3.4</td>
<td>Prophylaxis</td>
<td>None Cultured</td>
</tr>
<tr>
<td>18</td>
<td>Abdominal compartment syndrome</td>
<td>500</td>
<td>24</td>
<td>5.5</td>
<td>Septicaemia</td>
<td>Serratia marcescens</td>
</tr>
<tr>
<td>19</td>
<td>Pneumonia</td>
<td>1500</td>
<td>24</td>
<td>16.7</td>
<td>Septicaemia</td>
<td>Klebsiella pneumoniae</td>
</tr>
<tr>
<td>20</td>
<td>Chronic kidney disease</td>
<td>1000</td>
<td>24</td>
<td>11.8</td>
<td>Septicaemia</td>
<td>Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td></td>
<td>1071.5</td>
<td>24</td>
<td>12 (±5.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4.3: Participant gentamicin treatment regimen background.

<table>
<thead>
<tr>
<th>Participant number</th>
<th>Diagnoses</th>
<th>Initial dosage (mg)</th>
<th>Dosing interval (hours)</th>
<th>Dose per weight (mg/kg)</th>
<th>Indication/secondary diagnosis</th>
<th>Organism(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Cerebrovascular incident</td>
<td>240</td>
<td>24</td>
<td>4.8</td>
<td>Septicaemia</td>
<td>Acinetobacter baumanii, resistant to AG's Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>6</td>
<td>Chronic kidney disease Receiving dialysis</td>
<td>240</td>
<td>24</td>
<td>2.6</td>
<td>Septicaemia</td>
<td>Acinetobacter baumanii, resistant to AG's Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>7</td>
<td>Pedestrian vehicle accident</td>
<td>240</td>
<td>24</td>
<td>3.2</td>
<td>Septicaemia</td>
<td>Proteus mirabilis</td>
</tr>
<tr>
<td>9</td>
<td>Traumatic brain injury</td>
<td>240</td>
<td>24</td>
<td>3.7</td>
<td>Septicaemia</td>
<td>Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>15</td>
<td>Chronic kidney disease</td>
<td>240</td>
<td>24</td>
<td>2.2</td>
<td>Septicaemia</td>
<td>Enterobacter cloacae and Klebsiella pneumonia sensitive to gentamicin</td>
</tr>
<tr>
<td>16</td>
<td>Total abdominal hysterectomy</td>
<td>240</td>
<td>24</td>
<td>1.1</td>
<td>Prophylaxis</td>
<td>None Cultured</td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td></td>
<td>240</td>
<td>24</td>
<td>2.9 (±1.28)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4.4: Participant vancomycin treatment regimen background.

<table>
<thead>
<tr>
<th>Participant number</th>
<th>Diagnoses</th>
<th>Initial dosage (mg)</th>
<th>Dosing interval (hours)</th>
<th>Dose per weight (mg/kg)</th>
<th>Indication/Secondary diagnosis</th>
<th>Organism(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Osteo Sarcoma</td>
<td>1000</td>
<td>12</td>
<td>23.8</td>
<td>Septicaemia</td>
<td>Enterococcus faecalis; vancomycin MIC =1</td>
</tr>
<tr>
<td>2</td>
<td>TB-meningitis</td>
<td>1000</td>
<td>12</td>
<td>13.5</td>
<td>Empiric</td>
<td>None Cultured</td>
</tr>
<tr>
<td>4</td>
<td>Pedestrian vehicle accident</td>
<td>1000</td>
<td>8</td>
<td>11.1</td>
<td>Prophylaxis</td>
<td>None Cultured</td>
</tr>
<tr>
<td>8</td>
<td>Cerebrovascular haemorrhage</td>
<td>1000</td>
<td>8</td>
<td>11.1</td>
<td>Septicaemia</td>
<td>Enterococcus faecium</td>
</tr>
<tr>
<td>11</td>
<td>Hemicolectomy</td>
<td>1000</td>
<td>12</td>
<td>11.1</td>
<td>prophylaxis</td>
<td>Enterococcus faecium</td>
</tr>
<tr>
<td>12</td>
<td>Tuberculosis</td>
<td>1000</td>
<td>12</td>
<td>16.7</td>
<td>Septicaemia</td>
<td>Enterococcus faecalis</td>
</tr>
<tr>
<td>13</td>
<td>Subdural Haematoma</td>
<td>1000</td>
<td>12</td>
<td>14.3</td>
<td>Septicaemia</td>
<td>MRSA sensitive to vancomycin</td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td></td>
<td>1000</td>
<td>10.86 (±1.95)</td>
<td>14.51 (±4.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Drug dosage optimization greatly depends on the MIC values of various bacteria in the ICU (Bauer, 2014; Marsot, Guilhamou, Riff, Blin, 2016). Since these MIC values were not included in the Microbiology culture report it was more difficult to optimize therapy as best possible. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints was used for gentamicin and amikacin where possible. Micro-organisms that were sensitive to aminoglycosides are known to have an MIC of less than 4 μg/ml for gentamicin and 8 μg/ml for amikacin. Organisms that were resistant had MIC’s larger than: 4 μg/ml gentamicin and 8 μg/ml for amikacin.
Of the seven participants who received vancomycin, five had cultures to support the use thereof. *MRSA, Enterococcus faecalis* and *Enterococcus faecium* were positively cultured.

### 4.4 ANTIBIOTIC REGIMENS

**Aminoglycosides**

Commonly prescribed antibiotic regimes within the ICU include: amikacin 1g daily and gentamicin 240 mg daily. This is similar to the defined daily dose (DDD) who documented: amikacin at 1 g/day and gentamicin at 240 mg/day (WHO, 2016).

Amikacin and gentamicin were only prescribed when targeting susceptible organisms which had been cultured. In the ICU the most prevalent gram negative organisms included *Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa* and *Proteus mirabilis*. Acinetobacter infections were resistant toward gentamicin and amikacin in all cultured cases.

According to the standard treatment guidelines of South Africa, hospital acquired pneumonia can be treated with amikacin at a dose of 15 mg/kg. The South African medicine formulary also advocates the same dosage (Rossiter, Blockman and Barnes, 2015). The participants of the study received on average 12±5.9 mg per kilogram with a maximum dosage of 18.78 mg/kg and a minimum of 3.4 mg/kg.

According to the standard treatment guidelines of South Africa gentamicin should be prescribed at an initial dose of 6 mg/kg during various surgical procedures as prophylaxis. The South African STG recommends dosages up to 6 mg/kg for applicable indications. Similarly the SAMF also advocates dosage between 5-6 mg/kg (Rossiter, Blockman and Barnes, 2015). On average the participants from this study received 2.9±1.28 mg/kg, with a maximum of 4.8 mg/kg and a minimum of 1 mg/kg.

A study by Roger, Nucci, Molinari, *et al* (2015) conducted on 90 patients receiving standard dosages of amikacin and gentamicin concluded that only 17/90 patients achieved the desired therapeutic serum concentration. During this study, only 3 out of 13 participants were dosed higher than standard treatment guidelines recommended.
**Vancomycin**

Vancomycin was commonly prescribed as 1g twice daily, which is similar to the defined daily dose for vancomycin at 2 g/day (WHO, 2016). The use of vancomycin within the ICU of DGMAH was mostly for MRSA prophylaxis and Enterococcus infections.

According to the STG of South Africa vancomycin should be prescribed at an initial dose of 20 mg/kg for intravascular septicemia or surgical line associated sepsis. The SAMF also advocates dosage between 15-20 mg, stating that a loading dose of 25-30 mg may be used for critically ill patients (Rossiter, Blockman and Barnes, 2015). The Infectious Diseases Society of America recommends 15-20 mg per dose every 8-12 hours in patients with normal renal function and also state that the use of dosages in excess of 40 mg/kg may be required in some instances, and should be monitored closely through TDM (Rybak, et al, 2009) Participants receiving vancomycin had a mean dosage per kg bodyweight of 14.51±4.6 mg/kg, with a maximum of 23.4 mg/kg and a minimum of 11.1 mg/kg.

### 4.5 PHARMACOKINETIC AND PHARMACODYNAMIC PARAMETERS FOR ALL PARTICIPANTS

All the relevant pharmacokinetic parameters will be discussed for each drug separately, with the half-life and volume of distribution parameters combined for gentamicin and amikacin. Patients who received dialysis will also be discussed separately.

### 4.6 AMINOGLYCOSIDES

Table 4.5 and 4.6 contains a summary of the pharmacokinetic parameters for each participant who received amikacin or gentamicin respectively. These tables exclude participants who received any form of renal replacement therapy, which will be discussed separately.

#### Table 4.5: Summary of participant amikacin pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Peak (μg/ml)</th>
<th>Trough (μg/ml)</th>
<th>Half-life (hours)</th>
<th>VD (L/kg)</th>
<th>Clearance (L/hr)</th>
<th>Clearance (L/hr/kg)</th>
<th>Scr (μmol/L)</th>
<th>CrCl (ml/min)</th>
<th>CrCl kfh (ml/min)</th>
<th>eGFR (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>47.05</td>
<td>8.549</td>
<td>2.1</td>
<td>0.24</td>
<td>5.35</td>
<td>0.067</td>
<td>57</td>
<td>147</td>
<td>90.78</td>
<td>169</td>
</tr>
<tr>
<td>14</td>
<td>64.15</td>
<td>0.0029</td>
<td>7.49</td>
<td>0.25</td>
<td>6.87</td>
<td>0.115</td>
<td>45</td>
<td>188.51</td>
<td>154.62</td>
<td>257</td>
</tr>
<tr>
<td>17</td>
<td>43.9</td>
<td>3.43</td>
<td>6.24</td>
<td>0.317</td>
<td>2.39</td>
<td>0.034</td>
<td>51</td>
<td>168</td>
<td>33.105</td>
<td>175</td>
</tr>
<tr>
<td>19</td>
<td>52.11</td>
<td>12.3</td>
<td>10.7</td>
<td>0.32</td>
<td>4.82</td>
<td>0.054</td>
<td>38</td>
<td>151.34</td>
<td>17.06</td>
<td>188</td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td>51.80 (±8.899)</td>
<td>6.070 (±3.558)</td>
<td>6.63 (±0.04265)</td>
<td>0.28 (±1.860)</td>
<td>4.858 (±0.034)</td>
<td>76 (±50.24)</td>
<td>163.7 (±18.9)</td>
<td>73.9 (±62.43)</td>
<td>197.3 (±40.62)</td>
<td></td>
</tr>
</tbody>
</table>
### Table 4.6 Summary of participant gentamicin pharmacokinetic parameters:

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Peak (μg/ml)</th>
<th>Trough (μg/ml)</th>
<th>Half-life (hours)</th>
<th>VD (L/kg)</th>
<th>Clearance (L/hr)</th>
<th>Clearance (L/hr/kg)</th>
<th>Scr (μmol/l)</th>
<th>CrCl (ml/min)</th>
<th>CrCl k (ml/min)</th>
<th>eGFR (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>10.57</td>
<td>1.50</td>
<td>8.35</td>
<td>0.497</td>
<td>2.15</td>
<td>0.039</td>
<td>100</td>
<td>69.7</td>
<td>23.5</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td>6.75</td>
<td>0.35</td>
<td>5.4</td>
<td>0.51</td>
<td>4.64</td>
<td>0.062</td>
<td>139</td>
<td>77.6</td>
<td>38.9</td>
<td>71</td>
</tr>
<tr>
<td>9</td>
<td>12.18</td>
<td>0.008</td>
<td>3.2</td>
<td>0.3</td>
<td>4.24</td>
<td>0.065</td>
<td>48</td>
<td>190</td>
<td>68</td>
<td>237</td>
</tr>
<tr>
<td>9</td>
<td>14.01</td>
<td>0.0018</td>
<td>2.26</td>
<td>0.434</td>
<td>8.64</td>
<td>0.133</td>
<td>38</td>
<td>239</td>
<td>99</td>
<td>310</td>
</tr>
<tr>
<td>9</td>
<td>11.98</td>
<td>0.00121</td>
<td>1.79</td>
<td>0.5</td>
<td>12.68</td>
<td>0.195</td>
<td>37</td>
<td>246</td>
<td>127.6</td>
<td>320</td>
</tr>
<tr>
<td>15</td>
<td>14.4</td>
<td>0.00074</td>
<td>1.65</td>
<td>0.13</td>
<td>6.31</td>
<td>0.057</td>
<td>61</td>
<td>124.8</td>
<td>138.5</td>
<td>111</td>
</tr>
<tr>
<td>15</td>
<td>6.62</td>
<td>0.593</td>
<td>6.54</td>
<td>0.35</td>
<td>4.079</td>
<td>0.037</td>
<td>61</td>
<td>124.8</td>
<td>31.9</td>
<td>111</td>
</tr>
<tr>
<td>16</td>
<td>7.18</td>
<td>0.206</td>
<td>4.5</td>
<td>0.33</td>
<td>4.68</td>
<td>0.052</td>
<td>61</td>
<td>177</td>
<td>47.7</td>
<td>133</td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td>10.18</td>
<td>0.58</td>
<td>5.8</td>
<td>0.35</td>
<td>4.29</td>
<td>0.08</td>
<td>68.13</td>
<td>156.1</td>
<td>74.9</td>
<td>173.4</td>
</tr>
</tbody>
</table>

#### 4.6.1 AMINOGLYCOSIDE HALF-LIFE

The average half-life for the aminoglycosides is 1.5-3 hours according to (Lacy, et al, 1998; Bauer, 2014). Within the critically ill population group the average half-life is 3.22 hours (Marsot, Guilhaumou, Riff, Blin, 2016). Only four of the participants had a normal aminoglycoside elimination half-life within the suggested range and there was a large degree of variation between participants with elimination half-lives ranging from 1.65 hours to 10.7 hours. Since the elimination half-life is dependent on glomerular filtration, patients experiencing kidney impairment may present with an increased elimination half-life, which attributes to the inter-individual differences in terms of aminoglycoside pharmacokinetic parameters (Jenkins, et al, 2016; Marsot, Guilhaumou, Riff and Blin 2016; Roberts and Lipman, 2009).
4.6.2 AMINOGLYCOSIDE VOLUME OF DISTRIBUTION

Figure 4.2 illustrates the volume of distribution for each participant who received an aminoglycoside.

The average volume of distribution was 0.35 L/kg, which is larger than the population estimate of 0.3 L/kg (Jenkins, et al, 2016; Marsot, et al, 2016). Within critically ill patients these estimates are known to vary inter-individually (Marsot, et al, 2016; Roberts and Lipman, 2009). Participant five and seven both had a larger volume of distribution, calculated at 0.497 L/kg and 0.51 L/kg respectively, than the average volume of distribution calculated as 0.35 L/kg. This increased volume of distribution could be attributed to the participants having decreased kidney functioning and oedema secondary to SIRS/sepsis. Participant 15’s volume of distribution was calculated on two different occasions and illustrated the effect of sepsis on the Vd of AGs.

4.7 AMIKACIN PEAK AND TROUGH SERUM CONCENTRATIONS

Figure 4.3 illustrates peak and trough serum concentrations in participants who received amikacin and excludes participants who received any form of renal replacement therapy. This is an illustration of peak and trough serum concentration contained in Table 4.5.
If an organism is sensitive to amikacin, that would translate to a MIC $\leq 8$ μg/ml. Thus the optimal peak serum concentration to aim for would be 8-10 times 8 μg/ml (Bauer, 2014; Marsot, Guilhaumou, Riff, Blin, 2016). Optimal amikacin serum concentrations are 60–80 μg/ml (de Montmollin, Bouadma, Gault, Mourvillier, Mariotte, Chemam, Massias, Papy, Tubach, Wolff and Sonneville, 2014). One participant had a peak serum amikacin concentration above 60 μg/ml, with a peak of 64.15 μg/ml, after a 1 g amikacin dosage.

The mean trough serum amikacin concentrations for participants receiving amikacin were 6.1±5.4 μg/ml (excluding participants receiving dialysis). The accepted clinical range for amikacin trough levels is 5-10 μg/ml (Jenkins, Thomson, Brown, Semple, Sluman, MacGowan, Lovering and Wiffen, 2016). One patient did not have an adequate trough amikacin serum concentration; with 12.3 μg/ml, which was due to an increased elimination half life.

4.7.1 GENTAMICIN PEAK AND TROUGH SERUM CONCENTRATIONS

Figure 4.4 illustrates peak and trough serum concentrations in participants who received gentamicin and excludes participants who received any form of renal replacement therapy. This is an illustration of peak and trough serum concentration contained in Table 4.6.
Figure 4.4: Peak and trough gentamicin serum concentrations

If an organism is sensitive to gentamicin, that would translate to an MIC ≤4 μg/ml and 2 μg/ml for Enterobacteriaceae. Thus the optimal peak serum concentration to aim for would be 8-10 times 2-4 μg/ml. The French Infectious Diseases Society has in a recent guideline also advocated gentamicin peak concentrations of 30-40 μg/ml (Tabah, Lipman and Roberts, 2016). In this study, the mean gentamicin peak serum concentration was 10±3 μg/ml; maximum peak concentration was 14 μg/ml and the minimum peak gentamicin serum concentration 6.8 μg/ml. Peak gentamicin serum concentration where not adequate, with none of the participants achieving the desired peak gentamicin serum concentrations.

The mean trough gentamicin serum concentration was 0.58±0.69 μg/ml, with a maximum of 1.5 μg/ml and a minimum trough gentamicin serum concentration of 0.0007 μg/ml. The optimal trough concentration should be <0.5 μg/ml (Tabah, Lipman and Roberts 2016).

4.8 PARTICIPANTS WHO RECEIVED DIALYSIS

Four participants on dialysis were prescribed aminoglycosides. These four patients had renal failure, with two participants presenting with stage 5 renal failure and two participants with stage 4 renal failure. Renal failure caused drastic changes in their elimination half-lives for the aminoglycosides. Table 4.8 and 4.9 contain the calculated pharmacokinetic parameters for each participant who required dialysis. The pharmacokinetic parameters calculated reflect the patient's own kidney function and not while receiving dialysis.
### Table 4.7: Participant amikacin pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Half-life (hours)</th>
<th>Peak (μg/ml)</th>
<th>Trough (μg/ml)</th>
<th>VD (L/kg)</th>
<th>Clearance (L/hr)</th>
<th>Clearance (L/hr/kg)</th>
<th>Scr (μmol/l)</th>
<th>CrCl (ml/min)</th>
<th>CrCl k el (ml/min)</th>
<th>eGFR (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>43.3</td>
<td>40.54</td>
<td>11.39</td>
<td>0.56</td>
<td>1.39</td>
<td>0.015</td>
<td>390</td>
<td>19.76</td>
<td>10.23</td>
<td>18</td>
</tr>
<tr>
<td>18</td>
<td>93.6</td>
<td>69.8</td>
<td>51</td>
<td>0.39</td>
<td>0.25</td>
<td>0.003</td>
<td>636</td>
<td>17.257</td>
<td>1.34</td>
<td>11</td>
</tr>
<tr>
<td>20</td>
<td>71.4</td>
<td>29.05</td>
<td>23.16</td>
<td>0.41</td>
<td>0.34</td>
<td>0.004</td>
<td>590</td>
<td>13.19</td>
<td>1.44</td>
<td>8</td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td>69.43 (±25.21)</td>
<td>46.46 (±21.01)</td>
<td>28.52 (±20.34)</td>
<td>0.45 (±0.09)</td>
<td>0.66 (±0.63)</td>
<td>0.007 (±0.006)</td>
<td>538.7</td>
<td>16.74 (±3.32)</td>
<td>4.39 (±5.1)</td>
<td>12</td>
</tr>
</tbody>
</table>

### Table 4.8 Participant gentamicin pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Half-life (hours)</th>
<th>Peak (μg/ml)</th>
<th>Trough (μg/ml)</th>
<th>VD (L/kg)</th>
<th>Clearance (L/hr)</th>
<th>Clearance (L/hr/kg)</th>
<th>Scr (μmol/l)</th>
<th>CrCl (ml/min)</th>
<th>CrCl k el (ml/min)</th>
<th>eGFR (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>47.37</td>
<td>8.9</td>
<td>6.26</td>
<td>0.3</td>
<td>0.39</td>
<td>0.004</td>
<td>424</td>
<td>22</td>
<td>0.34</td>
<td>16</td>
</tr>
</tbody>
</table>

#### 4.8.1 ELIMINATION HALF-LIFE

All participants who received dialysis had severe renal failure, two had stage four renal failure and two had end stage renal failure. Renal failure had a marked effect on the participants' elimination half-lives with the mean half-life of 46.8±21 hours, which is prolonged when comparing with the population estimate of 1.5-3 hours (Bauer, 2014).
4.8.2 VOLUME OF DISTRIBUTION

Figure 4.5: Volume of distribution for aminoglycosides in patients receiving dialysis.

The volume of distribution (Vd) for participants with receiving dialysis and aminoglycosides is depicted in Figure 4.5. All participants receiving dialysis had sepsis, confirmed by blood culture results. The average volume of distribution for patients with severe renal failure was 0.42 L/kg, which is larger than the participants not requiring dialysis which was 0.32±0.11 L/kg. These participants were oedematous and oliguric. Severe infections, inflammation and aggressive fluid resuscitation all may contribute in increasing the volume of distribution reducing the peak concentration (Roberts and Lipman, 2009). High peak concentrations are important to achieve the desired bactericidal and post-antibiotic effects when using the aminoglycosides (Bauer, 2014).

4.8.3 PEAK AND TROUGH AMINOGLYCOSIDE CONCENTRATION

Participants on haemodialysis therapy had high trough amikacin serum concentrations in relation to the peak amikacin serum concentrations: 69.8 μg/ml peak, 51 μg/ml trough; 29.05 μg/ml peak, 23.16 μg/ml trough; 40.54 μg/ml peak and 11.39 μg/ml. None of the participants achieved the desired trough serum concentration of 5-10 μg/ml (Jenkins, et al, 2016).

One participant requiring dialysis was receiving 240mg gentamicin daily, resulting in a true peak serum gentamicin concentration of 8.9 μg/ml and a true trough serum concentration of
6.26 μg/ml. The high trough indicates that the patient had a prolonged elimination half-life for gentamicin. The participant did not achieve the desired trough serum concentration of <0.5 μg/ml (Tabah, Lipman and Roberts, 2016).
4.9 VANCOMYCIN

Table 4.12 is a summary of all the pharmacokinetic parameters for participants who received vancomycin.

### Table 4.9: Participant vancomycin pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Half-life (hours)</th>
<th>Peak (μg/ml)</th>
<th>Trough (μg/ml)</th>
<th>VD (L/kg)</th>
<th>Clearance (L/hr)</th>
<th>Clearance (L/hr/kg)</th>
<th>SCr (μmol/l)</th>
<th>CrCl (ml/min)</th>
<th>CrCl kel (ml/min)</th>
<th>eGFR (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.46</td>
<td>57.06</td>
<td>6.06</td>
<td>0.43</td>
<td>3.37</td>
<td>0.080</td>
<td>72</td>
<td>119.9</td>
<td>95.93</td>
<td>116</td>
</tr>
<tr>
<td>2</td>
<td>4.9</td>
<td>31.12</td>
<td>6.68</td>
<td>0.5</td>
<td>5.25</td>
<td>0.071</td>
<td>33</td>
<td>256</td>
<td>164.57</td>
<td>261</td>
</tr>
<tr>
<td>4</td>
<td>3.28</td>
<td>59.2</td>
<td>10.90</td>
<td>0.25</td>
<td>3.99</td>
<td>0.053</td>
<td>49.00</td>
<td>220.00</td>
<td>250</td>
<td>237</td>
</tr>
<tr>
<td>4</td>
<td>5.49</td>
<td>47.93</td>
<td>22.48</td>
<td>0.36</td>
<td>3.4</td>
<td>0.045</td>
<td>54</td>
<td>199.86</td>
<td>147</td>
<td>212</td>
</tr>
<tr>
<td>8</td>
<td>3.465</td>
<td>51.74</td>
<td>4.63</td>
<td>0.2</td>
<td>3.63</td>
<td>0.040</td>
<td>35</td>
<td>157</td>
<td>235.66</td>
<td>208</td>
</tr>
<tr>
<td>11</td>
<td>2.47</td>
<td>49.54</td>
<td>13.93</td>
<td>0.3</td>
<td>4.56</td>
<td>0.070</td>
<td>51</td>
<td>130.55</td>
<td>274.22</td>
<td>188</td>
</tr>
<tr>
<td>12</td>
<td>2.99</td>
<td>44.15</td>
<td>4.93</td>
<td>0.35</td>
<td>4</td>
<td>0.067</td>
<td>46</td>
<td>135.2</td>
<td>223.6</td>
<td>168</td>
</tr>
<tr>
<td>13</td>
<td>3.65</td>
<td>14.43</td>
<td>4.99</td>
<td>0.91</td>
<td>6.28</td>
<td>0.084</td>
<td>50</td>
<td>201</td>
<td>105.54</td>
<td>232</td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td>3.46 (±0.746)</td>
<td>43.89 (±15.98)</td>
<td>7.45 (3.577)</td>
<td>0.42 (±0.24)</td>
<td>4.44 (±1.021)</td>
<td>0.064 (±0.016)</td>
<td>48.75 (±12.07)</td>
<td>177.44 (±48.92)</td>
<td>187.07 (±67.88)</td>
<td>202.75 (±45.49)</td>
</tr>
</tbody>
</table>

### 4.9.1 VANCOMYCIN PEAK AND TROUGH SERUM CONCENTRATIONS:

Figure 4.6 is an illustration of peak and trough serum vancomycin concentration summarised in Table 4.9.

![Figure 4.6: Peak and trough vancomycin serum concentrations](image-url)
The mean peak serum vancomycin concentration was 44±16 μg/ml and the mean vancomycin trough concentration was 7.4±3.6 μg/ml. The maximum peak vancomycin serum concentration was 59 μg/ml and minimum peak vancomycin serum concentration was 14 μg/ml. The maximum trough vancomycin serum concentration was 14 μg/ml and minimum trough vancomycin serum concentration was 4.6 μg/ml. All patients received 1000 mg of vancomycin per dose. Participant four and eight received vancomycin eight hourly, the remaining five all received vancomycin 12 hourly.

Peak serum concentrations are indicative that dosages given to patients were large dosages, especially when considering that the average volume of distribution for the vancomycin in the study population was 0.42±0.24 L/kg. The mean Vd is smaller than two of three recent studies’ calculated mean Vd, within critically ill populations: 0.6-1.1 L/kg, 0.53-0.78 L/kg and 0.2-0.56 L/kg (Chaijamorn, et al, 2011; Shahrami, et al, 2016; Udy, et al, 2013). The decreased Vd of the patient population may have led to the high mean peak vancomycin serum concentrations (44±16 μg/ml). Upon conducting a Pearson’s correlation analysis, there is a significant correlation coefficient of -0.8874 (P-value= 0.0077) between the volume of distribution and the peak serum concentration.

Dosing intervals were long (10.86±1.95 hours), considering none of the patients achieved the optimal trough vancomycin serum concentrations and had high peak concentrations that do not add value to antibacterial activity of vancomycin (Gawronski, et al, 2013). This was due to the average clearance of vancomycin being 0.064±0.016 L/hr/kg which is close to the upper limit in the critically ill patient population who have a range of 0.042-0.065 L/hr/kg (Shahrami, et al, 2016). The fast clearance, lead to trough serum concentrations below the optimal therapeutic range (7.4±3.6 μg/ml) (Gawronski, et al, 2013; Rybak, et al, 2009).
4.9.2 VANCOMYCIN AREA UNDER THE CURVE:

Figure 4.7 is an illustration of calculated area under the curve values for each participant.

![Graph showing area under the curve (AUC) values for participants.]

Figure 4.7: Calculated area under the curve

Vancomycin AUC values had a mean of 616±212 units. The optimal calculated AUC should be 400 units if the MIC is one, thus a 400:1 ratio (Rybak, et al, 2009). The mean AUC of 616±212 units indicates that patients achieved the optimal AUC. Although the optimal AUC was achieved in all patients, it was subject to high peak concentrations with a mean of 44±16 μg/ml. Two Enterococcus cultures reported MIC's for vancomycin of 1 μg/ml for Enterococcus faecalis and 0.5 μg/ml for Enterococcus faecium during the study period. According to the American treatment guidelines, these enterococcal infections would require an AUC of 400 and 200 units to be optimal (Gawronski, Goff, Brown, Khadem, Bauer, 2013).

4.9.3 VANCOMYCIN VOLUME OF DISTRIBUTION:

The mean Vd for vancomycin was 0.42 ±0.24 L/kg with a minimum of 0.21 L/kg and a maximum of 0.91 L/kg. These results display a large degree of variation between participants which coincides with the statement that sever inter individual differences exists with regards to vancomycin PK parameters (Roberts and Lipman, 2009). Three studies conducted within critically ill populations found the following volume of distributions ranges: 0.6-1.1 L/kg, 0.53-0.78 L/kg and 0.2-0.56 L/kg (Chaijamorn, et al, 2011; Shahrami, et al, 2016; Udy, et al, 2013). Patient 13 had a volume of distribution of 0.91 L/kg, deviating from
the study mean of 0.42±0.24 L/kg. The mean volume of distribution of 0.42 ±0.24 L/kg was smaller than that of other studies conducted within a similar population. This is due to the enrolled participants being malnourished and in cases muscle wasted.

4.9.4 **ELIMINATION HALF-LIFE**

Vancomycin elimination half-life had a mean of 4.1±1.4 hours with a maximum half-life of 6.8 hours and a minimum of 2.5 hours. Reviewed literature ranged from 6-12 hours (Bauer, 2014; Gawronski, et al, 2013; Rybak, et al, 2009)

4.10 **RENAL FUNCTION QUANTIFICATION**

Renal function was quantified through the three different methods described in Chapter 3. The following abbreviations are used throughout Section 4.10: SCr, which refers to serum creatinine concentration, CrCl, which refers to creatinine clearance, CGE, which refers to the Cockroft-Gault equation, \( k_{el} \), which refers to drug elimination rate derived CrCl and eGFR, which refers to the MDRD formula for CrCl estimation Results will be discussed for participants who received aminoglycosides with normal kidney function, with impaired kidney function and who presented with augmented renal function. Results for participants who received vancomycin will be discussed in those with normal kidney function and those with augmented renal function.

4.11 **AMINOGLYCOSIDES**

Table 4.10 and 4.11 is a summary of each participant's different renal function parameters for those who received amikacin and gentamicin respectively. Patients with impaired renal function were excluded. Patients with augmented renal clearance (CrCL>130ml/min), were also included in each table.

<table>
<thead>
<tr>
<th>Study No.</th>
<th>SCr μmol/l</th>
<th>CrCl (ml/min)</th>
<th>CrCl ( k_{el} ) (ml/min)</th>
<th>eGFR (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>57</td>
<td>147</td>
<td>90.78</td>
<td>169</td>
</tr>
<tr>
<td>14</td>
<td>45</td>
<td>188.61</td>
<td>154.6</td>
<td>257</td>
</tr>
<tr>
<td>17</td>
<td>51</td>
<td>168</td>
<td>33.105</td>
<td>175</td>
</tr>
<tr>
<td>19</td>
<td>38</td>
<td>151.34</td>
<td>17.06</td>
<td>188</td>
</tr>
</tbody>
</table>

Mean (±SD) 76 (±50.24) 163.7 (±18.9) 73.9 (±62.43) 197.3 (±40.62)
Table 4.11 Renal function measurements in gentamicin participants

<table>
<thead>
<tr>
<th>Study No.</th>
<th>SCr μmol/l</th>
<th>CrCl (ml/min)</th>
<th>CrCl $_{kel}$ (ml/min)</th>
<th>eGFR (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>100</td>
<td>69.7</td>
<td>23.5</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td>139</td>
<td>77.6</td>
<td>38.9</td>
<td>71</td>
</tr>
<tr>
<td>9</td>
<td>48</td>
<td>190</td>
<td>68</td>
<td>237</td>
</tr>
<tr>
<td>9</td>
<td>38</td>
<td>239</td>
<td>99</td>
<td>310</td>
</tr>
<tr>
<td>9</td>
<td>37</td>
<td>246</td>
<td>127.6</td>
<td>320</td>
</tr>
<tr>
<td>15</td>
<td>61</td>
<td>124.8</td>
<td>138.5</td>
<td>111</td>
</tr>
<tr>
<td>15</td>
<td>61</td>
<td>124.8</td>
<td>31.9</td>
<td>111</td>
</tr>
<tr>
<td>16</td>
<td>61</td>
<td>177</td>
<td>47.7</td>
<td>133</td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td>68.13</td>
<td>156.1</td>
<td>74.9 (±44.57)</td>
<td>173.4 (±100.3)</td>
</tr>
</tbody>
</table>

Figure 4.8 depicts each participant’s renal function in ml/ml for methods, CGE refers to Cockroft-Gault method, $k_{el}$ refers to drug elimination derived CrCl and eGFR refers to the MDRD eGFR CrCl estimation method.

Figure 4.8: CrCl by different methods for aminoglycoside participants
Table 4.12 provides the correlation coefficients with $k_{el}$ derived CrCl as the control for a Pearson's correlation analysis.

**Table 4.12: Pearson correlation analysis aminoglycosides**

<table>
<thead>
<tr>
<th></th>
<th>$k_{el}$ vs. CGE</th>
<th>$k_{el}$ vs. eGFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson r</td>
<td>0.5080</td>
<td>0.5416</td>
</tr>
<tr>
<td>r</td>
<td>-0.09319 to 0.8377</td>
<td>-0.04706 to 0.8510</td>
</tr>
<tr>
<td>R square</td>
<td>0.2581</td>
<td>0.2933</td>
</tr>
<tr>
<td>P value</td>
<td>0.0918</td>
<td>0.0690</td>
</tr>
<tr>
<td>P (two-tailed)</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>P value summary</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Significant? (alpha = 0.05)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Number of XY Pairs</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

Upon conducting a Pearson correlation analysis there were no significant correlations found between the different methods of CrCl calculation.

**Impaired renal function:**

Four participants had stage 4 and 5 renal failure were also treated with an aminoglycoside. Figure 4.7 provides a side by side illustration of the CrCl measurements calculated through three different methods, the Cockroft-Gault equation, the MDRD eGFR and the Creighton elimination constant derived CrCl in participants who received aminoglycosides.

![Figure 4.7: Participant CrCl estimations](image)

**Figure 4.9: Participant CrCl estimations**

Table 4.10 is a summary of a Pearson correlation analysis for participants with renal failure. Aminoglycoside $k_{el}$ derived CrCl is the control to what different methods were compared during the analysis.
Table 4.13: Pearson correlation analysis in impaired renal function

<table>
<thead>
<tr>
<th></th>
<th>kel vs. CGE</th>
<th>kel vs. eGFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson r r</td>
<td>0.2417</td>
<td>0.6406</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>-0.9371 to 0.9761</td>
<td>-0.8340 to 0.9914</td>
</tr>
<tr>
<td>R square</td>
<td>0.05843</td>
<td>0.4104</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P (two-tailed)</td>
<td>0.7583</td>
<td>0.3594</td>
</tr>
<tr>
<td>P value summary</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Significant? (alpha = 0.05)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Number of XY Pairs</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

There were no significant correlations between the different methods of CrCl calculation methods used. kel derived CrCl estimations were lower than estimations from eGFR and CrCl.

**Augmented renal function aminoglycosides (CrCl>130 ml/min):**

Participants who had a CrCl or eGFR of over 130 ml/min classified as participants with augmented renal function. Figure 4.10 is a side by side illustration of CrCl estimations calculated through the CGE, kel derived CrCl and eGFR methods.
Table 4.14: Correlation of CrCl calculation methods

<table>
<thead>
<tr>
<th></th>
<th>keL vs. CGE</th>
<th>keL vs. eGFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson r r</td>
<td>0.5663</td>
<td>0.6672</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>-0.2305 to 0.9085</td>
<td>-0.07088 to 0.9332</td>
</tr>
<tr>
<td>R square</td>
<td>0.3207</td>
<td>0.4452</td>
</tr>
<tr>
<td>P value</td>
<td>0.1434</td>
<td>0.0707</td>
</tr>
<tr>
<td>P (two-tailed)</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>P value summary</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Significant? (alpha = 0.05)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Number of XY Pairs</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

Table 4.11 provides a summary of the results gathered from conducting a Pearson’s correlation between the CGE CrCl, keL derived CrCl and the eGFR. There was not a significant correlation between the different methods of calculating CrCl in the patients with augmented renal clearance. The creatinine clearance calculated through the Cockroft-Gault equation and the eGFR seems to overestimate the drug clearance. Of the eight participants who presented with a CrCl higher than 130 ml/min the mean clearance was 6.21±3.2 L/hr with a maximum of 12.68 L/hr and a minimum of 2.390 L/hr. The patients with CrCl estimated lower than 130 ml/min (excluding patients with severe renal failure) receiving an AG had a mean clearance of 4.295 L/hr, with a maximum of 6.31 L/hr and a minimum of 2.15 L/hr. In the critically ill patients receiving amikacin the average amikacin clearance is 4.0 l/h, while among healthy participants the clearance rate was approximately 7.0 L/hr (Marsot, et al, 2016). Participants enrolled had low serum creatinine concentrations with a mean of 72±50.24 μmol/L which could lead to an overestimation of kidney function when relying on the Cockroft-Gault and MDRD-eGFR equations to equate kidney function within this patient population.

The keL derived CrCl was viewed as the most accurate CrCl. It accounted for the patients Vd and was not dependent on the SCr, which is unlikely to be produced by the skeletal muscles normally, in a bedridden, muscle wasted critically ill patient (Chaudhry, Mayo and Mooradian, 2005). It would appear that a patient is excreting the SCr at an abnormally fast rate, but it is just as likely that the production of SCr is decreased in critically ill patients, giving the appearance of a pseudo augmented renal clearance. By removing deranged SCr from the equation and relying on the established linear relationship between CrCl and keL we can more accurately estimate CrCl in cases where the use of SCr may be questionable.
4.12 RENAL FUNCTION QUANTIFICATION IN VANCOMYCIN PARTICIPANTS

Table 4.15 is a summary of each participant’s different renal function parameters for those who received vancomycin. Patients with impaired renal function were excluded. Patients with augmented renal clearance (CrCl>130 ml/min), were also included in Table 4.15.

Table 4.15: Renal function estimates in vancomycin participants

<table>
<thead>
<tr>
<th>Study No.</th>
<th>SCr μmol/L</th>
<th>CrCl (ml/min)</th>
<th>CrCl k_city (ml/min)</th>
<th>eGFR (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>72</td>
<td>119.9</td>
<td>95.9</td>
<td>116</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>256</td>
<td>164.6</td>
<td>261</td>
</tr>
<tr>
<td>4</td>
<td>49.</td>
<td>220.0</td>
<td>250</td>
<td>237</td>
</tr>
<tr>
<td>4</td>
<td>54</td>
<td>199.9</td>
<td>147</td>
<td>212</td>
</tr>
<tr>
<td>8</td>
<td>35</td>
<td>157</td>
<td>235.7</td>
<td>208</td>
</tr>
<tr>
<td>11</td>
<td>51</td>
<td>130.6</td>
<td>274.2</td>
<td>188</td>
</tr>
<tr>
<td>12</td>
<td>46</td>
<td>135.2</td>
<td>223.6</td>
<td>168</td>
</tr>
<tr>
<td>13</td>
<td>50</td>
<td>201</td>
<td>105.5</td>
<td>232</td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td>48.75</td>
<td>177.44</td>
<td>187.07</td>
<td>202.7</td>
</tr>
</tbody>
</table>

Figure 4.11: CrCl through different methods

Figure 4.11 provides a side illustration of the CrCl measurements calculated through three different methods, the Cockroft-Gault equation, the MDRD eGFR and the Creighton elimination constant derived CrCl in participants who received vancomycin.
Table 4.16: Correlation of CrCl calculation methods vancomycin

<table>
<thead>
<tr>
<th></th>
<th>( k_{el} ) vs. CGE</th>
<th>( k_{el} ) vs. eGFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson r r</td>
<td>-0.1407</td>
<td>0.1709</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>-0.7692 to 0.6262</td>
<td>-0.6070 to 0.7815</td>
</tr>
<tr>
<td>R square</td>
<td>0.01980</td>
<td>0.02920</td>
</tr>
<tr>
<td>P value</td>
<td>0.7396</td>
<td>0.6858</td>
</tr>
<tr>
<td>P (two-tailed)</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Significant? (alpha = 0.05)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Number of XY Pairs</td>
<td>8</td>
<td>8</td>
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Table 4.16 provides a summary of the results gathered from conducting a Pearson's correlation between the CGE CrCl, \( k_{el} \) derived CrCl and the eGFR. There was not a significant correlation between the different methods of calculating CrCl in participants receiving vancomycin, the vancomycin derived CrCl did not have a significant correlation with the different methods of calculating CrCl.

4.13 AUGMENTED RENAL CLEARANCE IN PARTICIPANTS RECEIVING VANCOMYCIN

Figure 4.12 is a side comparison of the CrCl measurements calculated through three different methods, the Cockroft-Gault equation, the MDRD eGFR and the Creighton \( k_{el} \) derived CrCl.
Figure 4.12: CrCL calculated through the Cockcroft-Gault formula compared to the vancomycin derived $k_{el}$ CrCl.

Table 4.17: Correlation of CrCl calculation methods

<table>
<thead>
<tr>
<th></th>
<th>$k_{el}$ vs. CGE</th>
<th>$k_{el}$ vs. eGFR</th>
<th>$k_{el}$ derived CrCl vs. Vd(L/kg) vancomycin</th>
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</thead>
<tbody>
<tr>
<td>Pearson r</td>
<td>-0.5394</td>
<td>-0.4607</td>
<td>-0.8196</td>
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<td>95% confidence interval</td>
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<td>-0.9012 to 0.4479</td>
<td>-0.9725 to -0.1737</td>
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<td>R square</td>
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<td>P (two-tailed)</td>
<td>ns</td>
<td>ns</td>
<td>*</td>
</tr>
<tr>
<td>P value summary</td>
<td>ns</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Significant? (alpha = 0.05)</td>
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<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Number of XY Pairs</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 4.17 provides a summary of a Pearson's correlation analysis with $k_{el}$ derived CrCl as the control. There was not a significant correlation between the different methods of calculating the CrCl in participants receiving vancomycin who have augmented renal clearance. CrCl derived from the $k_{el}$ was perceived as the most accurate, taking into account more patient specific factors than the CGE or eGFR which is based from population estimates. The CGE and eGFR could not accurately predict vancomycin elimination rates.
4.14 ADVERSE EVENTS

The main adverse event monitored was nephrotoxicity associated with AG use. The criteria to state drug induced nephropathy were dependent on a 30% rise in serum creatinine from baseline serum creatinine concentration before AG or vancomycin initiation (Tisdale and Miller, 2010). No relevant rise in serum creatinine was noted during the course of the study.
4.15 PATIENT CASE STUDIES

Patient 3

Patient 3 was admitted to the hospital due to a stab wound. He had undergone a reparative laparoscopy. The patient received 1.5g of amikacin daily. Upon the first dose peak (A) and trough (B) serum amikacin concentrations were measured. These levels revealed that the patient had an amikacin half-life of 43.31 hours. Levels were taken before (B) and after dialysis (C) to establish to what extent the dialysis would clear the drug. The amikacin serum concentration before dialysis was 38.53 μg/ml, after the four hour haemodialysis session, the serum concentration had fallen to 15 μg/ml. The four hour haemodialysis session had decreased the amikacin serum concentration by 61%. The patient's half-life while receiving dialysis was 2.94 hours (B-C), which to the research team was very similar to the half-life a normal healthy patient, 3 hours (Marsot, et al, 2016). Physicians were thus advised that the patient be given the antibiotic before each dialysis session to best mimic amikacin normal excretion/clearance. By using TDM in this patient one could clearly see the effect that intermittent effect that haemodialysis (Fx-100 dialyzer) had on the amikacin serum concentrations. Figure 4.13 is an illustration of the elimination of amikacin during intermittent dialysis.

![Figure 4.13: Amikacin elimination during intermittent dialysis (participant 3).](image-url)
Chapter 4: Results and Discussion

Patient 4:

![Graph showing vancomycin serum concentration over time with dosage changes from 1g q8h to 750mg q6h]

Figure 4.14: Vancomycin serum concentration after dosage adjustment

A 22 year old 75kg male was admitted to the ICU after a pedestrian vehicle accident. Vancomycin was prescribed at a dose of 1g three times a day. Peak and trough blood levels were measured; this initially yielded a peak serum concentration of 100 μg/ml due to lab errors. Another peak sample was collected and reported a peak of 40.6 μg/ml, which seemed more in line with the patient’s profile than the 100 μg/ml peak reported earlier. Pharmacokinetic calculated true peak (59.2 μg/ml) and true trough (10.9 μg/ml) levels rendered an AUC of 841.2 units. The large AUC value is due to the high peak serum concentration. The dosing intervals were shortened to 6-hourly and the dose decreased to 750mg resulting in lower peak concentrations (47.93 μg/ml) and increase inadequate trough concentrations (22.48 μg/ml).

The patient's Vd was increased (0.36 L/kg), explaining the lower peak and higher trough serum concentration. No therapeutic regimen changes were recommended and upon monitoring the true trough serum concentration the following day it was within range (19.4 μg/ml). Shorter intervals and smaller dosages achieved the same AUC measurement but without the unnecessary high peak concentrations for this patient.
Patient 9

Figure 4.15: Gentamicin serum concentration throughout treatment course (participant 9)

A 25 year old male patient weighing approximately 65 kg was admitted to the ICU post craniotomy due to a severe traumatic brain injury. The patient received 240 mg gentamicin daily for *Pseudomonas aeruginosa* related surgical site infection. TDM was conducted and revealed a gentamicin half-life = 3.2 hours; true peak = 12.18 μg/ml; true trough = 0.0715 μg/ml, Vd = 0.301 L/kg)

No MIC values were reported, it was decided by the research team to aim for a MIC of 2 μg/ml, thus 16/20 μg/ml peak values, due to the microbiology report indicating that the *Pseudomonas* infection was susceptible to gentamicin, thus having an MIC of <2 μg/ml. The calculated dose to achieve a peak of 16 μg/ml was 384 mg. This was then rounded to 400mg of gentamicin daily and implemented on the 3rd day of therapy.

Repeat TDM analysis revealed a gentamicin half-life = 2.26 hours; True peak = 14.1 μg/ml; True trough = 0.057 μg/ml; Vd = 0.434 L/kg)

TDM was repeated taken on the 5th day of therapy (400 mg daily gentamicin) and revealed a gentamicin half-life = 1.786 hours; True peak = 11.98 μg/ml; True trough = 0.00121 μg/ml; Vd = 0.503 L/kg)

During the treatment course the patient had a marked increase in his gentamicin clearance and volume if distribution as the patient received blood transfusion during the course of five days. The volume of distribution and increase in clearance was linked to excessive blood
loss but also an increase of the intravascular space due to blood transfusions he received. Administered blood products and blood loss were directly linked to the patient's pharmacokinetic parameters for gentamicin.
Patient 15

A female patient, weighing approximately 110kg (visibly obese), was admitted to the ICU with chronic kidney disease and pulmonary oedema. The patient was treated with gentamicin 240mg daily for Enterobacter cloacae. TDM revealed: true peak = 14.4 μg/ml, true trough = 0.00739 μg/ml, Vd = 0.16 L/kg and t-half = 1.65 hours.

The patient deteriorated, presenting with temperature spikes and a sudden increase in white blood cell count. TDM was repeated four days after initial PK quantification. Which revealed: true peak = 6.62 μg/ml, true trough = 0.593 μg/ml, t-half = 6.54 hours and a Vd = 0.35 L/kg.

These changes were attributed to septic shock due to a resistant Klebsiella pneumoniae infection which was resistant toward gentamicin. The patient had experienced a decrease in renal function secondary to systemic inflammatory response syndrome (SIRS) which also caused the severe increase in volume of distribution.

Patient 18:

Male patient 40 year of age weighing approximately 90kg, admitted to the ICU after being assaulted by various individuals. After admission the patient soon developed compartment syndrome, which increased abdominal pressure and lead to acute kidney failure. The patient had been prescribed an arbitrary dosing regimen of amikacin (250mg three times daily) for a Serratia marcescens infection. Patient was switched to 500mg daily.

TDM was conducted and revealed: true peak = 69.8 μg/ml, true trough = 51 μg/ml, half-life = 93.6 hours, Vd = 0.39 L/kg. It was recommended to discontinue amikacin until a reasonable trough concentration was observed since the patient was due to receive dialysis. Excess peritoneal fluid was drained from the patient’s abdomen through a drainage system connected to a Bogota bag. TDM was repeated on the peritoneal fluid to establish how much amikacin was eliminated through the drainage system. Twenty one percent of the total serum amikacin was extracted through this apparatus. This was likely due to the patients severely decreased kidney function, which lead to a severely decreased amikacin clearance rate, thus allowing excessive amounts of amikacin to accumulate in the fluid compartments, which includes the peritoneal cavity.
Patient 20:

Patient is a 64 year old woman weighing 85 kg with end stage chronic renal failure. Blood cultures revealed a *Pseudomonas aeruginosa* infection susceptible to amikacin. The patient was initiated on 1 g amikacin daily. Peak and trough levels were taken and PK parameters calculated: true peak of 29.05 μg/ml, true trough of 23.16 μg/ml, elimination half-life of 71.4 hours and a Vd of 0.41 L/kg. Due to the prolonged elimination half-life the amikacin had to be stopped for fear of accumulation. She was initiated on continuous venovenous haemodialysis which would run for 72 hours. The research team opted for 1.5 g of amikacin daily for three days she was being dialyzed. The daily dosage of 1.5 g amikacin was estimated to grant a true peak serum concentration of 43.03 μg/ml, since the organism was susceptible the MIC could not be more than 4 μg/ml, thus a peak of 43.03 μg/ml was optimal.
5.1 INTRODUCTION

Chapter 5 will provide penultimate conclusions reached in this study and also conveys the limitations experienced by the researcher.

5.2 LIMITATIONS OF THE STUDY

5.3 UNAVAILABILITY OF AMIKACIN, GENTAMICIN AND VANCOMYCIN REAGENTS

Without reagents TDM could not be performed. This directly affected the researcher’s ability to intervene and make dosage adjustments.

5.4 UNWILLINGNESS FROM ICU STAFF

On some occasions ICU staff refused to assist with drawing blood samples, this had to be circumvented by asking a physician to draw samples.

5.5 PATIENT WEIGHT ESTIMATES

Weighing patients in the ICU of DGMAH is not possible, there is not a bed scale and patients are not able to stand on a scale and weigh themselves. Patient weight had to be estimated for all patients.

5.6 SMALL SAMPLE SIZE

The rate of vancomycin usage was much smaller than expected when starting the study, out of the seven patients who received vancomycin only one had an MRSA positive culture.
5.7 WORK ENVIRONMENT

Nurses and physicians were supportive about the presence of the researcher in the ICU. They did however become frustrated with the researcher when asking them to draw blood samples at inconvenient times. This made the researcher feel increasingly unwelcome over time as the staff grew tired of constantly drawing samples.

5.8 CHANGE OF STUDY PROTOCOL

After the study changed to include amikacin and gentamicin there was only 3 months left of the set out study period, the researcher had to be present in the ward every day to ensure that potential participants are all included.

5.9 LABORATORY ERRORS

When TDM results were abnormal they had to be repeated for correct interpretation, which was time consuming. In some instances where samples were frozen and stored for later review samples were thrown out after serum concentration quantification. These participants were also thrown out of the study due to the unreliability of those results.

5.10 INEXPERIENCE

When the researcher started the research, he made many mistakes concerning data collection and noting treatment progress. The research served as on the job training.

5.11 RECOMMENDATIONS

Creatinine clearance and estimated glomerular filtration did not have a significant correlation with AG and vancomycin clearance in the sample size. This raises questions whether dosage optimizations made according to creatinine clearance and eGFR have a place within a critically ill population, particularly in patients that were admitted with low SCr values due to malnutrition. Establishing the applicability of CrCl and eGFR in the critically ill is required. Conducting TDM to optimize gentamicin, amikacin and vancomycin dosages require MIC values of infecting organism, thus a collaborative effort with the microbiologist could help better individualize aminoglycoside and vancomycin dosages. The use of inulin compared to the aminoglycoside as a means of quantifying renal function.
5.12 CONCLUSION

Patients within the ICU had deranged PK parameters. Without therapeutic drug monitoring many abnormalities would not have been identified. SCr used within the Cockcroft-Gault equation and the MDRD eGFR could not accurately equate CrCl in all patients. Current dosing strategies do not accommodate each drug's optimal pharmacodynamic parameters. Routine TDM and MIC monitoring is required to optimise amikacin, gentamicin and vancomycin dosage within the ICU of DGMAH.
REFERENCES


References


Lesar T, Rotschafer J, Strand L, Solem L, Zaske D. Gentamicin dosing errors with four commonly used nomograms. JAMA 1982;248(10);1190-1193.


Stoltz A (2016). *Treatment of CAP and HAP presented at Respiratory Mini Congress hosted by SASOCP*. At the St George Hotel and Conference Centre, Centurion.
References


Appendices

APPENDICES

Appendix 1: Consent forms

Sefako Makgatho Health Sciences University English Consent Form
Statement concerning participation in a Clinical Research Project.

Name of the Study

**Optimizing antimicrobial dosages in the Intensive Care Unit of Dr George Mukhari Academic Hospital**

I have read the information on and heard the aims and objectives of the proposed study and was provided the opportunity to ask questions and given adequate time to rethink the issue. The aim and objectives of the study are sufficiently clear to me. I have not been pressurized to participate in any way.

I know that blood samples will be taken of me. I am aware that this material may be used in scientific publications which will be electronically available throughout the world. I consent to this provided that my name and hospital number is not revealed.

I understand that participation in this Clinical Study is completely voluntary and that I may withdraw from it at any time and without supplying reasons. This will have no influence on the regular treatment that holds for my condition neither will it influence the care that I receive from my regular doctor.

I know that this Study has been approved by the Sefako Makgatho University Research Ethics Committee (SMUREC), Sefako Makgatho Health Sciences University / Dr George Mukhari Hospital. I am fully aware that the results of this Study will be used for scientific purposes and may be published. I agree to this, provided my privacy is guaranteed.

I hereby give consent to participate in this Study.

............................................................  ............................................................

Name of patient/volunteer  Signature of patient or guardian.

............................................................  ............................................................  ............................................................

Place.  Date.  Witness

**Statement by the Researcher**

I provided verbal and/or written information regarding this Study
I agree to answer any future questions concerning the Study as best as I am able.
I will adhere to the approved protocol.

............................................................  ............................................................  ............................................................  ............................................................

Edward Upton  Signature  Date  Place
**Appendices**

**Sefako Makgatho Health Sciences University Setswana Consent Form**

**Seteitemente se sekaga go tsayakarolomoTekopatlisisong / PorojekeyaPatlisiso.**

Leina la Porojeke

*Karolo e phethoang ke pharmacist e tabeng ea ho sebelisa hlokomela phekolo lithethefatsi ho optimize tšebeliso loantsang likokoana ka matla Care Unit ea Dr George Mukhari Hospital Academic*

Ke buisitse tshedimosetso mo patlisiso e e tshitshintsweng mme ke filwe tšhono ya go botsa dipotso le go fiwa nako e e lekaneng ya go akanya gape kantlha e. Maitlhomo le maikemisetso a patlisiso e a thaloganyegasentle. Gake a patelediwakeopekatsela e pe go tsaya karolo.

Ke thaloganya gore go tsaya karolo ke Porojeke ke boithaopo le gore nkaigogela morago mo go yona ka nakonngwe le nngwe kwa ntle ga go neela mabaka. Se ga se kitla se nna le seabe sepe mo kalafong ya me ya go le gale ya bolwetsi jo ke nang le jona e bile ga se kitla se nna le tlhoteletse epe mo tlhokomelong e ke e amogelang mo ngakengya me ya go le gale.

Ke a itse gore Porojeke e e rebotswe ke Patlisiso le Molao wa Maitsholo tsa Khampase ya Sefako Makgatho University Research Ethics Committee (SMUREC), Yunibesithi ya Sefako Makgatho Health Sciences / Bookelo jwa Ngaka George Mukhari. Ke itse ka botlalo gore dipholo tsa Porojeke di tla dirisetswa mabaka a saentifiki e bile di ka nna tsa phasaladiwa. Ke dumelana le seno, fa fela go netefadiwa gore se e tla nna khupamarama.

Fano ke neela tumelelo ya go tsaya karolo mo Porojeke e.

................................................................................................................
Leina ka molwetse/moithaopi ................................................................. Tshaeno ya molwetse kgotsa motlamedi.
................................................................................................................

................................................................................................................
Lelelo. ................................................................. Paki
Lefelo. Letlha.

**SeteitementekaMmatlisisi**

Ke tlametse tshedimosetso ka molomo le/kgotsa e e kwadilweng malebana le Porojeke e.
Ke dumela go araba dipotso dingwe le dingwe mo nakong e e tleng tse di amanang le Porojeke ka moo nka kgonang ka teng.
Ke tla tshegetsa porotokolo e e rebotsweng.

................................................................................................................
Edward Upton Tshaeno Letlha Lefelo
Appendices

Appendix 2: Patient demographics capturing sheet

<table>
<thead>
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<th>Participant Number:</th>
<th>Participant name, surname, ethnicity and age:</th>
<th>Participant hospital number:</th>
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Appendices

Appendix 3: Data collection Form

TDM request form
Dr George Mukhari Academic Hospital, Pharmacology and Therapeutics
BMS 501S
DGMAH Hospital practice number : 560 2408

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<th>Patient number:</th>
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Medical Information:

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Patient prescribed regimen:

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Specimen information:

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<td>Time taken:</td>
<td></td>
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<tr>
<td>Taken to establish (X):</td>
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Results:

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Calculations:

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<th>True Trough concentration</th>
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Dosing recommendations:

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Medication

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<th>Total daily dose</th>
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Description of observed adverse event other than drug induced nephrotoxicity:
Appendices

Appendix 4: SMUREC clearance certificates

Sefako Makgatho Health Sciences University
Research & Postgraduate Studies Directorate
Sefako Makgatho University Research Ethics Committee
(SMUREC)

Molokadi Street, Ga-Rankuwa 0208
Tel: (012) 521 5517/3658 Fax: (012) 521 3749
Email: loreto.phiri@amu.ac.za
P.O. Box 163 Medunsa 0204

10 September 2015

To: Mr E. Unon
Department of Pharmacy
P.O. Box 216
Medunsa, 0204

Meeting: 07/2015

SMUREC Ethics Reference Number: SMUREC/2015/015-PG

The new application received on 14 August 2015 was reviewed by members of Sefako Makgatho University Research Ethics Committee on 10 September 2015 and was approved on 10 September 2015.

Title: Guidelines for optimizing veno-cannula placements using therapeutic drug monitoring within the intensive care unit of Dr. George Mukhari Academic Hospital

Researcher: Mr. P. Upena
Supervisor: Prof. AG. Sola
Co-supervisor: Prof. N. Shipela
Hospital Superintendent: Dr. N. M. Mokoena (KGMH)
Department: Pharmacy
School: Health Care Sciences
Degree: MSc. (Med) Clinical Pharmacy

Please note the following information about your approved research protocol:


Please remember to use your protocol number (SMUREC/2015/015-PG) on any documents or correspondence with the REC concerning your research protocol.

Please note that the REC has the prerogative and authority to ask further questions, seek additional information, require further modification, or monitor the conduct of your research and the consent process.

After Ethical Review: Please note a template of the progress report is obtainable in the Research Office and should be submitted to the Committee before the year has expired. The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit. Translation of the consent document in the language applicable to the study participants should be submitted.

International Organisation (OGO0103), Institutional Review Board (IREB0103), Federal Wide Assurance (FWA0000419)

Sincerely

Prof. G. D. B. Nane
Chairperson SMUREC

Date: 

71
Mr E Upton
Department of Pharmacy
P.O Box 218
Medunsa
0204

Dear Mr E Upton

RE: SMURECH/211/2015: PG - GUIDELINES FOR OPTIMIZING VANCOMYCIN DOSAGES USING THERAPEUTIC DRUG MONITORING WITHIN THE INTENSIVE CARE UNIT OF DR GEORGE MUKHARI ACADEMIC HOSPITAL

Researcher: Mr E Upton
Supervisor: Prof AGS Gous

SMUREC approved title: Guidelines for optimizing vancomycin dosages using therapeutic drug monitoring within the intensive care unit of Dr George Mukhari Academic Hospital

New title: Optimising antimicrobial dosages through the use of therapeutic drug monitoring in the intensive care unit of Dr George Mukhari Academic Hospital

SMUREC NOTED a letter dated 15 April 2016, requesting to amend this research proposal and change the title to:

"Optimising antimicrobial dosages through the use of therapeutic drug monitoring in the Intensive care unit of Dr George Mukhari Academic Hospital"

a) Additional literature review pertaining to aminoglycoside therapy

Motivation:
After commencing the study, researcher realized that he will not be able to reach the targeted sample size which he had stated in his research protocol. Thus he wish to broaden his search by including all patients who receive aminoglycoside therapy into the study, he added a literature review pertaining to aminoglycosides, to illustrate the need for patients receiving aminoglycoside therapy to be monitored, through the use of therapeutic drug monitoring.

b) Aim

Motivation: Previously, aim, objectives and research question were all formulated around the therapeutic drug monitoring and optimization of vancomycin. With the addition of aminoglycoside therapeutic drug monitoring, I thought it prudent to change the aim of the study. Which is now to optimize vancomycin and aminoglycoside dosages, within the ICU setting of DGM&H, through the use of therapeutic drug monitoring. This aim not only encompasses my previous goal which was, to investigate the use of therapeutic drug...