Antimicrobial surgical prophylaxis in the orthopaedic ward at a private hospital in Alberton, Gauteng Province, South Africa

A mini-dissertation submitted by

Anri Verwey

in partial fulfilment of the requirements for the degree

Master of Science (Medical) in Pharmacy

in the

Faculty of Health Sciences

(School of Health Care Sciences)

of the

Sefako Makgatho Health Sciences University

Department of Pharmacy

Supervisor: Professor N Schellack

Co-supervisor: Mrs L Thom

2016
DECLARATION

I, Anri Verwey declare that the mini-dissertation hereby submitted to the Sefako Makgatho Health Sciences University, for the degree of Master of Science (Medical) in 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.

__________________________________________________________  _________________
Verwey A (Mrs)                                  Date
DEDICATION

I dedicate this work to my parents, Eben and Magdaleen Boshoff. I hope that this achievement will complete the dream that they had for me all these years. Secondly, I dedicate it to my husband, JD Verwey, for all his patience, love, support and encouragement. And last but not least, I hope that all the hard work will one day be an inspiration to my son Reuben.
ACKNOWLEDGEMENTS

I would like to express my warm thanks to the following people who supported me throughout the course of this project. I am sincerely grateful to them and would not have been able to complete this without their immense support.

Professor Natalie Schellack, my supervisor, for her inspiring guidance, her patience, motivation, enthusiasm, and immense knowledge during this research project.

My co-supervisor, Lorraine Thom, for all her advice and assistance.

My manager, Elisma van der Merwe, for all her support, time and special allowances.

Netcare Union Hospital, for approval to conduct the research.

The statistician, Professor Herman Schoeman, for the analysis of the data.

Nikki Williamson and Juanita Krugel, for their logistical and administrative assistance and support.

Friends and family, for their support and encouragement.

The Department of Pharmacy, Sefako Makgatho Health Sciences University, for the opportunity to conduct the research.
TABLE OF CONTENTS

DECLARATION.......................................................................................................................... i
DEDICATION ............................................................................................................................ ii
ACKNOWLEDGEMENTS ........................................................................................................ iii
LIST OF TABLES ...................................................................................................................... vii
LIST OF FIGURES .................................................................................................................. viii
LIST OF APPENDICES ......................................................................................................... ix
ABBREVIATIONS AND ACRONYMS .................................................................................. x
ABSTRACT ............................................................................................................................. xi

CHAPTER 1 INTRODUCTION ......................................................................................................... 1
  1.1 INTRODUCTION .................................................................................................................. 1
  1.2 BACKGROUND AND RATIONALE FOR THE STUDY ....................................................... 1
  1.3 RESEARCH QUESTION ....................................................................................................... 3
  1.4 AIM OF THE STUDY .......................................................................................................... 4
  1.5 OBJECTIVES OF THE STUDY ............................................................................................ 4
  1.6 IMPORTANCE OR SIGNIFICANCE OF THE STUDY .......................................................... 4
  1.7 OUTLINE OF THE DISSERTATION ................................................................................... 6
  1.8 CONCLUSION .................................................................................................................... 6
  1.9 SUMMARY ....................................................................................................................... 7

CHAPTER 2 LITERATURE REVIEW ............................................................................................. 8
  2.1 INTRODUCTION ................................................................................................................ 8
  2.2 DEFINING ANTIMICROBIAL SURGICAL PROPHYLAXIS ............................................. 8
  2.3 ANTIMICROBIAL SURGICAL PROPHYLAXIS GOALS AND INDICATIONS .............. 8
  2.4 ANTIMICROBIAL SURGICAL PROPHYLAXIS OVERALL APPROACH ...................... 9
  2.5 CHARACTERISTICS OF AN APPROPRIATE ANTIMICROBIAL SURGICAL PROPHYLAXIS AGENT .................................................................................................................. 10
  2.6 SURGICAL SITE INFECTION (SSI) .................................................................................... 12
  2.7 WHEN IS ANTIMICROBIAL SURGICAL PROPHYLAXIS APPROPRIATE? ............... 12
  2.8 PREVALENT SURGICAL PATHOGENS ........................................................................... 13
  2.9 WHICH AGENTS SHOULD BE USED FOR ANTIMICROBIAL SURGICAL PROPHYLAXIS? ...................................................................................................................... 14
  2.10 EXCEPTIONS TO THE GUIDELINE RULES .................................................................... 15
    2.10.1 Allergies .................................................................................................................... 15
    2.10.2 Weight ....................................................................................................................... 15
    2.10.3 Dual antimicrobials .................................................................................................. 16
  2.11 DOSING OF ANTIMICROBIAL SURGICAL PROPHYLAXIS ........................................ 16
  2.12 TIMING OF ANTIMICROBIAL SURGICAL PROPHYLAXIS ........................................ 16
  2.13 REDOSING OF ANTIMICROBIAL SURGICAL PROPHYLAXIS .................................... 18
  2.14 DURATION OF ANTIMICROBIAL SURGICAL PROPHYLAXIS .................................... 18
2.15 INAPPROPRIATE USE OF ANTIMICROBIAL SURGICAL PROPHYLAXIS .................. 19
2.16 IMPORTANCE OF TIMING OF ADMINISTRATION OF ANTIMICROBIAL SURGICAL
PROPHYLAXIS ........................................................................................................ 20
2.17 INTRA-OPERATIVE RE-DOsing AND DURATION OF PROPHYLAXIS ................. 21
2.18 THE ROLE OF THE PHARMACIST IN EVALUATION AND MONITORING OF THE
APPROPRIATENESS OF ANTIMICROBIAL SURGICAL PROPHYLAXIS ............. 21
2.19 CONCLUSION ............................................................................................... 22
2.20 SUMMARY .................................................................................................... 22

CHAPTER 3 METHODOLOGY .............................................................................. 23
3.1 INTRODUCTION ............................................................................................. 23
3.2 STUDY DESIGN, SETTING AND POPULATION .................................................. 23
3.3 STUDY SAMPLING AND PERIOD ................................................................... 24
3.3.1 Inclusion criteria ......................................................................................... 24
3.3.2 Exclusion criteria ....................................................................................... 24
3.4 DATA COLLECTION PROCESS AND DATA COLLECTION INSTRUMENTS ........ 25
3.4.1 Data collection process ............................................................................... 25
3.4.2 Data collection instruments ....................................................................... 27
3.5 DATA ENTRY AND ANALYSIS ....................................................................... 29
3.6 RELIABILITY AND VALIDITY ...................................................................... 29
3.7 ETHICAL CONSIDERATIONS ........................................................................ 31
3.8 CONCLUSION ................................................................................................ 32
3.9 SUMMARY ..................................................................................................... 32

CHAPTER 4 MANUSCRIPT ................................................................................ 33
4.1 INTRODUCTION ............................................................................................. 33

CHAPTER 5 LIMITATIONS, RECOMMENDATIONS AND CONCLUSION ............... 46
5.1 INTRODUCTION ............................................................................................. 46
5.2 SUMMARY OF RESULTS ............................................................................... 46
5.3 LIMITATIONS ................................................................................................ 47
5.3.1 Data collection process ............................................................................... 47
5.3.1.1 Obtaining retrospective data from patient files .................................... 47
5.3.1.2 Compliance from nursing staff to document information appropriately .... 47
5.3.1.3 Pre-selected inclusion criteria ............................................................... 47
5.3.1.4 Peri-operative document insufficient ..................................................... 47
5.3.1.5 Distinguishing between antimicrobial prophylaxis and treatment ......... 48
5.3.2 Research .................................................................................................... 48
5.3.2.1 Small sample size ................................................................................. 48
5.4 RECOMMENDATIONS ................................................................................ 48
5.4.1 Data collection process ............................................................................... 48
5.4.1.1 Change of the peri-operative document .............................................. 48
5.4.1.2 Training of theatre staff................................................................. 49
5.4.1.3 Consultation with doctors ............................................................... 49
5.4.1.4 Availability of antimicrobials as ward stock ................................... 49
5.4.1.5 Implementation of regular monitoring of antimicrobial surgical prophylaxis........ 49
5.4.1.6 Awareness campaigns ................................................................ 50
5.4.2 Regarding the research................................................................... 50
  5.4.2.1 Small sample size......................................................................... 50
5.5 CONCLUSION TO THE STUDY............................................................... 50
REFERENCES.............................................................................................. 52
APPENDICES.............................................................................................. 56
<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>Key recommendations for practice</td>
<td>9</td>
</tr>
<tr>
<td>2.2</td>
<td>Antimicrobial surgical prophylaxis and subsequent rates of SSIs</td>
<td>18</td>
</tr>
<tr>
<td>3.1</td>
<td>Overview of the data collection instrument</td>
<td>28</td>
</tr>
<tr>
<td>3.2(a)</td>
<td>Threats to internal validity</td>
<td>30</td>
</tr>
<tr>
<td>3.2(b)</td>
<td>Threats to external validity</td>
<td>31</td>
</tr>
</tbody>
</table>
LIST OF FIGURES

Figure 1.1: Outline of the dissertation ................................................................. 6
Figure 3.1: Data collection process ................................................................. 27
LIST OF APPENDICES

Appendix A: Letter of Intent ...................................................... 56
Appendix B: Permission Letter from Orthopaedic Surgeons ....................... 57
Appendix C: SMUREC Clearance Certificate ...................................... 58
Appendix D: Data Collection Sheet .................................................. 59
Appendix E: Guidelines for Authors for the South African Journal for Infectious Diseases ........................................................................... 60
## ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMR</td>
<td>Antimicrobial Resistance</td>
</tr>
<tr>
<td>ASHP</td>
<td>American Society of Health System Pharmacists</td>
</tr>
<tr>
<td>ASP</td>
<td>Antimicrobial Surgical Prophylaxis</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomic Therapeutic Chemical Classification</td>
</tr>
<tr>
<td>CDC</td>
<td>Centre of Disease Control</td>
</tr>
<tr>
<td>CMS</td>
<td>Centres of Medicare and Medicaid Services</td>
</tr>
<tr>
<td>DCS</td>
<td>Data collection sheet</td>
</tr>
<tr>
<td>DDD</td>
<td>Defined daily dose</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>ECDC</td>
<td>European Centre for Disease Prevention and Control</td>
</tr>
<tr>
<td>HAI</td>
<td>Healthcare-associated infection</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>IDSA</td>
<td>Infectious Diseases Society of America</td>
</tr>
<tr>
<td>LOS</td>
<td>Length of Stay</td>
</tr>
<tr>
<td>MIC</td>
<td>Minimum Inhibitory Concentration</td>
</tr>
<tr>
<td>MRSA</td>
<td>Methicillin Resistant Staphylococcus aureus</td>
</tr>
<tr>
<td>NDoH</td>
<td>National Department of Health</td>
</tr>
<tr>
<td>NHSN</td>
<td>National Healthcare Safety Network</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Clinical Excellence</td>
</tr>
<tr>
<td>SAS</td>
<td>Statistical Analysis System</td>
</tr>
<tr>
<td>SCIP</td>
<td>Surgical Care Improvement Project</td>
</tr>
<tr>
<td>SHEA</td>
<td>Society for Healthcare Epidemiology of America</td>
</tr>
<tr>
<td>SIS</td>
<td>Surgical Infection Society</td>
</tr>
<tr>
<td>SMUREC</td>
<td>Sefako Makgatho University Research Ethics Committee</td>
</tr>
<tr>
<td>SSI</td>
<td>Surgical Site Infection</td>
</tr>
<tr>
<td>TRAPE</td>
<td>Trial to Reduce Antimicrobial Prophylaxis Errors</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
</tbody>
</table>
ABSTRACT

Introduction:
Prevention of surgical site and peri-prosthetic joint infections is crucial. It has been proven that antimicrobial surgical prophylaxis (ASP) reduces the occurrence of surgical site infections (SSIs). Infections are associated with serious morbidity, often requiring several re-operations, and are expensive to manage. This may also lead to other secondary complications, such as prolonged patient hospital stay and the use of more antimicrobials with unwanted drug side-effects, as well as the problematic challenge of increasing antimicrobial resistance (AMR). From a pharmacoeconomic perspective, it is beneficial to ensure appropriate prophylactic antimicrobial prescribing at a hospital. Aspects, such as using the correct prophylactic drug, at the correct dose and for an appropriate period of time are all entities that could be monitored to ensure effective and appropriate ASP.

Background:
Knee and hip arthroplasty patients are particularly at risk for SSIs due to the fact that the procedure involves insertion of a prosthetic device. It is of the utmost importance to prevent such infection by implementing several precautions, of which ASP is an important key element. Although numerous studies have been conducted worldwide on this topic, there is limited data available for the South African setting.

Objectives:
The objectives of this study were to determine the appropriateness of ASP with regards to the choice of antimicrobial used, the dose thereof and the prescribed duration. Problem areas were then identified and addressed accordingly.

Methodology:
This study followed a quantitative retrospective design with a descriptive approach. Patient records were reviewed from the orthopaedic ward at a private hospital located in Johannesburg, South Africa. The hospital consists of 222 beds and is an accredited Level One Trauma Centre with a high number of orthopaedic patients. Data were collected and assessed from 250 files of discharged patients, captured onto a structured Microsoft® Excel™ spreadsheet, and subsequently interpreted and analysed by the researcher with the assistance of a statistician. Problem areas were identified and addressed with individual prescribers and nursing staff and challenges were noted.
Results:

Antimicrobial surgical prophylaxis was provided in all patients, of which the most commonly used agents were cefazolin (77.45%), teicoplanin (14.7%), clindamycin (2.6%), ceftriaxone (2%), amoxicillin/clavulanic acid (2%), amikacin (0.65%), ciprofloxacin (0.33%) and linezolid (0.33%). Assessed in accordance with international guidelines, the antimicrobials most frequently used inappropriately were ciprofloxacin, amoxicillin/clavulanic acid, amikacin, linezolid and ceftriaxone. Patients who received more than one agent for surgical prophylaxis comprised 22.4%. All procedures included in the study received a pre-operative prophylactic antimicrobial and in most cases (66.7%) antimicrobial therapy was continued post-operatively. A total of 86.6% of prescriptions were appropriately discontinued within 24 hours following the initial prophylactic dose. It was found that in 70.7% of prescriptions, the correct dose was prescribed according to weight, whereas 29.3% actually required a higher dose than what was prescribed. For patients who were documented to be allergic to penicillin and who ought to have received clindamycin, only 25% received the correct agent, yet none at the correct dose. Penicillin allergic patients who received ceftriaxone rather than cefazolin comprised 21.4%. Of all the studies and observed procedures, only 20.3% of hip and 21.3% of knee arthroplasties were compliant with all the different aspects regarding ASP in comparison with the stated guidelines (evaluating antimicrobial selection, dose and duration). Adherence to the antimicrobial selection for prophylaxis (76.4%), prescribed initial dose of the antimicrobial (52.9%), subsequent dose (10.4%), as well as the post-operative duration (86.9%) all deviated significantly from published international guidelines. The quantity of teicoplanin prescriptions (14.7%) needs further investigation in terms of appropriateness.

Conclusion:

The breaches in adherence to ASP in the orthopaedic ward could possibly be explained by a lack of guidelines for peri-operative prophylaxis. The choice of antimicrobial and overall duration thereof scored high for overall compliance, although subsequent doses were prescribed incorrectly in many cases. Extended spectrum antimicrobials were sometimes used, but the overall quantity of teicoplanin prescriptions were concerning. Both insufficient documentation of incision time and the time of drug administration should be addressed in order to carry out comprehensive ASP evaluation. Extended awareness amongst the multi-disciplinary team seems to be an important aspect to be emphasised, as well as the adoption of appropriate ASP guidelines in the unit. There is a strong need for the clinical pharmacist, who functions within the multi-disciplinary team, to intervene in prophylactic antimicrobial prescriptions.
Recommendations:

Follow-up studies are recommended after interventions are made to record incision time as well as the time of administration of the antimicrobial, in order to accurately determine compliance to the time the dose was administered. Interventions should be implemented in order to address problem areas and ASP guidelines to be made available for each discipline in the hospital.
CHAPTER 1
INTRODUCTION

1.1 INTRODUCTION

This chapter describes the background and rationale for the study. It includes the research question, aim and the objectives of the study. The importance and significance of the study are described. This chapter ends with a short overview of the outline of this dissertation.

1.2 BACKGROUND AND RATIONALE FOR THE STUDY

Antimicrobials are the most commonly prescribed medicine in both the community and hospital health care setting. Thus, throughout health care communities, an increased desire to reduce practice pattern variation of antimicrobials have grown. One of these focus areas is ASP (Romano, 2016). ASP accounts for 30-50% of all antimicrobial use (Chandrasekaran, Saeed, Gandhiraj, Prasad & Rajasekaran, 2016). By demonstrating how appropriately ASP is used during surgery, ASP serves as a vital quality indicator (Sviestina, Mozgis & Mozgis, 2016). The overall goal of ASP is to prevent SSIs by using an antimicrobial that is safe and cost-effective with a spectrum of activity that covers the most common pathogens for the specific surgical procedures (Anderson & Sexton, 2016). SSIs account for one of the most common complications associated with significant morbidity and mortality (Sandora, Fung, Melvin, Graham & Rangel, 2016).

It has been estimated that, by the year 2030, more than four million primary total hip arthroplasty and total knee arthroplasty procedures will be performed annually in the United States of America (USA) (Bosco, Bookman, Slover, Edusei & Levine, 2015). The projected estimation of deep infections associated with these arthroplasties is approximately 2% within two years after the procedure. If it continues to escalate at the current rate, the estimated number of deep infections following joint arthroplasty will approximately be in the range of between 40,000 and 80,000 annually by the year 2030. The management of such infections has serious cost implications, as a single uncomplicated peri-prosthetic joint infection has been shown to cost approximately $50,000.00 (equivalent to about R700,000.00), and even more when dealing with antimicrobial-resistant organisms. The management thereof often requires several follow-up operations, which go hand-in-hand with serious morbidities. If the conservative estimated figure of $50,000.00 per infection is used, the cost of treating infections will be two to four billion dollars (R28 - 56 billion) annually by 2030 in the USA alone. Although there is no data available for the South African context, it is well supported locally that the repercussions of infections following knee and
Chapter 1: Introduction

hip arthroplasties have a large impact on both private and public health care, as well as for the patient in terms of quality of life.

This private hospital has a large orthopaedic unit with a high number of knee and hip arthroplasties being performed annually. Despite the great number of these procedures being performed at the hospital, a small sampling revealed several aspects that needed improvement regarding ASP. This was the initiative to start an extensive data collection process in order to prove that dramatic changes are needed for quality improvement regarding surgical prophylaxis at the hospital (Bosco et al., 2015).

SSIs may result in significant post-operative morbidity and mortality. Many of these infections can be prevented with appropriate ASP, which includes timely administration of the correct antimicrobial at an appropriate dose for an indicated duration. Unfortunately, according to the literature, data still suggest that many patients do not receive such therapy (Meehan, Jamali & Nguyen, 2009). The consequences of SSIs are well documented, and include, but are not limited to, prolonged hospital stay, as well as additional interventions and treatment which all divert resources away from other priority areas.

Antimicrobial prophylaxis may be beneficial in surgical procedures associated with high rates of infection, such as clean-contaminated (a wound that shows no sign of infection, but is at high risk in becoming infected due to its location, e.g. in the gut) or contaminated (an outside object came in contact with the skin, which causes a high risk of infection). ASP may also be beneficial in clean surgery where prosthetic devices are implanted. Although the infection rate is low with prosthetic implants, the consequence of an infection is severe (Bratzler, Dellinger, Olsen, Perl, Auwaerter, Bolon, Fish, Napolitano, Sawyer, Slain, Steinberg & Weinstein, 2013).

The goal of ASP is to achieve serum and tissue drug levels that exceed the minimum inhibitory concentration (MIC) for the duration of the procedure and to cover the most likely organisms prevalent to cause SSIs in the specific scenario. All infections cannot be prevented by the use of prophylactic antimicrobials, nevertheless the goal of ASP is to decrease the bacterial burden and not to sterilise the patient (Meehan, Jamali & Nguyen, 2009).

The use of broad-spectrum antimicrobials adds to the development of multi-drug resistant organisms, which in turn are associated with a worse clinical outcome for the patient as well as the possible effects on the hospital ecology, which may have detrimental outcomes to other patients (Meehan, Jamali & Nguyen, 2009).
Globally, AMR is an increasingly serious threat to public health that requires action across all government sectors and society (O’Neill, 2016). A retrospective study conducted on ASP used in paediatrics, looked at the following parameters: the indication, choice of antimicrobials, timing, dose, duration and dosing interval. It concluded that adherence to all parameters was achieved in only 25.3% of cases (Groselj, Derganc, Trisnar & Cizman, 2006).

The use of antimicrobial prophylaxis in the prevention and reduction of the incidence of SSIs is widespread and evidence has proved the importance of appropriate use. Despite this evidence, the recommendations are not routinely followed and antimicrobials are used excessively and inappropriately for the prevention of SSIs. The clinical pharmacist, together with a multi-disciplinary team, can play a very important role in the control and management of ASP by ensuring optimal prescribing in terms of drug choice, dose, timing of dose and duration thereof, as well as individualised treatment in terms of patient-specific factors (Nicolau, Ho & Dakin, 2012). The lack of data made it difficult to identify and address specific problem areas in this particular hospital, but also in the group of private hospitals as a whole. This study therefore underlines the need to study ASP selection, the timing of administration and duration of use in this population (Brink, Ritchie, Barnard, Karim, Du Toit, Lawrence, Cruickshank, Miszka, Kantor, Walsh and Greyling, 2011).

To this effect, the study described was an observational study, which evaluated the prevalence, origin and description of matters contributing to poor adherence at the hospital according to well-researched international ASP guidelines. This study highlighted many of the challenges, which should be rectified to ensure optimal patient care.

1.3 RESEARCH QUESTION

The primary research question for this study was ‘How appropriate was the prescribing of antimicrobial surgical prophylaxis in the orthopaedic ward of this private hospital?’

The secondary questions posed were as follows:

1. How appropriate was the choice of antimicrobial agents, defined as dose and duration prescribed for prophylaxis for a specific surgical procedure?
2. What were the problem areas regarding prescribing and administration of antimicrobial surgical prophylaxis?
1.4 **AIM OF THE STUDY**

The aim of the study was to determine the appropriateness of antimicrobial surgical prophylaxis according to international guidelines for knee and hip arthroplasties in the orthopaedic ward at a private hospital.

1.5 **OBJECTIVES OF THE STUDY**

Objectives of the study were to:

1. List the type of antimicrobials prescribed for ASP in the orthopaedic ward at a private hospital.
2. Assess if the antimicrobials prescribed was appropriate according to international guidelines with regards to:
   a) Antimicrobial selection
   b) Dose
   c) Duration
3. Identify and address problem areas regarding antimicrobial surgical prophylaxis in the orthopaedic ward.

1.6 **IMPORTANCE OR SIGNIFICANCE OF THE STUDY**

AMR threatens not only the fundamentals of modern medicine, but also the sustainability of an effective global public health response to infectious disease threats (O’Neill, 2016).

A global action plan was thus initiated to curb the increasingly serious threat towards a post-antibiotic era and to ensure a sustainable investment in defying AMR. This study, though undertaken retrospectively, supported the objective to limit AMR, by monitoring the use of ASP (Global Action Plan on Antimicrobial Resistance, 2015).

In line with the global action plan’s aim to conserve effective antimicrobials through stewardship, this study set out the objectives outlined, specifically by improving awareness and understanding of AMR via the monitoring of ASP. Presenting and communicating this objective to all medical practitioners taking part in the survey further enhanced the importance and understanding of AMR. Moreover, it highlighted the importance of staying up-to-date with the latest guidelines. Secondly, this study in itself strengthened knowledge by researching and surveying ASP use and the appropriateness thereof grounded on evidence-based guidelines. By performing this study in a private health care setting, it highlighted the importance of optimal use of ASP along with the importance of evidence-
based prescribing and dispensing. Lastly, the global action plan highlights the imperative role that health care personnel have in the protection of antimicrobials.

A national response to AMR is required to complement the development of the above-mentioned global action plan. Although the AMR national strategy framework of the National Department of Health (NDoH) is focused on a national level, this study nevertheless addressed some of the strategic objectives; which include surveillance of ASP use, prescribing and administering errors, as well as ASP quality (NDoH, 2014).

Prior to the AMR strategic framework a domain of patient safety, clinical governance and clinical care was established in 2011 by the NDoH termed the National Core Standards for Health Establishments in South Africa (NDoH, 2011). This domain provided guidelines on how to ensure quality nursing, clinical care and ethical practice. As SSIs are a major cause of post-operative morbidity and mortality, patient safety is thus at risk and therefore one of the cross-cutting domains addressed by the National Core Standards. Patient safety was a major concern of this study. This concern was addressed by retrospectively assessing, and thereby in future, contributing to quality clinical care and ethical practice to reduce unintended harm. Another domain that was not addressed was public health; collateral damage was restricted, which highlighted the importance of appropriate use of ASP according to the latest literature (NDoH, 2011).

Finally, to the researcher’s knowledge, this study was the first to focus specifically on the appropriateness of ASP in a private health care setting. This study consequently opened the opportunity to establish whether equitable and evidence-based care was provided. Thus, the importance of optimised use of ASP to limit AMR was innovatively highlighted.

SSIs remain a major cause of post-operative morbidity and mortality and have significant cost implications due to prolonged hospital stay accompanied by increased medical expenses involved (Bosco et al, 2015).

It has been proven that appropriate prophylactic antimicrobial administration before surgery significantly decreases the risk of SSIs by eradicating endogenous microorganisms, provided that it is prescribed and administered correctly (Shah, Maharjan, Manandhar, Shrestha, Piya & Basnet, 2011).

Despite the cost-effectiveness and easy intervention of ASP, incorrect prescribing and administration is still a commonly-found phenomena in most disciplines, including orthopaedic surgery (Bosco et al, 2015). This created the need for further study and the implementation of sustainable solutions on problem areas identified, as well as the
establishment of protocols based on well-researched international guidelines (Bratzler et al., 2013).

1.7 OUTLINE OF THE DISSERTATION

This dissertation consists of five chapters, as illustrated in Figure 1.1. Chapter 1 introduces the reader to the background and rationale of the study, together with the stated research questions, the aim and the objectives of the study. Chapter 2 is a review of the literature of ASP in knee and hip arthroplasties. Chapter 3 is a discussion of the methodology related to this study. This includes the study design, study site, study population and the period in which the study was conducted. It further describes the sample selection, the data collection process, data analysis, the validity and reliability of the study and all the ethical principles that were considered for the duration of the study. Chapter 4 presents the article containing the results of the study, followed by the discussion of the results. Chapter 5 concludes the dissertation with a summary, limitations of the study, recommendations for future studies and a conclusion.

![Figure 1.1: Outline of the dissertation](image)

1.8 CONCLUSION

ASP forms an integral part of antimicrobial stewardship. Problem areas were identified regarding the use of prophylactic agents in the orthopaedic unit of the hospital. Prevention of SSIs through the use of ASP is of utmost importance in order to prevent the consequences associated with SSIs. The clinical pharmacist practising antimicrobial stewardship can play a major role in ensuring optimum ASP by ensuring that the correct
agent is prescribed at the recommended dose, administered at the right time and continued for an appropriate duration. This baseline data accumulated in the study were needed in order to implement sustainable changes regarding the prescribing and administration of these agents in the hospital.

1.9 SUMMARY

A brief background on ASP for knee and hip arthroplasties and the rationale for the study were described in this chapter. The research question, the main aim and the different objectives of the study and lastly the outline of the dissertation were clearly stipulated in this chapter. The next chapter will focus on a literature review with regards to ASP in knee and hip arthroplasties.
CHAPTER 2
LITERATURE REVIEW

2.1 INTRODUCTION

In order to determine the appropriateness of ASP in the orthopaedic ward, several factors should be taken into account, such as the entities of the drugs to be used for the specific procedure; prevalent pathogens to be covered by the drugs; choice of antimicrobial to be used; timing of drug administration before the procedure; intra-operative re-dosing and the duration of the prophylactic drug prescribed (Bratzler et al, 2013).

This chapter starts with a description of the characteristics of an appropriate ASP agent, followed by a discussion on which antimicrobial surgical prophylactic agent is appropriate for each surgical procedure. The most prevalent organisms associated with knee and hip arthroplasties are mentioned followed by a short overview of the appropriate agents that should be used in ASP. Subsection 2.6 describes exceptions to the rules, followed by a discussion on the importance of timing of ASP. This chapter concludes with an overview of when intra-operative re-dosing of the antimicrobial is necessary as well as the optimal duration to continue with the agent.

2.2 DEFINING ANTIMICROBIAL SURGICAL PROPHYLAXIS

The Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery (Bratzler et al, 2013), termed the ASHP Guidelines, define prophylaxis as a method of preventing an infection. Prophylaxis is further classified as primary prophylaxis, secondary prophylaxis or eradication. The term primary prophylaxis refers to the prevention of an initial infection. Secondary prophylaxis suggests the prevention of a recurrent infection or the reactivation of a pre-existing infection. Eradication refers to the elimination of a colonised organism to prevent the development of an infection. Primary peri-operative prophylaxis is thus applicable to this study, which is defined as the intra-operative administration of antimicrobials to patients to reduce the risk of post-operative wound infection (NDoH, 2014).

2.3 ANTIMICROBIAL SURGICAL PROPHYLAXIS GOALS AND INDICATIONS

Anderson and colleagues (2015) stated that the purpose of ASP is to prevent a SSI during an operative procedure by decreasing the load of organisms at the surgical site. Furthermore, the aim is to decrease the associated morbidity and mortality, length of stay (LOS) and the accompanied cost.
In order to accomplish these goals, ASP should cover the most common pathogens associated with the type of surgery, be administered in an appropriate dose, at an appropriate time to ensure sufficient serum and tissue concentrations throughout the period of potential infection risk, and lastly be administered for the shortest effective period of time to minimise adverse effects, emergence of resistance and cost (Anderson et al, 2015).

ASP efficacy in reducing SSIs, should an infection develop, has been evidently recognised and is necessary in surgeries with high infectious risks and harmful outcomes (Anderson et al, 2015). Sandora and colleagues (2016) agree and further explain that appropriate use of ASP reduces a significant and preventable source of morbidity and mortality in hospitalised patients.

2.4 ANTIMICROBIAL SURGICAL PROPHYLAXIS OVERALL APPROACH

General factors to consider for ASP selection in the prevention of SSIs include cost, safety, pharmacokinetic profile and bactericidal activity (Salkind & Kavitha, 2011). Furthermore, the need for ASP should be based on the risk of wound contamination. The medication chosen should be active against the pathogens most likely to be associated with the type of surgical procedure, and finally, prophylaxis must be given within 30 minutes of the first incision, usually at induction of anaesthesia (NDoH, 2014). Evidence on key recommendations for ASP practices is highlighted in Table 2.1.

Table 2.1: Key recommendations for practice

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Evidence rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASP should be infused within one hour prior to incision to prevent SSI</td>
<td>A</td>
</tr>
<tr>
<td>ASP use should be consistent with published guidelines</td>
<td>C</td>
</tr>
<tr>
<td>Discontinuation of ASP should generally be within 24 hour after surgery</td>
<td>C</td>
</tr>
</tbody>
</table>

Adapted from Salkind & Kavitha (2011).

A = Consistent, good-quality patient-oriented evidence
C = Consensus, disease-oriented evidence, usual practice, expert opinion or case series
ASP = Antimicrobial surgical prophylaxis

In support of the above-mentioned principles, the Surgical Care Improvement Project (SCIP) performance measures further elaborate on three fundamental infection prevention measures, such as the importance of administering an antimicrobial appropriate for the specific surgical procedure, within one hour prior to surgical incision and two hours in the case of vancomycin or fluoroquinolone use, together with the discontinuation within 24 hours of surgery completion (48 hours in cardiothoracic surgery). Other measures include controlled post-operative 6 a.m. blood glucose levels in cardiac surgery (11.10 mmol/L or less) and the removal of hair at the site of incision. Contrary, the National Institute for
Clinical Excellence (NICE) guidelines (2008) state that hair removal should not be done routinely to reduce the risk of an SSI. If it is however required, the use of a single-head electric clipper is recommended on the day of surgery. Razors are contraindicated and may increase the risk of an SSI. Lastly, colorectal surgical patients should be normothermic (36°C or greater) within the first 15 minutes after discharge from theatre (Salkind & Kavitha, 2011). Ideally, ASP should cause no adverse drug effects to the patient, the patient’s microbial flora or to the hospital (Anderson et al, 2015).

Lastly, recommendations for ASP are limited to Class II. Class II entails clean procedures with limited contamination and exposure to microorganisms colonising the epithelial surfaces and/or lumen of the respiratory, gastrointestinal, and urinary or genital tract, with no evidence of infection (NDoH, 2014).

2.5 CHARACTERISTICS OF AN APPROPRIATE ANTIMICROBIAL SURGICAL PROPHYLAXIS AGENT

When an antimicrobial agent is chosen for surgical prophylaxis, the most important factor to be taken into account is its spectrum of activity. Even though the entire spectrum of organisms prevalent during the procedure may not be covered, the agent should cover the bacteria known to commonly cause post-operative infection associated with the specific procedure (Bratzler et al, 2013).

Another aspect to be considered is whether an antimicrobial agent is bacteriostatic or bactericidal. Bacteriostatic agents, such as clindamycin, inhibit bacterial growth by limiting bacterial protein production or by interruption of folic acid synthesis and deoxyribonucleic acid (DNA) replication. Bactericidal agents, such as the beta-lactams (penicillins and cephalosporins), vancomycin and aminoglycosides are known to eliminate bacteria completely. The mechanism to do so is by inhibiting cell wall synthesis and the induction of cytolysis. Bacteriostatic agents are often bactericidal in high doses, which is the reason for clindamycin being prescribed in higher than normal doses for surgical prophylaxis (Meehan, Jamali & Nguyen, 2009).

Other entities of the drug to be taken into account are the pharmacodynamics (study of the mechanisms of action of the drug and biochemical and physiological effects) and pharmacokinetics (study of the process by which a drug is absorbed, distributed, metabolised, and eliminated by the body). The half-life of the chosen drug should be long enough to at least be efficient in the first two hours after incision when the possibility of contamination is at its highest. Drug tissue concentration should also be maintained above
the MIC to reduce the risk of wound infection. The clearance of the drug plays a role in terms of re-dosing as well as when multiple blood transfusions were needed during the procedure. In such cases more than one dose may be needed intra-operatively to ensure adequate tissue concentrations (Bosco et al, 2015).

Last, but not least, the cost of the antimicrobial prophylactic treatment should be feasible to ensure continuous availability thereof. This includes the price of the drug, the expense of drug monitoring, administration and adverse effects. Possible failure of prophylaxis and the consequences of wound infection also play a key role in the assessment process in choosing the most appropriate agent (Meehan, Jamali & Nguyen, 2009).

The concepts discussed above are echoed by Bratzler and colleagues (2013), which state that the ideal chosen prophylactic drug should:

- prevent SSIs;
- reduce morbidity and mortality linked to SSIs;
- have no major negative economic impact on health care;
- cause no unwanted side-effects to the patient; and
- preferably not influence the microbial flora of the patient.

To ensure that the above criteria are met, the drug should:

- act against the organisms which will most likely cause contamination during surgery;
- be administered at an appropriate dose and time to ensure optimal tissue concentration when contamination is most likely to occur;
- cause no harm to the patient; and
- only be prescribed for the minimum time necessary to prevent infection, which will minimise contribution to resistance, adverse effects and cost (Bratzler et al, 2013).

Furthermore, several factors should be taken into account when a prophylactic antimicrobial is chosen, namely each individual patient should be evaluated in terms of medication allergies as well as the safety-profile of the chosen agent with regard to renal function and co-morbidities. In order to be classified as appropriate, the selected antimicrobial should be efficient for the specific surgical procedure that will be performed (Musmar, Ba´ba & Owai, 2014).
2.6 SURGICAL SITE INFECTION (SSI)

An SSI is classified as a healthcare-associated infection (HAI) in which a wound infection occurs after an invasive surgical procedure. SSIs account for 20% of all HAIs and at least 5% of all surgical patients develop an SSI (NICE, 2008). The Centre for Disease Control (CDC) and the National Healthcare Safety Network (NHSN) further define an SSI as a superficial, deep, or organ space infection occurring within 30 days of a surgical procedure. However, in the case of patients with surgical implants, a time period of within one year is used (Khoshbin, So, Aleem, Stephens, Matlow & Wright, 2015).

Additionally, one or more of the following clinical criteria are required to define an SSI (NICE, 2008):

- A purulent exudate draining from the surgical site;
- A positive fluid culture obtained from the surgical site that was closed primarily;
- A surgical site that is reopened in the setting of at least one clinical sign of infection (pain, swelling, erythema or warmth) with no culture, or with a positive culture;
- Diagnosis of infection by the surgeon.

SSIs are classified as either incisional or as an organ/space SSI. Incisional SSIs are divided into either a superficial or deep incision. An organ/space SSI involves any part of the anatomy (other than the incision) that was opened or manipulated throughout the operative procedure. One-third of all SSIs are attributed to organ/space SSIs, but accounts for more than 90% of SSI-related deaths (Anderson & Sexton, 2015). Salkind and Kavitha (2011) further state that SSIs are the leading cause of nosocomial infections after surgery. Approximately 40% of all nosocomial infections are a result of SSIs.

Additionally, compared to surgical patients without an SSI occurring during the first eight weeks after hospitalisation, an SSI results in an estimated threefold higher cost of care, decreased quality of life and increased hospital length of stay. Furthermore, these patients have a fivefold increase for readmission, are 60% more likely to spend time in the intensive care unit (ICU) and are twice as likely to die.

2.7 WHEN IS ANTIMICROBIAL SURGICAL PROPHYLAXIS APPROPRIATE?

In light of the serious potential consequences, antimicrobial prophylaxis is well accepted in procedures involving the implantation of foreign materials (Bratzler et al, 2013).
An important aspect highlighted by Burke (2001), is that antimicrobial prophylaxis is normally acceptable in clean contaminated procedures. Use in ‘dirty’ procedures where infection is already present, is classified as treatment rather than prophylaxis.

Although ASP plays and important role in preventing the occurrence of an SSI, other factors of importance should also be taken into account. These include infection prevention control, technique of the surgeon, type of procedure and duration thereof, as well as the operating environment which includes sterilisation of instruments, pre-operative preparation, such as appropriate hair removal, skin cleansing and the implementation of correct surgical scrub procedures. Aspects such as peri-operative management, which includes glycaemic and temperature control and patient-specific co-morbidities, are also entities that could contribute to a higher risk of developing an SSI (Koopman, Nix, Erstad, Demeure, Hayes, Ruth & Matthias, 2007).

The financial impact and the morbidity associated with SSIs should also be taken into consideration when considering prophylactic treatment, as stated by the European Centre for Disease Prevention and Control (ECDC, 2013).

### 2.8 PREVALENT SURGICAL PATHOGENS

When a specific antimicrobial agent is chosen for knee or hip arthroplasty surgical prophylaxis, the particular microorganisms associated with post-operative SSIs should be known (Nicolau, Ho & Dakin, 2012).

Numerous studies (Bratzler et al, 2013) have indicated that normal skin flora such as *Staphylococcus aureus* and coagulase-negative staphylococci (e.g. *Staphylococcus epidermidis*), are the most likely pathogens to cause SSIs after knee and hip arthroplasties. The primary reason is that other possible human contributing reservoirs, such as the gastrointestinal tract, is not entered, therefor skin or exogenous airborne bacteria are mainly responsible. Even though *Staphylococcus epidermidis* is usually regarded as non-pathogenic, as in the case of a joint replacement, it is more difficult to treat due to the biofilm produced by the organism. The glycocalyx layer formed around the prosthetic device prevents the antimicrobial from entering the biofilm and makes it very difficult to treat, to such an extent that it usually requires removal of the prosthesis with the glycocalyx layer in order to eliminate the infection. Therefore it is of utmost importance that the chosen antimicrobial has activity against this gram-positive spectrum (Bratzler et al, 2013). *Enterococcus, Streptococcus* and gram-negative organisms such as *Escherichia coli, Pseudomonas-* and *Klebsiella* species are less common, but have been reported to cause
SSIs after knee and hip arthroplasties. The above-mentioned can also be part of normal skin flora and could cause infection by means of direct inoculation or airborne contamination (Bosco et al, 2015).

Although the patient's endogenous flora is the main cause for SSIs, Meehan and colleagues (2009) stated that factors, such as the operating environment as well as attending personnel, might also play a vital role. The number of people in theatre should be kept to a minimum in order to reduce the risk of infection. Basic infection prevention strategies should be in place, such as hand hygiene and eradication of possible bacterial sources, such as artificial nails. The bottom line is that ASP is a very important link in the chain in the prevention of SSIs, but can only be successful when other infection prevention strategies are in place (Bratzler et al, 2013).

2.9 WHICH AGENTS SHOULD BE USED FOR ANTIMICROBIAL SURGICAL PROPHYLAXIS?

Agents listed in international guidelines for ASP include cefoxitin, cefazolin, cefuroxime, clindamycin, vancomycin and ertapenem (Al-Momany, Al-Bakri, Makahleh & Wazaify, 2009). According to Bosco and colleagues (2015) a first- or second-generation cephalosporin should be the first-line treatment for ASP in knee and hip arthroplasties. Cefazolin and cefuroxime are the first-choice antimicrobials to be used in total joint arthroplasty when there is no contraindication due to beta-lactam allergy. Both these cephalosporins have a very good safety profile; and are effective against the most common gram-positive organisms as well as 40% of the gram-negative organisms known to cause SSIs after knee and hip arthroplasties.

For patients who are allergic to the above-mentioned agents, clindamycin is used as the alternative and when a patient has a known risk factor such as methicillin-resistant staphylococcus aureus (MRSA) colonisation, the use of vancomycin is recommended. Although clindamycin is effective against many MRSA species, vancomycin is the first choice to cover MRSA, because vancomycin has bactericidal properties and has been shown to cover a greater number of MRSA species (American Academy of Orthopaedic Surgeons, 2002).

Furthermore, it is advised that vancomycin should not be used routinely, although it is included in the guidelines. The recommendation is that it should only be considered for prophylaxis when a patient is confirmed or is at high risk to be colonised with MRSA. It is
occasionally used in hospitals where MRSA SSIs are prevalent in the institution (Bratzler et al., 2013).

Vancomycin is a large tricyclic glycopeptide molecule that has historically been the first-line of treatment for MRSA infections. The bactericidal action of vancomycin is a result of the inhibition of bacterial cell wall synthesis through the disruption of peptidoglycan biosynthesis. It is active against most gram-positive organisms including Staphylococcus aureus, Staphylococcus epidermidis (including heterogeneous methicillin-resistant strains), Streptococci, Enterococci, and Clostridium. Vancomycin lacks activity against gram-negative bacteria, fungi or mycobacteria. Similar to cefazolin, vancomycin reaches high concentrations in bone, synovial tissue and muscle within minutes after administration (Meehan, Jamali & Nguyen, 2009).

The recommended dose for vancomycin is calculated according to body weight at 10-15mg/kg for patients with normal renal function (Catanzano, Phillips, Dubrovskaya, Hutzler & Bosco, 2014). Nephro- and ototoxicity occur in <1% of patients. Other adverse effects include reversible neutropenia and drug fever. Daptomycin could be used as an alternative to patients with known anaphylactic or hypersensitivity reactions to vancomycin (Bosco et al., 2015).

2.10 EXCEPTIONS TO THE GUIDELINE RULES

2.10.1 Allergies

Each patient profile should be assessed according to its own merit when selecting a prophylactic antimicrobial. Unfortunately, patients are often allergic to beta-lactam antimicrobials, of which the cephalosporins are usually the drugs of choice used for surgical prophylaxis. In such a scenario, clindamycin, which has sufficient gram-positive cover, may be the first choice to prescribe to patients with a life-threatening risk for anaphylaxis (File, 2013).

2.10.2 Weight

Dosing according to patient weight is a concept that is not always implemented across the board. Obesity influences pharmacokinetic principles of drugs and therefore dose adjustments based on body weight may be required for optimal prevention of SSIs in this higher risk population. The dose of cefazolin should be increased to 3g instead of the normal dose of 2g when a patient weighs more than 120kg (Edmiston, 2009). Cefuroxime is dosed at 1.5g, and a clindamycin dose of 900mg, instead of the standard dose of 600mg,
Chapter 2: Literature Review

is recommended due to superior prophylactic efficacy at the higher dose (Nicolau, Ho & Dakin, 2012). Patient-specific factors should be considered with respect to vancomycin dosage. One report found that 69% of patients who received vancomycin at the standard 1g dose were being under-dosed based on their actual body weight. This suggests that, given the high rates of obesity in arthroplasty patients, a weight-based vancomycin dose of 15mg/kg should be used (Bratzler et al, 2013).

2.10.3 Dual antimicrobials

Another aspect, which often occurs in practice, is the use of more than one drug for ASP. The routine use of dual antimicrobials is generally not supported by literature (Sewick, Makani, Wu, O'Donnell, Baldwin & Lee, 2012).

2.11 DOSING OF ANTIMICROBIAL SURGICAL PROPHYLAXIS

ASP should be administered in an appropriate dose to achieve adequate serum and tissue concentration for the time interval during which the surgical site is open. There are sufficient pharmacokinetic studies available for the surgical antimicrobial prophylactic agents to demonstrate the recommendations for effective exposure and efficacy (Anderson et al, 2015).

2.12 TIMING OF ANTIMICROBIAL SURGICAL PROPHYLAXIS

ASP should be administered 60 minutes prior to surgical incision to optimise adequate drug tissue concentrations at the time of initial incision. Limited studies found a decrease in infection risk with initiation of antimicrobial surgical prophylaxis administration within 30 minutes prior to surgical incision. However, data is inadequate to motivate this method as a routine practice. It is important to note that if the 60-minute ASP window has passed, administration 30 to 60 minutes prior to incision seems to be more effective than administration immediately prior to incision (Anderson et al, 2015).

Contrary to the above-mentioned, the NICE guidelines (2008) recommend consideration of a single-dose of ASP during induction of anaesthesia, unless a tourniquet is used, in which case ASP should be administered earlier.

According to Anderson et al, (2015) errors in the choice of ASP, together with dosing thereof, occurs frequently. A study performed in centres around the USA evaluated 34,133 patients who underwent surgical procedures. Results found that only 56% of patients received ASP within one hour before incision and in a mere 41% of patients ASP was discontinued within 24 hours.
A prospective study (Salkind & Kavitha, 2011), performed on patients who underwent either hysterectomy, hip or knee arthroplasties or cardiac surgery, evaluated the problems related to the timing, duration, and intra-operative redosing of ASP and the risk of SSIs. Patients were assigned to one of four groups for analysis. Group 1 received ASP with a short infusion time within 30 minutes prior to incision, or either vancomycin or a fluoroquinolone within 60 minutes prior to incision. Group 2 received ASP with a short infusion time of 31 to 60 minutes prior to incision or vancomycin or a fluoroquinolone 61 to 120 minutes prior to incision. Group 3 received ASP earlier than recommended, and Group 4 received initial ASP after incision. The study illustrated that a short infusion time of 0-30 minutes prior to incision has the least risk of developing an SSI. Additionally, a study involving total hip arthroplasty reported the lowest risk of an SSI in the case where ASP was administered within one hour prior to incision. This finding was supported by a recent multi-centre study in the USA involving 29 hospitals who also indicated a possible reduced risk of SSI during administration within 30 minutes prior to incision. Significantly lower SSI rates with the administration of ASP just before or at the time of anaesthesia in spinal surgery patients were reported in a meta-analysis of randomised controlled trials (Salkind & Kavitha, 2011).

However, the American Society of Health-System Pharmacists (ASHP) Therapeutic Guidelines (2015), that were jointly developed by the ASHP, the Infectious Diseases Society of America (IDSA), the Surgical Infection Society (SIS), and the Society for Healthcare Epidemiology of America (SHEA), counters the recommendation of the NICE guidelines by confirming that the optimal time for ASP administration is within 60-minutes prior to surgical incision. It further states that it is a more specific time frame than the previously “at induction of anaesthesia” recommendation, except for the fluoroquinolones and vancomycin, where there is consensus on the administration over one to two hours.

As seen in Table 2.2, ASP administration within zero to two hours before the initial incision has shown lower rates of SSIs in comparison with administration outside of this window.
Table 2.2: Antimicrobial surgical prophylaxis and subsequent rates of SSIs

<table>
<thead>
<tr>
<th>TIME OF ADMINISTRATION</th>
<th>DEFINITION</th>
<th>% WITH SSI</th>
<th>ODDS RATIO</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>2-24 hours prior to incision</td>
<td>3.8</td>
<td>4.3</td>
<td>1.8-10.4</td>
</tr>
<tr>
<td>Pre-operative</td>
<td>0-2 hours prior to incision</td>
<td>0.6</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Peri-operative</td>
<td>Within 3 hours after incision</td>
<td>1.4</td>
<td>2.1</td>
<td>0.6-7.4</td>
</tr>
<tr>
<td>Post-operative</td>
<td>More than 3 hours after incision</td>
<td>3.3</td>
<td>5.8</td>
<td>2.4-13.8</td>
</tr>
</tbody>
</table>

Adapted from (Anderson et al, 2015)

2.13 REDOSING OF ANTIMICROBIAL SURGICAL PROPHYLAXIS

During either surgical procedures surpassing two half-lives of the drug or excessive blood loss (more than 1500ml), intra-operative redosing is necessary to ensure adequate serum and tissue concentrations. Redosing may also be necessary in patients with a shortened antimicrobial half-life, such as the case with extensive burn patients. On the contrary, in patients with a prolonged half-life, such as renal failure patients, redosing is not required. The ASP dosing interval is measured from the time of the pre-operative dose (Anderson et al, 2015).

Most study results support a single dose of ASP within one hour prior to incision. The ASP agent should be redosed as frequently as one to two times the half-life of the drug. A retrospective study of cardiac surgical patients undergoing surgeries lasting more than four hours, found a decreased SSI risk from 16 to 7.7% with intra-operative cefazolin redosing. Another study found an increased risk of SSI in colorectal surgical patients with low gentamycin levels at wound closure (Salkind & Kavitha, 2011).

2.14 DURATION OF ANTIMICROBIAL SURGICAL PROPHYLAXIS

The results of a systematic review of randomised trials found no difference in the occurrence of an SSI with single dose compared to multiple-dose regimens given for less or more than 24 hours. Generally, if ASP is necessary past the period of surgery the duration should be less than 24 hours (Anderson et al, 2015). According to recommendations of present guidelines ASP should be discontinued within 24 hours of surgery completion (Salkind & Kavitha, 2011). Repeat antimicrobial dosing following wound...
Chapter 2: Literature Review

closure is generally not warranted, due to the possibility of an increased risk of developing antimicrobial resistance (Anderson et al, 2015). There is also no supporting evidence that ASP administration beyond 48 hours after completion of surgery reduces the risk of SSIs (Salkind & Kavitha, 2011).

However, the Society of Thoracic Surgeons recommends continuing ASP up to a period of 48 hours after the completion of cardiothoracic surgery. This statement is motivated by the effects of a cardiopulmonary bypass on the immune system, as well as antimicrobial pharmacokinetics (Salkind & Kavitha, 2011). In the case of implantation of a pacemaker or defibrillator, the recommendation is discontinuation within 24 hours of surgery.

2.15 INAPPROPRIATE USE OF ANTIMICROBIAL SURGICAL PROPHYLAXIS

In 2003, the CDC, Centres for Medicare and Medicaid Services (CMS), and 10 additional national organisations developed SCIP, incorporating the Surgical Infection Prevention Project measures. These measures were created to ensure evidence-based ASP selection, administration and discontinuation for patients who underwent clean-contaminated surgeries. Decreased SSI incidences following the execution of the SCIP measures were reported. However, a recent survey in the USA established that the recommendations were not routinely followed. A mere 55.7% of surgical patients received ASP within one hour of incision. In only 40.7% of patients ASP was terminated within 24 hours after surgery. Further studies have indicated that in approximately 80-90% of surgical patients who received ASP, 25-50% received an inappropriate regimen, untimely administration of ASP, or incorrect duration thereof (Salkind & Kavitha, 2011).

Another study performed in the orthopaedic surgical population found that in 62% of patients, antimicrobials without a documented infection were continued. A survey carried out on cardiothoracic surgeons in the USA, reported that 68% of the surgeons continued ASP for longer than 48 hours, despite adult literature indicating comparable worth within 24 hours of coverage (Sandora et al, 2016).

The significance of the consequences of both overuse and underuse of ASP cannot be disregarded. Augmented incidence rates of SSIs and increased HAI-related hospital costs can be attributed to the underuse of ASP. Major infection-related complications may increase hospital LOS by up to 20 times and hospitalisation costs by up to five times. Overuse again contributes to the growing emergence of the resistant organisms, which may also increase diagnosis and treatment costs (Sandora et al, 2016).
Additionally, there is increasing evidence which suggests a potential harmful practice in the administration of unwarranted antimicrobials. This practice facilitates the emergence of resistant organisms and exposes patients to avoidable risk of side-effects and antimicrobial associated complications, e.g. Clostridium difficile infection (Sandora et al., 2016).

South African hospitals are battling with the growing emergence of resistant organisms and are facing several challenges. Moreover, 49% of South African surgical patients receive ASP, but only 19% of these patients receive an inappropriate drug. This highlights the importance of monitoring the consumption of antimicrobials in order to ensure appropriate use (Mendelson, Whitelaw, Nicol & Brink, 2012).

2.16 IMPORTANCE OF TIMING OF ADMINISTRATION OF ANTIMICROBIAL SURGICAL PROPHYLAXIS

According to Hawkins (2013) another important factor that determines the efficacy of antimicrobial prophylaxis is the time of administration of the prophylactic drug. Although timing is important, the antimicrobial drug concentration must be above the MIC at the time of incision, when contamination is most likely to occur, in order to be effective (Meehan, Jamali & Nguyen, 2009).

In TRAPE (Trial to Reduce Antimicrobial Prophylaxis Errors), a prospective multi-centred study performed in 2005, it was found that there is a correlation between administration time and the risk for SSIs. Where cephalosporins were administered 30-60 minutes before incision, the risk of infection was significantly lower. Current international guidelines recommend that the administration time should be less than 60 minutes before incision. Some drugs, such as vancomycin and the fluoroquinolones need to be infused over longer periods of time, and therefore should be initiated two hours before incision (Steinberg, Braun, Hellinger, Kusek, Bozikis, Bush, Dellinger, Burk, Simmons & Kritchevsky, 2009). Bosco and colleagues (2015) emphasised the fact that vancomycin should be infused slowly over 60-120 minutes (rather than the typical 30-60 minutes for other antimicrobials) because if vancomycin is administered too rapidly, it may result in the release of histamine, which then causes hypotension and a skin reaction known as ‘Red Man Syndrome’.

When vancomycin is used for prophylaxis, its infusion should begin one to two hours before initiation of the operation (compared to within one hour for cefazolin) to ensure that the entire dose is administered and adequate concentrations are in the tissue prior to the surgical incision. For extended operative times, repeat administration is recommended 6-12 hours after the initial dose (Rybak, Lomaestro & Rotschafer, 2009).
When a tourniquet is used for the procedure, the aim is to infuse the antimicrobial one hour before it is inflated to ensure optimal antimicrobial serum levels at the surgical site before blood flow to the area is limited (Meehan, Jamali & Nguyen, 2009).

### 2.17 INTRA-OPERATIVE RE-DOsing AND DURATION OF PROPHYLAXIS

The preceding outline of the literature stated that in order to prevent surgical SSIs, proper antimicrobial prophylaxis should be prescribed in terms of drug choice; correct dose as per individual, duration not exceeding 24 hours and to ensure the agent is administered at the correct time to achieve adequate serum drug concentrations (Bratzler et al, 2013).

Furthermore, the crude analysis in the TRAPE trial also proved that continuing antimicrobials 24 hours post-operatively is beneficial to reduce the risk of infection, when compared to those who only received a single antimicrobial dose (Steinberg et al, 2009). Many studies have failed to demonstrate any benefit associated with the use of antimicrobials beyond 24 hours in elective, clean-surgical cases. The risks of excessive antimicrobial treatment, including toxicity and the development of antimicrobial-resistant organisms, have led to the recommendation of a 24-hour course of antimicrobials. Limiting unnecessary antimicrobial exposure can minimise adverse effects associated with overuse, such as *Clostridium difficile* infection (Bosco et al, 2015). Duration of antimicrobial prophylaxis plays a vital role in the appropriateness of ASP and also antimicrobial stewardship. According to the current guidelines, it should not exceed 24 hours, irrespective of factors such as drains and catheters (File, 2013).

Other aspects to keep in mind is the re-dosing of the antimicrobial dose when the procedure exceeds four hours, the scenario of excessive blood loss and fluid resuscitation of more than 2000ml (Swoboda, Merz, Kostuik, Trentler & Lipsett, 1996). Surgical procedures lasting longer than two half-lives of the agent qualify for a second dose of antimicrobial to be administered intra-operatively, in order to maintain a sufficient therapeutic concentration (Meehan, Jamali & Nguyen, 2009). Bosco and colleagues (2015) illustrated the concept that cefazolin should be re-dosed every two to five hours during an extended surgical procedure, whereas cefuroxime, clindamycin and vancomycin should be re-dosed every three to four hours, three to six hours and six to 12 hours, respectively.

### 2.18 THE ROLE OF THE PHARMACIST IN EVALUATION AND MONITORING OF THE APPROPRIATENESS OF ANTIMICROBIAL SURGICAL PROPHYLAXIS

Pharmacists can play a vital role in each hospital by managing ASP as part of antimicrobial stewardship. This, however, needs resources such as skills and time, but could make a
huge impact to each patient and also reduce further contribution to AMR. Problem areas are identified in this way and the opportunity to address each entity must be embraced by a multi-disciplinary team in order to establish sustainable solutions (Nicolau, Ho & Dakin, 2012).

2.19 CONCLUSION

There are two main reasons why it is important for pharmacists to become involved in ASP. The first reason is to ensure the individual patient receives the correct treatment for his/her procedure in order to prevent devastating complications due to SSIs. This involves monitoring the drug choice, at the correct time and dose, for a specific time frame. Most prevalent organisms in the hospital should also be considered together with the commonly-found resistant pathogens, e.g. MRSA, in order to adjust guidelines according to the unique sensitivity profile of the hospital. The second reason involves antimicrobial stewardship; where the pharmacist could make an immense difference in terms of correct prescribing and duration of the antimicrobials. This all forms part of the international antimicrobial stewardship drive to limit the use of antimicrobials, and to ensure proper and responsible use thereof when it is indicated (Bond & Raehl, 2007).

2.20 SUMMARY

This chapter explored the literature on ASP, more specifically in knee and hip arthroplasties. Individual entities that need to be monitored in prescribing patterns were described and the opportunity for pharmacists to make sustainable changes as part of a multi-disciplinary team were highlighted. The pharmacist plays an essential role in ensuring that prescribing is in line with international guidelines. The following chapter will focus on the methodology involved in this study.
3.1 INTRODUCTION

This chapter introduces the reader to the methodology of the study by firstly explaining the study design, followed by a description of the study context. The study population and study period are discussed followed by the discussion of the sample selection. A full description of the process of data collection and the data collection instruments used in this study are discussed thereafter. The data collection process is then analysed and discussed. The last two sections of this chapter focus on the reliability and validity of the study and the necessary ethical considerations that were taken into account.

3.2 STUDY DESIGN, SETTING AND POPULATION

This study followed a quantitative retrospective design with a descriptive approach. Patient records were reviewed from the orthopaedic ward at a private hospital located in Johannesburg, South Africa. The hospital consists of 222 beds and is an accredited Level One Trauma Centre with a high number of orthopaedic patients. The hospital's ICUs are open units; therefore any specialist with admission rights can admit a patient and prescribe accordingly. Surgical prophylaxis in this hospital is practised according to non-written guidelines and individual judgement of the surgeon. A nurse in the ward or the anaesthetist in the operating room administers the prophylactic antimicrobial. This study included patients who had knee and hip replacements done at the hospital. Only patients older than 18 years of age, who had received ASP agents before and/or during the procedure, were included in the study. Written consent from all the orthopaedic surgeons were first obtained before the selection of patient files commenced.

Patient files were obtained after a computer selection criterion was applied to identify patients who had knee or hip arthroplasties done during the chosen time frame. A total number of 328 files were obtained from the hospital group’s Head Office, but after evaluation only 250 met the inclusion criteria. Unfortunately, very few files had the time of administration of the ASP agent documented, and therefore this important aspect was unable to be evaluated in this study. Further attention is needed to address the matter of documenting all information properly not only in the ward, but also in theatre.
3.3 STUDY SAMPLING AND PERIOD

The inclusion criteria were applied to all patients who had undergone knee and hip arthroplastic surgical procedures during the period of January 2010 to December 2014. Cases where antimicrobial surgical prophylaxis were indicated, but not used, were excluded, together with the cases where treatment was prescribed before the procedure and not solely used as prophylaxis. Purposive sampling was used to identify patients who received ASP. This was based on the fact that files could be selected with similar diagnostic codes, which made it possible to purposively select subjects/patients who met the criteria (Hungler & Polit, 1997). This method of sample selection is applicable to this research study as only patients who received ASP were included. Upon request, the private hospital group’s Head Office provided a list of all patients who received knee and hip arthroplasties during the selected time period based on the international classification of diseases (ICD-10) diagnostic codes specified. This list then stated each patient’s name and surname as well as their identification and hospital numbers, the type of procedure and the date thereof. As soon as this information became available, the selected files were obtained from the hospital’s archives and taken to site. Due to the fact that these files were medical legal documents, the researcher collected the data on site from each patient’s file. Of all the patients who had undergone knee and hip arthroplasties during the stipulated time frame, the researcher only selected those who received ASP. This was done to ensure that all possible patients were included in this study and confirmed objectivity in the sampling selection.

3.3.1 Inclusion criteria

The following inclusion criteria were applied:

- Knee and hip arthroplastic surgical procedures;
- Adult patients ≥ 18 years of age;
- Patients who received ASP.

3.3.2 Exclusion criteria

The following exclusion criteria were applied:

- Orthopaedic procedures other than knee and hip arthroplasties;
- Treatment prescribed before surgical procedure and not solely used as prophylaxis;
- Patients younger than 18 years of age.
Chapter 3: Method

3.4 DATA COLLECTION PROCESS AND DATA COLLECTION INSTRUMENTS

3.4.1 Data collection process

The proposed study was communicated with the Pharmacy Manager at the hospital, who then discussed it at the Executive Committee meeting to obtain approval for continuation.

A protocol for the proposed study was formulated and sent to Sefako Makgatho University Research Ethics Committee (SMUREC) for ethical approval.

Once ethical approval was obtained from the Sefako Makgatho Health Sciences University (SMUREC/H/54/2015) (see Appendix C), the protocol and the approval letter were sent to the research department at the private hospital group’s Head Office.

The company approved the proposed study on the condition that written consent from the involved doctors was obtained.

The researcher then supplied the private hospital group’s Head Office with a list of diagnostic codes (ICD-10 codes) together with the dates on which data collection was needed with the letter of approval to conduct research at the hospital. A list of patient names, hospital numbers and their identity numbers were then supplied by them for patients who had undergone knee and hip arthroplasties during the period between January 2010 and December 2014. These patient files were then retrieved from the archives and sent to the study site.

Data collection then took place during May 2015 by the researcher at the hospital site. Data were collected on a data collection sheet (DCS) (see Appendix D) as approved by SMUREC in the research protocol. The DCS contained patient demographic information such as the identity number and weight of the patient, any allergies to penicillin, the date of the procedure and the date on which data was collected, as well as the ward to which the patient was admitted. The time that the patient went into theatre and the time he/she came out of theatre were indicated, as well as the specific ICD-10 codes to document the procedure the patient had undergone. Information regarding the drug administered included the generic name of the drug that was used, together with the anatomic therapeutic chemical classification (ATC) code in order to standardise the drug choice internationally for identification purposes. The dose that was given immediately (stat dose) as well as the continued dose of the drug with the total number of doses given was indicated, together with the total daily dose that the patient received. The data sheet made provision for a
“yes/no” box next to each of the variables in order to indicate correct or incorrect choices at each of the individual contributing factors.

Data collected were then interpreted by the researcher in order to make comparisons with international guidelines for decision-making on whether to choose “yes/no” at each contributing factor.

The statistician modified completed DCSs to be interpretable in order to obtain statistical analysis on the Statistical Analysis System (SAS) programming.

Results from the study were obtained after statistical analysis, and problem areas were identified. The Antimicrobial Stewardship Committee chairperson was informed, and necessary actions were taken in order to address areas which were non-compliant to current international guidelines.

After discussions, changes were made in order to rectify incorrect ASP prescribing in the orthopaedic ward. These changes will need further monitoring by the clinical pharmacist in order to ensure sustainability thereof.

The data collection process is outlined in Figure 3.1.
### Chapter 3: Method

#### 3.4.2 Data collection instruments

Retrospective data were collected by means of documentation onto a single page DCS compiled by the researcher on Microsoft® Excel™ (see Appendix D). It was then analysed and made compatible for SAS, release 9.3. All information required according to the ASP.
guidelines (Bratzler et al, 2013) was documented under the appropriate headings. Table 3.1 below provides a summary of the layout of the DCS.

Table 3.1: Overview of the data collection instrument

<table>
<thead>
<tr>
<th>Column</th>
<th>Data collected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Column 1</td>
<td>Patient ID number</td>
</tr>
<tr>
<td>Column 2</td>
<td>Patient age</td>
</tr>
<tr>
<td>Column 3</td>
<td>Patient gender</td>
</tr>
<tr>
<td>Column 4</td>
<td>Patient weight</td>
</tr>
<tr>
<td>Column 5</td>
<td>Allergies/Risk factors</td>
</tr>
<tr>
<td>Column 6</td>
<td>Date of procedure</td>
</tr>
<tr>
<td>Column 7</td>
<td>Procedure</td>
</tr>
<tr>
<td>Column 8</td>
<td>Specific ward patient was admitted to after theatre</td>
</tr>
<tr>
<td>Column 9</td>
<td>Time the patient went in to theatre</td>
</tr>
<tr>
<td>Column 10</td>
<td>Time the patient came out of theatre</td>
</tr>
<tr>
<td>Column 11</td>
<td>Calculated time in theatre</td>
</tr>
<tr>
<td>Column 12</td>
<td>Time of incision</td>
</tr>
<tr>
<td>Column 13</td>
<td>Choice of antimicrobial</td>
</tr>
<tr>
<td>Column 14</td>
<td>Dose of antimicrobial</td>
</tr>
<tr>
<td>Column 15</td>
<td>Dose interval</td>
</tr>
<tr>
<td>Column 16</td>
<td>Total number of doses prescribed</td>
</tr>
<tr>
<td>Column 17</td>
<td>Daily dose</td>
</tr>
<tr>
<td>Column 18</td>
<td>Defined Daily Dose</td>
</tr>
<tr>
<td>Column 19</td>
<td>ATC-code</td>
</tr>
<tr>
<td>Column 20</td>
<td>ICD-10 code</td>
</tr>
</tbody>
</table>

A brief summary of each section of the DCS is discussed below.

Columns 1-5: Demographic information: The patient’s identity number rather than name and surname was collected for identification purposes, to ensure patient confidentiality. Demographic details were recorded for each patient. This information included the age, gender, weight, and allergy status of the patient. This information provided an overview of the population group, as well as necessary information that determined whether appropriate weight-based dosing was prescribed, together with the correct choice of drug in patients with documented penicillin allergies.
Columns 6-12: Theatre information: This included information such as the procedure type, date of the procedure, the ward the patient was admitted to after theatre, the time the patient went in to theatre, the time patient came out of theatre as well as the calculated total time in theatre. Ideally, the time of incision should be documented as this is a critical aspect of ASP, but very few files had it documented. Further improvement is thus required to address this matter. The above-mentioned data were compulsory in order to determine whether the patient required a repeat dose of ASP in prolonged theatre cases. The time of incision is needed to determine whether the antimicrobial dose was given at the appropriate time, i.e. 30-60 minutes prior to the time of incision.

Columns 13-18: Information on the drug prescribed: This section included information on the choice of antimicrobial prescribed as well as the dose and dose interval thereof. The total number of doses prescribed reflects the duration of treatment. The daily dose and defined daily dose (DDD) converted the dose and duration of the drug to universal consumption measures. This information is required to determine appropriate dose and duration of ASP.

Columns 19-20: Universal coding: The ATC code is a universal code given to each drug. This code enables uniformity across the world in terms of the drug used. The ICD-10 code is the procedure diagnostic code, which distinguishes one procedure or diagnosis from another. These codes were provided for each antimicrobial and each theatre procedure for the purposes of standardisation.

3.5 DATA ENTRY AND ANALYSIS

Data collected were captured on a spreadsheet constructed in Microsoft®Excel™, which was used for the analysis. Different sections of the ASP checklist were analysed.

The statistical analysis was considered exploratively. All analysis was performed on SAS, release 9.3, which ran under Microsoft® Windows for a personal computer.

The analysed data was summarised, described and organised in accordance with the objectives of the study.

3.6 RELIABILITY AND VALIDITY

Two aspects were taken into account when considering the validity of a research study, i.e. internal and external validity (Hungler & Polit, 1997). Leedy & Ormrod (2001) defined internal and external validity as follows.
Internal validity refers to the extent to which the research design and data obtained allowed the researcher to draw accurate conclusions about relationships within the data, whilst external validity refers to the extent to which the results obtained during the study could be generalised to other contexts.

When evaluating studies, careful review of study methodology for sources of bias enables the researcher to evaluate internal validity (Panucci & Wilkins, 2011).

Threats to both internal and external validity were taken into account, as shown in Tables 3.2(a) and 3.2(b) below.

**Table 3.2(a): Threats to internal validity**

<table>
<thead>
<tr>
<th>Threat</th>
<th>Definition</th>
<th>Applicability to current study</th>
<th>What was done to minimise the effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implementation bias</td>
<td>Occurs when the protocol designed for the intervention is not followed as initially indicated</td>
<td>Could occur if same procedure is not followed throughout for all the patients involved; e.g. that all patients included had undergone the same surgical procedures</td>
<td>Population group was pre-determined to only knee and hip arthroplasty patients to ensure that a standard procedure was followed</td>
</tr>
<tr>
<td>Attrition</td>
<td>Occurs when participants who have been selected to take part in the study, do not take part at all or fail to take part during every stage of the research process</td>
<td>This can occur when patients selected to participate in the study do not meet all the inclusion criteria, and therefore cannot be included</td>
<td>Patient data of those who did not meet all the inclusion criteria were excluded from the study</td>
</tr>
<tr>
<td>Researcher bias</td>
<td>Occurs when the researcher has a personal bias/preference towards an outcome</td>
<td>The researcher may create a predetermined hypothesis regarding the results that were obtained during the pilot phase</td>
<td>The researcher kept in mind that the outcome of the pilot phase was influenced by several factors such as small sample size</td>
</tr>
<tr>
<td>Effect size</td>
<td>It is the incorrect interpretation of statistical significance and related failure to interpret intervals</td>
<td>P-values can be over or under interpreted if the sample size is not correct</td>
<td>A statistician was consulted to accurately define statistical significance of the data obtained</td>
</tr>
</tbody>
</table>

Adapted from Hungler & Polit, 1997
Table 3.2(b): Threats to external validity

<table>
<thead>
<tr>
<th>Threat</th>
<th>Definition</th>
<th>Applicability to the current study</th>
<th>What will be done to minimise the effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population validity</td>
<td>Refers to the extent to which the findings can be generalised from the sample group towards a larger population</td>
<td>Due to internal factors, the sample may not be representative of the population. Convenience sampling was used. The researcher may incorrectly assume the opposite</td>
<td>Data collected was specific to certain prescribing doctors, and only to patients who received antimicrobial surgical prophylaxis</td>
</tr>
<tr>
<td>Ecological validity</td>
<td>The extent to which the findings from a given study can be generalised across settings, conditions, variables and contexts</td>
<td>The data and final results in this study were dependent on the setting and the location in which it was obtained in</td>
<td>More specific data collection was done; i.e. only in one specific ward, and only patients who either had undergone knee- or hip arthroplasty</td>
</tr>
</tbody>
</table>

Adapted from Hungler & Polit, 1997

Reliability is the extent to which a measuring instrument or tool is able to provide the same results when the entity being measured has not changed (Leedy & Ormrod, 2001). Neuman (2003) stated that the reliability during a research study can be improved with the use of a pilot study. In order to optimise the reliability in this study, a pilot study was conducted which allowed the researcher to become familiar with the current procedures and to identify many of the problem areas before it was used during the research study.

3.7 ETHICAL CONSIDERATIONS

Ethical clearance was obtained from the Sefako Makgatho University Research Ethics Committee (SMUREC/H/54/2015:PG), before the commencement of data collection (Appendix C). The SMUREC letter was submitted to the private hospital’s Head Office in order to obtain approval from them to conduct the research at this hospital.

A letter of intent (Appendix A) was sent to the involved orthopaedic surgeons to obtain signed consent (Appendix B) in order to retrieve and use the retrospective data on antimicrobial surgical prophylaxis from their patients who had undergone knee- or hip arthroplasties during the period of January 2010 to December 2014.
Patients’ privacy was maintained throughout the study and all information was handled confidentially. The patient's identity and hospital numbers were used for identification and no patient names were disclosed throughout the process. None of the information of the prescribing doctors involved was ever made available during the research.

3.8 CONCLUSION

The data collection process plays a vital role in the validity and reliability of results obtained in a study. It is thus of the utmost importance to ensure that the most appropriate methodology is chosen before conducting a study in order to obtain valuable outcomes.

3.9 SUMMARY

Chapter 3 described the methodology that was chosen for this particular study. It included the study design, the study site, the study population, the study period and the sample selection for this study. The data collection process and the analysis thereof were also explained. Reliability and validity of the study, as well as ethical considerations that had to be implemented, were included in this chapter. The following chapter will include an article of the results obtained in this study and the conclusion of these results.
CHAPTER 4
MANUSCRIPT

4.1 INTRODUCTION

The results and discussion are prepared and presented in an article format that will be submitted to the South African Journal of Infectious Diseases, which is a peer reviewed journal. Guidelines for authors are attached (see Appendix E).

ARTICLE

An evaluation of antimicrobial surgical prophylaxis in patients undergoing hip and knee arthroplasty at a private hospital in Gauteng Province South Africa

Verwey A, B.Pharm

Schellack N, PhD (Pharmacy)

Thom L, MSc (Pharmaceutics)

Department of Pharmacy, Sefako Makgatho Health Sciences University

Email: anriverwey@yahoo.com

Abstract

Antimicrobial surgical prophylaxis is an entity that is used daily in surgical units of hospitals across the world, yet correct prescribing and implementation thereof is still a dilemma in many surgical departments. This study included a retrospective review of 250 patient files that underwent either a knee- or hip arthroplasty. It was done as part of antimicrobial stewardship in order to identify problem areas in terms of prescribing of these antimicrobials, as well as with the practicalities with the administration of the drugs. It also elaborates on the individual factors that need to be adhered to in order to ensure appropriate antimicrobial surgical prophylaxis.

Keywords: Antimicrobial surgical prophylaxis adherence, orthopaedic, knee- and hip arthroplasty.
• The authors declare that they do not have any commercial interest or association that may pose a conflict of interest
• No funding was received for this study

The paper has not been presented at a meeting or conference.

Email: anriverwey@yahoo.com

Introduction

Globally, antimicrobial resistance (AMR) threatens not only the fundamentals of modern medicine, but also the sustainability of an effective global health response to infectious disease. Antimicrobials are the most commonly prescribed medicine in both the community and hospital healthcare setting. Thus, throughout health care communities, an increasing desire to reduce the practice pattern variation of antimicrobials has grown. One of these focus areas is antimicrobial surgical prophylaxis (ASP). ASP accounts for 30-50% of all antimicrobial use. ASP serves as a vital quality indicator by demonstrating how appropriately it is used during surgery. The overall goal for ASP is to prevent surgical site infections (SSI’s) by using an antimicrobial that is safe and cost-effective with a spectrum of activity that covers the most common pathogens for the specific surgical procedures. SSI’s accounts for one of the most common complications associated with significant morbidity and mortality of adult but more so paediatric surgery. Despite numerous advances in arthroplasty, infections do still occur. Although uncommon, infection is a devastating complication and often results in revision surgery.

Hospitalised patients who obtain infections whilst being treated for other conditions usually have a considerably longer length of stay in hospital and are also more likely to require further medical attention, which implies an increased health care expenditure. Various measures are used to prevent this devastating complication in arthroplasty patients, including improvement of medical comorbidities, management of the operating room environment, implementing proper skin preparation, and last but not least, selecting and effectively using antimicrobial surgical prophylaxis. Here, we discuss current concepts of antimicrobial prophylaxis in knee- and hip arthroplasty, including the rationale for antimicrobial use, drug selection, proper dosing and duration.

Prophylactic antimicrobials have been described as antimicrobials given for the purpose of preventing infection that does not occur currently, but the risk of post-operative infection is viable. The purpose of antimicrobial surgical prophylaxis is to achieve serum and tissue drug levels that exceed, for the duration of the operation, the minimum inhibitory concentration for the microorganisms likely to be encountered during the procedure. While the benefits of preventing surgical infections are evident, the disadvantages of excess antimicrobial use should not be
Antimicrobial prophylaxis for surgical procedures represents one of the most common reasons for prescribing antimicrobials in hospital. It has been suggested to contribute up to 20-30% of the overall in-hospital antimicrobial consumption. Furthermore, this is critical in light of the fact that extended use of antimicrobial agents endorses the development of bacterial resistance to antimicrobials, being the main reason why responsible use of these agents is of the utmost importance.

Numerous studies have been conducted across the globe describing the appropriateness and shortcomings of prophylactic antimicrobial use in knee- and hip arthroplasty patients. However, limited information is available for the South African setting. Therefore, the purpose of this study was to evaluate the appropriateness of the prescribing of antimicrobial prophylaxis amongst knee- and hip arthroplasty patients at a private hospital in Gauteng, South Africa.

**Methodology**

**Study design, setting and population**

This study followed a quantitative retrospective design with a descriptive approach. Patient records were reviewed from the orthopaedic ward at a private hospital located in Johannesburg, South Africa. The hospital consists of 222 beds and is an accredited Level One Trauma Centre with a high number of orthopaedic patients. Surgical prophylaxis in this hospital is practiced according to non-written guidelines and individual judgement of the surgeon. A nurse in the ward or the anaesthetist in the operating room administers the prophylactic antimicrobial.

**Study sampling and period**

Convenient sampling was used for all patients over the age of 18 years who had undergone knee- and hip arthroplastic surgical procedures during the period of January 2010 to December 2014. Cases where antimicrobial surgical prophylaxis were indicated, but not used, were excluded, together with the cases where treatment was prescribed before the procedure and not solely used as prophylaxis.

**Data assessment protocol**

The appropriateness of the ASP was evaluated with regards to indication, administration and compliance to ASP guidelines. Compliance was defined as; appropriate agent selection, dose, timing of administration, re-dosing and duration of use. All the criteria had to be met, in order for the ASP use to be deemed compliant (Table 1).

**Table 1: Criteria used to access compliance to guidelines**
Criteria | Description
--- | ---
**Drug** | Appropriate ASP agent selected for the surgical procedure performed<sup>a</sup>
**Dose** | Appropriate dose of the selected ASP agent administered based on patient’s body weight (in kg)<sup>a</sup>
**Timing** | ASP administered within 60 minutes prior to incision<sup>b</sup>
**Redosing** | If required, redose at one to two times the half-life of the drug<sup>a</sup>
**Duration** | Within 24 hours post-surgery

ASP= antimicrobial surgical prophylaxis. Adapted from ASHP guidelines (2013), Anderson et al (2015), <sup>a</sup>based on ASP guidelines recommendations, <sup>b</sup>except during the use of fluoroquinolones and vancomycin, when administration over one to two hours is recommended.

In order to define in which surgical procedures ASP is indicated, a comprehensive literature search was conducted, using the following search engines:

- Science Direct, PubMed and Google Scholar.
- Keywords were identified that were used in the internet search related to ASP use in orthopaedics.

Speciality-specific ASP guidelines and consensus statements were cross referenced with the Clinical Practice Guidelines for Antimicrobial prophylaxis in Surgery (ASHP) (2013).

**Study variables**

The following three aspects of antimicrobial prophylaxis were assessed according to the Clinical Practice Guidelines for Antimicrobial prophylaxis in Surgery (ASHP) (2013):

1. **Antimicrobial selection:** In general, narrow-spectrum antimicrobials are used, unless otherwise contraindicated. Cefazolin is the most likely drug of choice, unless in penicillin-allergic patients where clindamycin is preferred. Vancomycin could be used when MRSA (methicillin-resistant *Staphylococcus aureus*) is confirmed or suspected.
2. **Duration**: To prevent the emergence of resistance, it is advised that the antimicrobial should be discontinued within 24 hours post-operatively.

3. **Dosage of antimicrobial**: The prescribed dose of the chosen antimicrobial should be sufficient according to the patient's weight, in order to achieve adequate plasma concentrations prior to incision.

**Data collection and data collection instruments**

Data was collected retrospectively with a paper-based system by the clinical pharmacist researcher from selected patients. Files from 328 patients who had undergone knee- and hip arthroplasties during the study period were selected from the archives and manually evaluated. Out of the 328 reviewed patient files, 250 cases met the inclusion criteria, and formed part of the study. Data was collected using a standardised data collection instrument derived from the published guidelines of the American Society of Health-System Pharmacists (ASHP) and the Infectious Diseases Society of America (IDSA). The review aimed to document patient length of stay, procedure type, time in theatre, choice and dose of the selected antimicrobial, time of first drug administration and duration of antimicrobial prophylaxis. Compliance of prophylactic antimicrobial administration was evaluated based on current guideline recommendations.

**Data analysis**

Data were captured on a Microsoft®Excel™ spreadsheet, which was used for the analysis. Different sections of the antimicrobial surgical prophylaxis criteria were individually analysed. The statistical analysis was considered explorative. All analyses were performed on SAS, Release 9.3, which ran under Microsoft® Windows™ for a personal computer. The analysed data were summarised, described and organised in accordance with the objectives of the study.

**Ethical considerations**

Data collection commenced after formal proposal of the study was submitted and approved by the Sefako Makgatho University Research Ethics Committee (Certificate SMUREC/H/54/2015:PG) as well as the national ethics committee of the hospital group and all surgeons involved. Antimicrobial surgical prophylaxis forms an integral part of antimicrobial stewardship, and therefore the hospital group welcomed the research project.

**Results**
During the five-year study period a total of 328 patients files were reviewed; of which 250 met the inclusion criteria for the study. At this private hospital a global electronic based system (Systems, Applications and Products (SAP) in data processing) is used, but the bulk of the information was obtained from the paper-based patient filing system.

**Patient demographics**

The main characteristics of the patient population (n = 250) are listed in Table 2. More than 52% was female and the average age was 70 (33-93) years. The proportion of knee arthroplasties was 44%, compared to hip arthroplasties 56%. The average patient weight was 84kg, and only 3.6% of patients exceeded 120kg, who required higher than normal doses. The number of patients documented to be allergic to penicillin was 10.8%.

**Table 2: Baseline characteristics described in the study**

<table>
<thead>
<tr>
<th>BASELINE CHARACTERISTICS</th>
<th>N=250</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>AGE IN YEARS, MEAN (SD)</td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>3 1.2</td>
</tr>
<tr>
<td>40-49</td>
<td>11 4.4</td>
</tr>
<tr>
<td>50-59</td>
<td>35 14</td>
</tr>
<tr>
<td>60-69</td>
<td>61 24.4</td>
</tr>
<tr>
<td>70-79</td>
<td>91 36.4</td>
</tr>
<tr>
<td>&gt;80</td>
<td>49 19.6</td>
</tr>
<tr>
<td>GENDER, NUMBER (%)</td>
<td></td>
</tr>
<tr>
<td>MALE</td>
<td>119 47.6</td>
</tr>
<tr>
<td>FEMALE</td>
<td>131 52.4</td>
</tr>
<tr>
<td>ALLERGIES</td>
<td></td>
</tr>
<tr>
<td>PENICILLIN</td>
<td>27 10.8</td>
</tr>
<tr>
<td>NO ALLERGIES</td>
<td>223 89.2</td>
</tr>
<tr>
<td>WEIGHT (KG)</td>
<td></td>
</tr>
<tr>
<td>FEMALE</td>
<td>79.9</td>
</tr>
<tr>
<td>MALE</td>
<td>88.2</td>
</tr>
<tr>
<td>LENGTH OF STAY (DAYS)</td>
<td></td>
</tr>
<tr>
<td>FEMALE</td>
<td>7.29</td>
</tr>
<tr>
<td>MALE</td>
<td>7.43</td>
</tr>
<tr>
<td>SURGICAL PROCEDURE</td>
<td></td>
</tr>
<tr>
<td>HIP ARTHROPLASTY</td>
<td>140 56</td>
</tr>
</tbody>
</table>
Medicines used for surgical antimicrobial prophylaxis

Medicines used in the orthopaedic ward for antimicrobial prophylaxis, the number of study patients per entity as well as the median duration of use are shown in Table 3. Antimicrobial prophylaxis was provided in all the patients, and the most commonly used agents were cefazolin (77.45%), teicoplanin (14.7%) clindamycin (2.6%), ceftriaxone (2%), amoxycillin/clavulanic acid (2%), amikacin (0.65%), ciprofloxacin (0.33%) and linezolid (0.33%). The most frequent antimicrobials used inappropriately were ciprofloxacin, amoxycillin/clavulanic acid, amikacin, linezolid and ceftriaxone. The number of patients who received more than one agent for surgical prophylaxis was 22.4% and 75% of patients allergic to penicillin received the incorrect choice of antimicrobial.

All procedures included in the study received a pre-operative prophylactic antimicrobial but most of them (66.7%) continued with the antimicrobial post-operatively, although 86.6% of the total number of prescriptions was appropriately discontinued within 24 hours. The average duration of the knee arthroplasties was observed to be 2h39 and for hip 2h21, however 3.6% of all cases exceeded a 4-hour duration for which intra-operative re-dosing is advocated. None of the cases that required a second dose intra-operatively received it.

It was found that in 70.7% of prescriptions the correct dose was prescribed according to weight, whereas 29.3% required a higher dose than what was prescribed for patients weighing more than 120kg. For patients who were documented to be allergic to penicillin and ought to receive clindamycin, only 25% received the correct agent but none at the correct dose. The number of penicillin allergic patients who incorrectly received ceftriaxone to replace cefazolin was 21.4%. 
Table 3: Medicines used in the orthopaedic ward for antimicrobial prophylaxis: Number of study patients per entity and median duration of use

<table>
<thead>
<tr>
<th>SYSTEM Antibiotics for systemic use</th>
<th>INTERNATIONAL NONPROPRIETARY NAME (INN)</th>
<th>NUMBER OF PRESCRIPTIONS (N=306)</th>
<th>MEAN NUMBER OF DOSES (std deviation)</th>
<th>TDD (mg) (mean;SD)</th>
<th>DDD (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>J01C Beta-lactam + enzyme inhibitor</td>
<td>amoxycillin/clavulanic acid</td>
<td>6</td>
<td>7.33 (7.51)</td>
<td>8800 (9006)</td>
<td>3000</td>
</tr>
<tr>
<td>J01D Other Beta-lactam Ceftriaxone</td>
<td>Ceftriaxone</td>
<td>6</td>
<td>2 (0*)</td>
<td>2666 (1032)</td>
<td>2000</td>
</tr>
<tr>
<td>J01B Cefazolin</td>
<td></td>
<td>237</td>
<td>3.22 (2.05)</td>
<td>3505 (2143)</td>
<td>3000</td>
</tr>
<tr>
<td>J01M Quinolones</td>
<td>Ciprofloxacin</td>
<td>1</td>
<td>13 (n/a*)</td>
<td>10400 (n/a)</td>
<td>500</td>
</tr>
<tr>
<td>J01F Lincosamides</td>
<td>Clindamycin</td>
<td>8</td>
<td>3.38 (2.72)</td>
<td>2025 (1633)</td>
<td>1800</td>
</tr>
<tr>
<td>J01X Glycopeptides</td>
<td>Teicoplanin</td>
<td>45</td>
<td>2 (1.41)</td>
<td>800 (565)</td>
<td>400</td>
</tr>
<tr>
<td>J01G Aminoglycosides</td>
<td>Amikacin</td>
<td>2</td>
<td>1 (0*)</td>
<td>750 (353)</td>
<td>1000</td>
</tr>
<tr>
<td>J01X Oxazolidinones</td>
<td>Linezolid</td>
<td>1</td>
<td>1 (n/a*)</td>
<td>600 (n/a)</td>
<td>1200</td>
</tr>
</tbody>
</table>

- Standard deviation = 0 because all doses were the same
- n/a = Standard deviation not calculable in the case of only 1 prescription
Compliance to guidelines

Table 4 describes the compliance with antimicrobial surgical prophylaxis in the orthopaedic ward using multivariate analysis. Of all the studies and observed procedures, only 20.3% for hip- and 21.3% for knee arthroplasties were compliant in all the different aspects regarding antimicrobial surgical prophylaxis in comparison with the stated guidelines (antimicrobial selection, dose and duration).

Table 4: Compliance with antimicrobial surgical prophylaxis in the orthopaedic ward using multivariate analysis

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>ALL PRESCRIPTIONS (n=306)</th>
<th>HIP ARTHROPLASTY (n=164)</th>
<th>KNEE ARTHROPLASTY (n=142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHERENCE TO CORRECT DOSE</td>
<td>81</td>
<td>81</td>
<td>0.2069</td>
</tr>
<tr>
<td>ADHERENCE TO CORRECT AB SELECTION</td>
<td>131</td>
<td>103</td>
<td>0.1392</td>
</tr>
<tr>
<td>ADHERENCE IN DURATION OF ANTIMICROBIAL USE</td>
<td>138</td>
<td>127</td>
<td>0.1276</td>
</tr>
<tr>
<td>ADHERENCE TO CORRECT DOSING INTERVAL</td>
<td>99</td>
<td>90</td>
<td>0.7666</td>
</tr>
<tr>
<td>ADHERENCE TO OVERALL</td>
<td>33</td>
<td>30</td>
<td>0.2499</td>
</tr>
</tbody>
</table>
Discussion

Retrospectively, this study aimed to access compliance to current evidence based ASP guidelines\textsuperscript{13} for adult patients over the age of 18 who underwent knee- or hip arthroplasty. To our knowledge, this was the first study of its kind performed in this adult population in a private hospital in South Africa.

More than 52% was female and the average age was 70 (33-93) years. The proportion of knee arthroplasties was 44%, compared to hip arthroplasties 56%. The average patient weight was 84kg, and only 3.6% of patients exceeded 120kg, who required higher than normal doses. The number of patients documented to be allergic to penicillin was 10.8%. The average length of stay for female patients was 7.29 days, and for male 7.43 days including both knee- and hip arthroplasties. The overall adherence to ASP between knee- and hip arthroplasty patients did not significantly differ in this setting.

The most important finding in this study is the absence of any written standardised guideline for antimicrobial surgical prophylaxis in the hospital. This could explain the very low adherence to published international guidelines.\textsuperscript{12}

Poor adherence to ASP is a universal concern. Even in the USA where adhering to surgical prophylaxis guidelines is an expected practice, a study that involved different disciplines demonstrated that in only 40.7% of patients, antimicrobial prophylaxis were discontinued within 24 hours.\textsuperscript{13}

Time of antimicrobial administration before surgery is a very important aspect. The highest risk for micro-organisms to enter the sterile site is at the time of incision and therefor the antimicrobial tissue concentration should be at inhibitory level at that time for optimal infection prevention.\textsuperscript{15} Unfortunately, due to the retrospective nature of this study, this data was not documented and could not be evaluated. It is however expected to be an area that needs to be addressed.

Adherence to the antimicrobial selection for prophylaxis (76.4%), together with the prescribed stat dose of the antimicrobial (52.9%) and subsequent dose (10.4%), as well as the duration thereof post-operative (86.9%), deviated significantly from published international guidelines.

The infection rates within a one-year period post-operatively did not significantly differ when vancomycin was used in combination with cefazolin for ASP, compared to cefazolin monotherapy in a trial where 1828 knee- and hip arthroplasty patients were followed.\textsuperscript{16} The high number of patients (22.4%) in this study for whom more than one prophylactic agent were prescribed is thus concerning.
The number of teicoplanin prescriptions (14.7%) needs further investigation in terms of appropriateness, as cefazolin still remains the first choice agent unless MRSA is a viable risk. This study did not investigate the incidence of MRSA in the hospital.

Although some aspects are concerning, these findings also collaborate with other studies such as the Jordanian study which found that neither antimicrobial choice (1.7%) nor duration (39.4%) were appropriate.\textsuperscript{14} Contrary to this, a study from the USA where protocols are usually followed, showed superb compliance (92.6%) in antimicrobial selection.\textsuperscript{15} Due to the lack of substantial guidelines, personal judgements of treating physicians may explain the tendency to use broad spectrum or combination antimicrobials and to escalate therapy beyond 24 hours.

**Limitations**

Due to a small sample size and the study being limited to only one surgical specialty, consideration should be given before the study results can be extrapolated further to ASP practices across South Africa. This study did not investigate the cause and relationship of the results. Additionally, hospital charts were used for data collection, thus precision would depend on the accuracy of the hospital files as well as the data collection process. Further studies are needed in which these limitations are taken into consideration.

**Conclusion**

The breaches in adherence to antimicrobial surgical prophylaxis in the orthopaedic ward could possibly be explained by a lack of guidelines for peri-operative prophylaxis. The choice of antimicrobial and overall duration thereof scored very high numbers for overall compliance, although subsequent doses are prescribed incorrectly in most of the cases. Extended spectrum antimicrobials are sometimes used, but the overall quantity of teicoplanin prescriptions are concerning. Both insufficient documentation of incision time and the time of drug administration should be addressed in order to do comprehensive antimicrobial surgical prophylaxis evaluation. Extended awareness amongst the multi-disciplinary team seems to be an important aspect to be emphasized, as well as the adoption of appropriate surgical prophylaxis guidelines in the unit. The importance of appropriate ASP use cannot be overstressed as it contributes to AMR and is associated with a significant decrease in SSI associated morbidity and mortality.

**References**


5. Anderson DJ, Sexton DJ. Surgical antimicrobial prophylaxis: is the glass half empty or more than 99% full? Infect Control Hosp Epidemiol 2014;35: 240-2.


**Funding:** None to declare.

**Transparency declarations:** None to declare.
CHAPTER 5
LIMITATIONS, RECOMMENDATIONS AND CONCLUSION

5.1 INTRODUCTION

For the duration of this study a few limitations were encountered, which are discussed in Section 5.3. These are addressed as limitations with regard to the process of obtaining retrospective data, as well as the limitations with regard to the research. Section 5.4 focuses on recommendations for the improvement of compliance to ASP, and recommendations for future research. The chapter ends with a conclusion.

5.2 SUMMARY OF RESULTS

ASP was provided in all the patients, of which the most commonly used agents were cefazolin (77.45%), teicoplanin (14.7%), clindamycin (2.6%), ceftriaxone (2%), amoxicillin/clavulanic acid (2%), amikacin (0.65%), ciprofloxacin (0.33%) and linezolid (0.33%). Assessed in accordance with international guidelines, the antimicrobials most frequently used inappropriately were ciprofloxacin, amoxicillin/clavulanic acid, amikacin, linezolid and ceftriaxone. Those patients who received more than one agent for surgical prophylaxis comprised 22.4%. All procedures included in the study received a pre-operative prophylactic antimicrobial, and in most cases (66.7%) antimicrobial therapy was continued post-operatively. The number of prescriptions which were appropriately discontinued within 24 hours following the initial prophylactic dose comprised 86.6%. It was found that in 70.7% of prescriptions, the correct dose was prescribed according to weight, whereas 29.3% actually required a higher dose than what was prescribed. Of patients who were documented to be allergic to penicillin and who should have received clindamycin, only 25% received the correct agent, yet none at the correct dose. The number of penicillin allergic patients who received ceftriaxone rather than cefazolin comprised 21.4%. Of all the studies and observed procedures, only 20.3% for hip and 21.3% for knee arthroplasties were compliant in all the different aspects regarding ASP in comparison with the stated guidelines (evaluating antimicrobial selection, dose and duration). Adherence to the antimicrobial selection for prophylaxis (76.4%), prescribed initial dose of the antimicrobial (52.9%), subsequent dose (10.4%), as well as the post-operative duration (86.9%) all deviated significantly from published international guidelines. The quantity of teicoplanin prescriptions (14.7%) needs further investigation in terms of appropriateness.
5.3 LIMITATIONS

5.3.1 Data collection process

5.3.1.1 Obtaining retrospective data from patient files

As this study was done retrospectively, a large number of selected patient files contained inadequate information for the study. Many of the selected patient files did not meet the inclusion criteria for the study and others had no incision time documented. Because the latter was a critical point in ensuring appropriate ASP, which indicated a significant area that needed intervention, the data was collected for both the patients for whom the incision time was indicated, as well as those who had no indication thereof.

5.3.1.2 Compliance from nursing staff to document information appropriately

Due to the fact that nursing staff were responsible for recording information on the peri-operative document in theatre, compliance to do so effectively was an enormous challenge faced by the researcher. The main problem was that the time of incision was only documented in very few patient files, and this information could not be obtained elsewhere in a retrospective study such as this. The incision time is a critical part of the data collection due to the fact that it is needed in order to determine whether the ASP drug was given at an appropriate time in order to reach maximum plasma concentration at the time of incision, and therefore to optimally prevent an SSI. Patient demographic information, as well as weight, allergies of the patient, date of procedure and medication information were not always properly recorded.

5.3.1.3 Pre-selected inclusion criteria

The inclusion criteria selected for this study to only evaluate knee and hip arthroplasty patients resulted in a smaller number of cases in the pre-selected period as what was initially anticipated. A longer study period was then selected to ensure that a substantial number of patient files were included in the research.

5.3.1.4 Peri-operative document insufficient

Due to the retrospective nature of this study, no changes or improvement to the peri-operative document could be made that would positively influence data collection for this study. A colossal challenge to obtain the incision time for the surgical procedure emerged primarily because the peri-operative document did not make provision for this to be recorded. This aspect has only recently been addressed by the company's Head Office,
resulting in new peri-operative documents being designed to make provision for the recording of incision time. Training was initiated after the implementation of the new document in theatre.

5.3.1.5  Distinguishing between antimicrobial prophylaxis and treatment

Another challenge faced by the researcher was to distinguish between whether or not the prescribed antimicrobial's purpose was solely to be used as treatment, and whether it was indicated as prophylaxis, but continued for an unnecessarily long duration and therefore classified as inappropriate ASP. In such a scenario, the researcher had to decide whether the prescribed drug was commonly used as treatment, and not truly indicated as prophylaxis, and in what point in time therapy was initiated and terminated. The choice of agent and the duration thereof was used in order to distinguish between prophylaxis and treatment, e.g., whether amoxycillin/clavulanic acid was prescribed and initiated long before and continued after the theatre procedure, and whether it was granted as treatment and not prophylaxis. But if cefazolin, a drug commonly used for prophylaxis, was used for a prolonged period of time, it was granted as inappropriate prophylactic duration.

5.3.2  Research

5.3.2.1  Small sample size

Due to the small sample size no statistical significant correlations could be made.

5.4  RECOMMENDATIONS

5.4.1  Data collection process

5.4.1.1  Change of the peri-operative document

The peri-operative document used in theatre did not make provision for the recording of the incision time, which is an extremely important aspect in ASP. Training was arranged for the involved theatre staff to document incision time elsewhere on the document, but this failed to deliver any consistent change. The company's national antimicrobial stewardship team then identified the problem and recent changes were made (recording of incision time as well as time of antimicrobial administration) to the document in order to obtain all the necessary information needed for monitoring ASP. Training and education of staff will be needed in all the wards and theatres as soon as the new document is in place, in order to ensure proper compliance in completion of the form.
5.4.1.2 Training of theatre staff

Training sessions will be arranged whereby nursing staff in each surgical ward in the hospital will be trained in the proper documentation of information. This will need to be an on-going process, as nursing staff who work shifts and personnel who are contracted out by agencies and often work temporary periods, create a challenge in ensuring consistency. These particular staff needs to be trained in the procedure to be followed in terms of the documentation of ASP and have an understanding of the importance of ASP to be able to administer prophylactic antimicrobial at the appropriate time.

5.4.1.3 Consultation with doctors

After completion of the data collection for this research, many problem areas arose that were not previously identified in terms of incorrect prescribing patterns by the surgeons. Inappropriate drugs were prescribed for the procedure, at ineffective doses and for prolonged durations. Individual doctor protocols containing incorrect information were in place as guidance for nursing staff. After a brainstorming session with the Antimicrobial Stewardship Committee of the hospital, a meeting was scheduled with the orthopaedic surgeons to discuss the above-mentioned issues. Data for this hospital were presented, as well as evidence-based guidelines and well-researched publications. Most of the attending doctors responded positively to the aspects proposed, which resulted in changes in prescribing patterns.

5.4.1.4 Availability of antimicrobials as ward stock

One of the concerns that emerged from this research was the challenge that nursing staff faced regarding the administration of the ASP agent at the appropriate time. The process to obtain stock from pharmacy was often the reason for late administration, or even omitting the dose that should have been given 30 minutes prior to theatre. This problem was addressed by ensuring availability of ward stock of the identified agents and education sessions with nursing staff and unit managers was arranged in order to implement changes.

5.4.1.5 Implementation of regular monitoring of antimicrobial surgical prophylaxis

The growing need to implement and expand antimicrobial stewardship in every hospital has increased the focus on ASP. Therefore, the surgical wards have been divided amongst the pharmacists for regular monitoring purposes. By regularly collecting data on ASP, problem areas can be identified and addressed as they occur.
5.4.1.6 Awareness campaigns

The necessity to create awareness regarding ASP, as part of antimicrobial stewardship, could no longer be ignored. An awareness campaign was therefore initiated in order to inform nursing staff about the importance of antimicrobial stewardship as a whole, together with the importance of ASP in terms of preventing SSIs when prescribed and administered correctly.

A meeting with the orthopaedic surgeons was scheduled with regard to problem areas that were detected during the collection of retrospective data. Evidence obtained from guidelines was then presented in order to address the above-mentioned challenges.

5.4.2 Regarding the research

5.4.2.1 Small sample size

In future, a longitudinal sampling method at multiple sites may increase the possibility for statistical significant correlations.

5.5 CONCLUSION TO THE STUDY

The overall aim of the study was to gather baseline data regarding ASP for knee and hip arthroplasties in the orthopaedic ward. The retrospective data were then evaluated with current guidelines in order to determine problem areas, as well as to seek resolutions for the identified challenges.

The following objectives were met for this study: The type of antimicrobials prescribed for ASP were listed and evaluated in correlation with international guidelines. The appropriateness in terms of indication, dose, duration and timing was determined according to compliance with the guidelines. Cost implications of incorrect prescribing were calculated and compared with correct prophylactic prescriptions. With regard to the above-mentioned criteria, areas for improvement could then be identified and focused on to provide better outcomes.

The effect of incorrect ASP on antimicrobial stewardship has been emphasised in this study, which in turn highlights the need for a clinical pharmacist in the multi-disciplinary team to participate in evaluation and monitoring of patients for whom ASP is prescribed. The clinical pharmacist has an important role to play in evaluating the prescribed drug of choice, dose and duration together with any possible contraindications for the specific patient. It was
evident from this study that continuous nursing education regarding this topic is needed from time to time throughout the hospital in order to implement a sustainable system.

A longitudinal study with a larger sample size is recommended for a baseline assessment in a chosen surgical ward in the hospital. A follow-up study, which includes the impact of a clinical pharmacist on ASP should then be done in order to determine the holistic outcome each pharmacist could have on appropriate ASP as part of practising good antimicrobial stewardship.
REFERENCES


Dear Orthopaedic Surgeon (Union and Clinton Hospitals)  

Re: Master’s degree on Antimicrobial surgical prophylaxis in the orthopaedic ward at a private hospital in Alberton, Gauteng Province.

I, Anri Verwey am a post graduate student completing my Master’s degree in Clinical Pharmacy.

A research component needs to be completed, which includes a retrospective study on the appropriateness of Antimicrobial Surgical Prophylaxis in the Orthopaedic ward.

All information obtained will be confidential, and only be used for research purposes. No patient information will be made available what so ever.

Information collected mainly constitutes of type of prophylactic antimicrobial, weight of the patient, dose, duration and time of administration.
This information is currently collected for Netcare’s antibiotic stewardship program.

Please authorize via email that I may include this data in my research project.

Yours sincerely
Anri Verwey (B.Pharm; NWU Potch)  
Clinical Pharmacist  
Netcare Union Hospital  
anriverwey@netcare.co.za
Appendix B: Permission Letter from Orthopaedic Surgeons

Dear Anri Verwey

2015.04.28

Re: Research for Master’s degree on Antimicrobial Surgical Prophylaxis in the Orthopaedic ward at a private hospital in Alberton, Gauteng Province.

I, Dr., am aware of Ms Anri Verwey’s research regarding Antimicrobial Surgical Prophylaxis and has no objections to the data being collected regarding my patients whom I treated.

Please kindly return your approved Consent-Form to anri.verwey@netcare.co.za
Your assistance is appreciated.

Regards,
Ms Anri Verwey
B.Pharm (NWU Potch)

Name of Orthopaedic Surgeon _______________________________ Date ____________________________
Appendix C: SMUREC Clearance Certificate

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

Motlalegi Street, Ga-Rankuwa 0208
Tel: (012) 521 5617/33995 | fax: (012) 521 3749
Email: brato.phili@smu.ac.za
P.O. Box 103 Medunsa 0204

APPROVAL NOTICE - NEW APPLICATION

05 March 2015

Ms A Verwey
Department of Pharmacy
P.O. Box 218
MEDUNSA, 0204

MEETING: 02/2015

SMUREC Ethics Reference Number: SMUREC/05/4/2015 - PG

The New Application received on 18 February 2015, was reviewed by members of Sefako Makgatho University Research Ethics Committee on 05 March 2015 and was approved on 05 March 2015.

TITLE: Anti-infectivel surgical prophylaxis in the orthopedic ward of a private hospital in Alberton, Gauteng Province

Researcher: Ms A Verwey
Supervisor: Dr N Schallack
Co-supervisor: Dr L Thom
Department: Pharmacy
Hospital Superintendent: Dr. O. Abraham (Hospital Manager)
Other Involved HOD: E. van der Merwe (Pharmacy Manager)
School: Health Care Sciences
Degree: MSc Mod Clinical Pharmacy

Please note the following information about your approved research protocol:

Protocol Approval Period: 05 March 2015 – 05 March 2016

Please remember to use your protocol number (SMUREC/05/4/2015 - 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 that a template of the progress report is available 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 Organization (ICRG/0063419), Institutional Review Board (RB00201122), Federal Wide Assurance (FWA00003419)

Expiry date: 11 October 2015 and IHREC No: REC 219408-003

Sincerely,

[Signature]

PROF DA COLUMBAU
CHAIRPERSON, SMUREC

Members of the Interim Council:
Prof O Shisana (Chairperson), Dr SA Michau, Mrs P Stok, Dr N Sanielska, Prof AM Segone, Dr E van Staden
## Appendix D: Data Collection Sheet

### Antimicrobial Prophylaxis Assessment

<table>
<thead>
<tr>
<th>Patient ID number</th>
<th>Patient age</th>
<th>Patient gender</th>
<th>Affiliated Risk factor</th>
<th>Date of procedure</th>
<th>Procedures</th>
<th>Specific agent used</th>
<th>Time the patient went in Theatre</th>
<th>Time the patient came out of Theatre</th>
<th>Scheduled time in Theatre</th>
<th>Time of isolation</th>
</tr>
</thead>
</table>
Appendix E: Guidelines for Authors for the South African Journal for Infectious Diseases

Author Guidelines

Manuscripts submitted to the SAJID must be in the form of Research Articles, Brief Reports, Clinical Case Studies, Correspondence, Reviews, State-of-the-Art Articles, Commentaries and Opinion Papers, Editorials or Supplement Articles. The Journal welcomes the publication of Guidelines, Conference Proceedings Newsletters or Press Releases, and Book Reviews. Articles, Brief reports and Reviews are peer reviewed; other categories are reviewed by the Editors. Commentaries and Editorials are generally invited contributions, indicating the authors’ identity, while manuscripts in the form of Reviews, and State-of-the-Art Articles may also be requested by the Editors.

All manuscripts must have conflict of interest and funding statements. When authors submit a manuscript, whether an article or a letter, they are responsible for disclosing all financial and personal relationships that might bias their work. To prevent ambiguity, authors must state explicitly whether potential conflicts do or do not exist. Authors should do so in the manuscript on a conflict-of-interest notification page that follows the title page.

Manuscripts describing research in human subjects or animals must indicate ethics clearance from appropriate research review committees. When reporting experiments on human subjects, authors should indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.

Articles describe original investigations at an acceptable degree of completion, constituting an advance in the field. Articles must not exceed 3500 words of text, without counting the abstract, references or legends, and illustrations and tables must be limited to the minimum necessary for clear and concise presentation. The abstract must either be structured, using Background, Methods, Results, and Conclusions as headings and comprising no more than 250 words, or unstructured with a 200 word limit. Articles are limited to a maximum of 7 insets (tables and figures combined) and 50 references.

Brief Reports present complete studies that are narrower in scope than those described in Articles or that present new developments. Manuscripts that are descriptive or primarily methodological in nature, or that describe in vitro chemotherapeutic studies should, in
general, be submitted as Brief Reports. Brief Reports include an abstract (no more than 100 words) and are limited to a total of no more than 2000 words of text, a total of 2 inserts (tables or figures), and 15 references.

Correspondence (letters) must be submitted in reference to a previous publication in SAJID (within the previous 12 months), or relate to a topical matter in line with the interests of FIDSSA, PHASA or their affiliated societies. Please prepare the letter in manuscript format, including a title page. The letter must not exceed 750 words of text, 1 insert (table or figure) and 10 references.

Commentaries and Editorials are generally invited by the Editor and are overviews of articles in SAJID, or of other research in epidemiology or infectious diseases, or matters relating to public health and other issues of special interest to FIDSSA, PHASA or their associated societies. Unsolicited commentaries are also considered.

Reviews and State-of-the-Art Articles that are research oriented or fall within the fields of interests of FIDSSA, PHASA or any of their affiliated societies will be considered for publication by SAJID. Prospective authors of such manuscripts are advised to communicate with the Editor in advance to ensure that a specific contribution is deemed appropriate and timely. Manuscripts of Reviews and State-of-the-Art Articles will be peer-reviewed.

Reviewers

The Journal would encourage authors to supply the names of at least 2 potential reviewers for their manuscript, as well as to indicate any reviewers they would feel may have a potential conflict of interest with regard to their submission.

Supplements

Requirements for supplement manuscripts generally follow those for SAJID manuscripts, including conflict of interest and funding statements. Inquiries relating to suitability of topic, programme organisation, production and costs should be made to the Editor.

Evaluation of manuscripts

Review procedure. The Editor-in-Chief and Emeritus Editor screen all unsolicited manuscript submissions and some of these are rejected without further review. All other manuscripts are sent to a minimum of two outside experts for review. After receipt of the reviewers’ reports, the Editor-in-Chief and the Emeritus Editor with administrative assistance of the Journal Secretary discuss the merits of the manuscripts and the Editor-
in-Chief makes the final decision to accept, reject, or request revision of the manuscript. A request for revision does not guarantee ultimate acceptance of the revised manuscript.

Related manuscripts. If there appears to be significant overlap between a manuscript submitted to SAJID and another submitted manuscript by the same authors to SAJID or another journal, the editors will take the matter up with the corresponding author, and based on the response, take appropriate action (ask for modification, or reject with detailed explanation). Further action may include informing the appropriate authority in the authors’ resident institution and if overlapping is discovered after publication in SAJID, publishing an appropriate announcement to that effect in the journal.

DOCUMENT REQUIREMENTS

Checklist

The following are required for your manuscript to be processed:

Covering letter

Word count limits

Conflict of interest statement

Funding statement

List of potential reviewers

Covering Letter

All manuscripts submitted to SAJID must be accompanied by a letter declaring that the manuscript has not been submitted or accepted for publication elsewhere. This letter must confirm and declare that all authors have seen and approved the content and have contributed significantly to the work. Authors should suggest potential unbiased reviewers who are qualified to review their manuscript. A covering letter must also accompany a revised submission and must address issues raised in the review process.

Manuscript Preparation

The SAJID complies with the Uniform Requirements for Manuscripts Submitted to Biomedical Journal Journals (Ann Intern Med 2000; 133:229-231 [editorial]; http://www.icmje.org, full text). Text, tables, references, and legends must be double-
Appendices

spaced. Italics should be used for genus and species names and for genes but not for in vivo, in vitro, in situ, et al., or other Latin-derived expressions. For layout of manuscript and appropriate style see a recent issue of SAJID.

Title page. On the title page, please supply a running head of not more than 40 characters and spaces, a title of not more than 160 characters and spaces, the names and affiliations of all the authors, and word counts of the abstract and text. Each author’s first name, subsequent initials and surname must be used.

Footnote page. Footnotes must include: Statement that authors either have or have not a commercial or other association that might pose a conflict of interest (e.g. pharmaceutical stock ownership, consultancy, advisory board membership, relevant patents, or research funding)

Statement naming sources of financial support (including grant numbers)Name, date (month and year), and location (city, and country if not South Africa) of a meeting at which all or part of the information has been presented (include an abstract number, if availableName, address, telephone and fax numbers, and e-mail address of the person to whom correspondence should be addressedCurrent affiliations and addresses for authors whose affiliations have changed since completion of the study

Abstract. The abstract for an Article may be structured with the headings Background, Methods, Results, and Conclusions (250-word limit) or unstructured (200-word limit). Abstracts of Brief Reports should be no more than 100 words. Whether structured or unstructured, the abstract must state the purpose of the research, the methods used, the results, and the conclusions. Do not cite references in the abstract. Include up to 10 key words, separate from the abstract. Please remember that the abstract is particularly useful for literature retrieval purposes.

Text. The text of Articles must be no longer than 3500 words, and that of Brief Reports no longer than 2000 words. The Methods section must include a statement that informed consent was obtained from patients or their parents or guardians, and human experimentation guidelines of the National Department of Health (http://www.doh.gov.za) or the South African Medical Research Council (MRC; http://www.sahealthinfo.org/ethics/index.htm) and /or those of the authors’ institution(s) were followed in the conduct of clinical research or that animal experimentation guidelines (see MRC website above) were followed in animal studies.

References
Appendices

Articles are generally limited to 50 references, Brief Reports to 15 references. Only works that have been published or accepted for publication can be included in the reference list. Unpublished observations by the authors (authors’ unpublished data) personal communications (SP Stanley, personal communication), and manuscripts submitted for publication (J Odendaal, S Coovadia and J Radebe, submitted) should be mentioned parenthetically in the text Please number references in order of appearance; those cited only or first in tables or figures are numbered according to the order in which the table or figure is cited in the text. Example: If table 3 is cited in the text after reference 20, a new reference cited in table 3 will be reference 21.

References must follow the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org, full text). Provide all authors’ (or editors’) names when there are fewer than 7; for 7 or more, list the first 3 and add “et al.” Titles of journals not listed in Index Medicus should be spelt out in full. Reference to a doctoral thesis or Master’s dissertation should include the author, title, institution, location, year and publication information, if published. For online resources, include a URL and date accessed. Accuracy of references is the responsibility of the authors.

Examples of the proper format are as follows:


Acknowledgment(s). The page preceding the references may include a statement thanking those who assisted substantially with work relevant to the study.

Statistical analysis. The statistical analyses used should be identified both in the text and in all tables and figures where the results of statistical comparison are shown.

Units of measure. All Data should be expressed in metric units; use of SI units is encouraged. Use °C for temperature.

Tables and figures. Articles are limited to a maximum of seven inserts (tables and figures combined), Brief Reports to a maximum of two inserts. Data should not be repeated in both a table and a figure. Abbreviations and acronyms used in tables and figures must be explained in the table footnotes and figure legends, even if already defined in the text.

Tables should be numbered in the order of mention in the text. Tables should be typed double-spaced throughout, with no vertical or internal rules. Footnotes and accompanying explanatory material should be kept to a minimum. Footnotes should be placed below the table and designated by superscript lowercase letters (listed in order of location when the table is read horizontally). Each column must have an appropriate heading describing the data in the column below, and units of measure must be clearly indicated. For further instructions on the preparation of tables in Word, consult the Special Instructions for Tables.

Figures should be also numbered in the order of mention in the text and should appear at the end of the manuscript and references. Your figures should be prepared in accordance with the Guidelines for Submission of Artwork. Letters, numbers, and symbols should be clear and of sufficient size to be legible when the figures are reduced. Photomicrographs should have internal scale markers. Figures reproduced from other publications must be accompanied by permission from the copyright holder. If the manuscript is accepted, the author will be required to send one complete set of glossy, hard-copy figures.

Figure legends should be double-spaced and appear on a separate page preceding the figures. Any abbreviations or symbols used but not defined in the figure itself must be defined in the legend.


For commercially obtained products mentioned in the text, list the full names of manufacturers. Generic names of drugs and other chemical compounds should be used.
Nomenclature. SAJID recommends the latest widely accepted nomenclature, as set out in documents prepared by recognised international agencies e.g. the International Journal of Systematic and Evolutionary Microbiology, Bergey’s Manual of Determinative Bacteriology (9th ed., revised, Williams& Wilkins, 1993), Virus Taxonomy – The Classification and Nomenclature of Viruses: Sixth Report of the International Committee on Taxonomy of Viruses (Springer-Verlag, 1995). The latter document also supplies standard abbreviations for virus species.

Clinical trials registration. All clinical trials must be registered in a registry that is electronically accessible to the public, free of charge. Registration should occur before patient enrolment and the registry’s URL and the trial’s registration number must be supplied at the end of the manuscript’s abstract. For information on acceptable registries, consult the ICMJE Web site, http://www.icmje.org. The National Library of Medicine’s registry which is free and open to all investigators, generally meets with the requirements of journals for the publication of clinical trials.

MANUSCRIPT SUBMISSION

Procedure

Authors are advised to retain a copy of submitted manuscripts, including tables, figures and photomicrographs. The journal is not responsible for manuscripts lost or damaged.

All manuscripts must be submitted online at www.sajei.co.za. Register as an author, login in and click on CLICK HERE TO FOLLOW THE FIVE STEP SUBMISSION PROCESS. The covering letter must please be submitted as a supplementary file. For assistance to upload your manuscript or further instructions please contact Ms Robyn Marais at toc@sajei.co.za.

Editorial Committee

Editor-in-Chief
Professor Charles Feldman
E-mail address: Charles.Feldman@wits.ac.za

Emeritus Editor
Professor Hendrik J Koornhof
E-mail address: hendrik.koornhof@nhls.ac.za.

Journal Secretary
Ms Priscilla May  
Southern African Journal of Infectious Diseases  
National Health Laboratory Service  
Private Bag X8  
Sandringham 2131  
E-mail address: priscillam@nicd.ac.za