Antimicrobial stewardship at Dr George Mukhari Hospital

A dissertation submitted by

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2012
DECLARATION

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

__________________________________  __________________
Surname, Initials (Title)  Date
DEDICATION

This research is dedicated to all the patients who come to health institutions seeking medical attention. It is because of their needs which need to be met with the utmost of care and consideration that we undertook this study as a means to optimize the quality level of care provided. Their confidence and trust in the health care system and their willingness to participate in any means aimed at improving services has played a big role as well.
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DISSEMINATION OF FINDINGS

PODIUM PRESENTATIONS

LOCAL CONFERENCES
1. Antimicrobial stewardship in DGMH University of Limpopo, Faculty of Health Sciences 8th Research day 21-22 August 2012
2. Antimicrobial stewardship. Presentation at DGMH pharmacy 12 Sept 2012
3. Antimicrobial stewardship presentation. SAAHIP meeting 11 April 2011

NATIONAL CONFERENCE
1. Antimicrobial stewardship in DGMH. SASOCP 2nd conference Rhodes University 2012

PUBLICATIONS
1. Antimicrobial stewardship article with Dr Natalie Schellack 2012
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<th>Full Form</th>
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<tbody>
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<td>AFB</td>
<td>Acid Fast Bacilli</td>
</tr>
<tr>
<td>AS</td>
<td>Antimicrobial Stewardship</td>
</tr>
<tr>
<td>ASP</td>
<td>Antimicrobial Stewardship Programme</td>
</tr>
<tr>
<td>CAP</td>
<td>Community Acquired Pneumonia</td>
</tr>
<tr>
<td>CCF</td>
<td>Congestive Cardiac Failure</td>
</tr>
<tr>
<td>CNS</td>
<td>Coagulase Negative <em>Staphylococci</em></td>
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<tr>
<td>COAD</td>
<td>Chronic Obstructive Airway Disease</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disorder</td>
</tr>
<tr>
<td>CRP</td>
<td>C-Reactive Protein</td>
</tr>
<tr>
<td>DGMH</td>
<td>Dr. George Mukhari Hospital</td>
</tr>
<tr>
<td>DKA</td>
<td>Diabetic Ketoacidosis</td>
</tr>
<tr>
<td>DS</td>
<td>Double Strength</td>
</tr>
<tr>
<td>ESR</td>
<td>Erythrocyte Sedimentation Rate</td>
</tr>
<tr>
<td>GIT</td>
<td>Gastrointestinal tract</td>
</tr>
<tr>
<td>HAART</td>
<td>Highly Active Antiretroviral Therapy</td>
</tr>
<tr>
<td>HAP</td>
<td>Hospital Acquired Pneumonia</td>
</tr>
<tr>
<td>HFV</td>
<td>Human Foamy Virus</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immune Virus</td>
</tr>
<tr>
<td>HPT</td>
<td>Hypertension</td>
</tr>
<tr>
<td>ID</td>
<td>Infectious Disease</td>
</tr>
<tr>
<td>IRIS</td>
<td>Immune Reconstitution Syndrome</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
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<tr>
<td>LRTI</td>
<td>Lower Respiratory Tract Infection</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
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</tr>
<tr>
<td>MDR</td>
<td>Multiple Drug Resistance</td>
</tr>
<tr>
<td>MREC</td>
<td>Medunsa Research Ethics Committee</td>
</tr>
<tr>
<td>MVR</td>
<td>Mitral Valve Replacement</td>
</tr>
<tr>
<td>NPO</td>
<td>Nil-Per-Os</td>
</tr>
<tr>
<td>NRH</td>
<td>Norman Regional Hospital</td>
</tr>
<tr>
<td>PCT</td>
<td>Procalcitonin</td>
</tr>
<tr>
<td>PJP</td>
<td>Pneumocystis jiroveci pneumonia</td>
</tr>
<tr>
<td>PO</td>
<td>Per Os</td>
</tr>
<tr>
<td>PTC</td>
<td>Pharmacy and Therapeutics Committee</td>
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<tr>
<td>PVO</td>
<td>Pulmonary Vein Obstruction</td>
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<tr>
<td>RVD</td>
<td>Retroviral Disease</td>
</tr>
<tr>
<td>SAMF</td>
<td>South African Medicines Formulary</td>
</tr>
<tr>
<td>SASCM</td>
<td>South African Society of Clinical Microbiology</td>
</tr>
<tr>
<td>SJS</td>
<td>Steven Johnson's Syndrome</td>
</tr>
<tr>
<td>SLE</td>
<td>Systemic Lupus Erythematosus</td>
</tr>
<tr>
<td>SOL</td>
<td>Space Occupying Lesion</td>
</tr>
<tr>
<td>SREC</td>
<td>School Research Ethics Committee</td>
</tr>
<tr>
<td>STG/EML</td>
<td>Standard Treatment Guidelines and Essential Medicines List</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TBM</td>
<td>Tuberculous Meningitis</td>
</tr>
<tr>
<td>TTOs</td>
<td>Medicines to Take Out</td>
</tr>
<tr>
<td>VTE</td>
<td>Venous Thromboembolism</td>
</tr>
<tr>
<td>WCC</td>
<td>White Cell Count</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>XDR</td>
<td>Extensively Drug Resistant</td>
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</tbody>
</table>
Abstract

Introduction: The use of antimicrobial agents has greatly improved patient care in hospitals since the mid-1900s and as such clinicians have always emphasized the importance of using these agents wisely. The overuse or irrational use of antimicrobials brings about a lot of unwanted effects e.g. microorganisms developing resistance, increase in drug costs, poor patient management, just to name a few. Therefore, antimicrobial stewardship is a tool that is used to manage, preserve and reduce or prevent resistance to existing antimicrobial agents (Fishman, 2006). Furthermore, antimicrobial stewardship programmes integrate several strategic methods, including evaluation and feedback regarding the necessity and appropriateness of antimicrobial therapy, staff education, and formulary restrictions (Rybak, 2007). This study was conducted to determine the extent to which antimicrobial stewardship is implemented and to strengthen the antimicrobial stewardship programme at DGMH by ensuring appropriate antibiotic usage and preventing resistance and most importantly contributing to improved patient outcomes.

Objectives: The objectives of the study were; to collect data on antimicrobial usage at the internal medicine wards at DGMH, to determine the most common microorganisms encountered at the internal medicine wards and their sensitivity patterns, to determine the most prevalent infectious disease, to compare prescribing patterns with existing antibiotic protocols, to determine prescriber knowledge of existing antimicrobial stewardship strategies and to make recommendations for strengthening antimicrobial stewardship.

Method: This was a prospective and descriptive study. The study sample comprised of all adult patients admitted to the internal medicine wards who received antimicrobials, as well as the prescribers at internal medicine during the study period. The study was conducted in three phases, where Phase 1 included baseline data collection from patient files and administration of the self-administered questionnaire to prescribers. Phase 2 was the intervention phase which was based on the results of Phase 1. Lastly, Phase 3 comprised of data collection from patient files so as to determine any changes post intervention.
Data on prescribing patterns were collected and analysed in comparison with existing treatment guidelines. Knowledge of physicians regarding antimicrobial stewardship and antibiotic policies was also collected using a self-administered questionnaire.

Results: This study revealed that ceftriaxone and Rifafour® were the top two most prescribed antimicrobials in all phases. However, after interventions were made, the number of prescriptions for these antimicrobial agents was relatively lower than Phase 1. The usage of metronidazole decreased by (50%) in Phase 3, signalling that discussing over usage with the physicians had an impact on prescribing decisions. In general there was a noticeable reduction in the usage of antimicrobials without properly documenting the indications in Phase 3 compared to Phase 1. A reduction was observed in the use of certain antimicrobials without documenting the indication and those included Rifafour®, metronidazole and cefuroxime. Blood cultures were collected more often after the educational interventions were made as compared to Phase 1, even though the majority of the blood culture results were negative. WCC, CRP and ESR were the only infection and inflammation markers investigated in more than 70% of the patients in this study, even though a slightly higher number of patients were investigated in Phase 1. This study revealed *C. neoformans* as the most isolated microorganism followed by *K. pneumoniae* in Phase 1 and coagulase-negative *Staphylococci*.

Conclusion: Minor changes were noticed after the interventions were implemented e.g. on usage of antimicrobials without documenting the indication or over usage of certain antimicrobials. Antibiotic prescribing patterns and knowledge about the antibiotic policy were not optimum and the implementation of an antibiotic stewardship programme is necessary to optimize antimicrobial use in DGMH.

Recommendations: To establish a feasible, but effective antimicrobial stewardship programme. To provide prescribers with more education on antimicrobial stewardship strategies including the prescribing of antibiotics such as co-trimoxazole. To regularly equip prescribers with more knowledge on appropriate specimen collection and also encourage them to use local approved antibiotic protocols more often. The low level of usage of penicillin antibiotic in internal medicine also needs to be further evaluated.
1.1 INTRODUCTION

Antimicrobial stewardship (AS) is usually initiated by the pharmacy department as a cost-saving means for antimicrobials. However, a multidisciplinary approach is mandatory for its successful implementation and progress. Antimicrobial stewardship is a tool used to manage, preserve and reduce or prevent resistance to existing antimicrobial agents (Fishman, 2006).

Antimicrobials have been at the centre of patient management in the hospital setting for decades. Since their development in the 1970’s their use has increased together with their development, unfortunately so has the resistance towards these agents. Thus measures have to be put in place to preserve the available antimicrobials as there are none-to-a-few in the pipeline (Owens, 2008).

1.2 BACKGROUND AND RATIONALE FOR THE STUDY

Antibiotics play a very important role in the provision of health care. They form part of a large group of medicines that are used to manage patients in healthcare facilities. In a hospital setting, the misuse or irrational use of antibiotics can result in numerous consequences for example, organisms developing resistance to available antibiotics, wasting of funds, prolonged hospital stay and iatrogenic diseases- just to name a few (Fishman, 2006). Therefore proper stewardship or management of antibiotics is essential. “Good antimicrobial stewardship involves the optimal selection, dosing and duration of an antimicrobial therapy that leads to the best clinical outcomes for the treatment or prevention of infection while producing the fewest toxic effects and the lowest risk for subsequent resistance” says Gerding (2001) in (Owens, 2008). Some studies conducted in the United States and around the world over the years indicate that antibiotic use is unnecessary in as many as 50% of cases and this is a clear sign of misuse of antibiotics (Fishman, 2006; Paskovaty et al., 2005).
Chapter 1: Introduction

Preventing the development of resistance is one of the major goals of antimicrobial stewardship. South African hospitals are battling with the growing emergence of micro-organisms that are resistant to routine or first line antibiotic therapy (Best care always, 2011). Some challenges with resistance have been noted in most areas around South Africa. For instance, in South Africa approximately 60% of *Klebsiella pneumoniae* in major academic hospitals in the public sector have developed resistance to broad spectrum antibiotics frequently used to treat them resulting in life-threatening infections amongst hospitalized patients and also, outbreaks of *Pseudomonas aeruginosa* resistant to all conventional antibiotics have been observed in both public and the private sectors, hence the need for an antimicrobial stewardship programme (South African Society for Clinical Microbiology, 2011).

Antimicrobial stewardship is achieved through the implementation of different strategies and these will be discussed in chapter 2. Development and implementation of antimicrobial policies is one of the strategies used in stewardship programmes. At Dr George Mukhari Hospital (DGMH) an antimicrobial protocol does exist. This protocol provides guidelines on how to treat some of the most common infectious disease encountered in the hospital e.g. pneumonia, meningitis, infective exacerbations of Chronic Obstructive Pulmonary Disorder (COPD). These guidelines are not complete as some prevalent conditions are not included and they have not been updated for a while. Other stewardship strategies like antimicrobial de-escalation or intravenous-to-oral switch are not fully implemented and monitored.

The study was therefore conducted to determine the extent to which antimicrobial stewardship is implemented and to strengthen the antimicrobial stewardship programme at DGMH by ensuring appropriate antibiotic usage and preventing resistance and most importantly contributing to improved patient outcomes.

### 1.3 RESEARCH QUESTION

Does an antimicrobial stewardship programme exist at DGMH and if so which aspects of this programme need to be strengthened?
1.4 **AIM OF THE STUDY**

The aim was to determine whether the stewardship programme exists, and if present to determine whether all stakeholders abide by the programme, and what the stumbling blocks in abiding by this programme were, if any.

1.5 **OBJECTIVES OF THE STUDY**

The objectives of the study were as follows:

- To collect data on antimicrobial usage at the internal medicine wards at DGMH
- To determine the most common microorganisms encountered at the internal medicine wards and their sensitivity pattern
- To determine the most prevalent infectious disease at the internal medicine wards
- To compare prescribing patterns with the existing antibiotic protocol
- To determine prescriber knowledge of existing antimicrobial stewardship strategies
- To make recommendations for strengthening antimicrobial stewardship

1.6 **SIGNIFICANCE OF THE STUDY**

Establishing an effective antimicrobial stewardship programme (ASP) is one of the ways to manage the use of available antimicrobials within an institution. ASPs prevent misuse/over use of antimicrobials, thus contributing in preventing resistance, waste of funds etc. (Owens, 2008). An antibiotic policy is one of the strategies used to promote good antibiotic stewardship but the effectiveness of the policy can never be maintained if the policies used are not updated regularly. Which is why in this study the antibiotic protocol used at the internal medicine wards was reviewed and updated, Other AS strategies like, antimicrobial de-escalation, intravenous-to-oral switch and education were strengthened as well.
1.7 SUMMARY

In this chapter, the background and rationale for the study was offered. This chapter also stated the main aim of the study, which focuses on strengthening the antimicrobial stewardship programme at DGMH followed by the objectives. The chapter is ended with an elaboration of the importance of this study. Chapter 2 focuses on the literature reviewed based on the study topic.
CHAPTER 2
LITERATURE REVIEW

2.1 INTRODUCTION

In this chapter, the literature reviewed focuses on antimicrobial resistance across the globe and some examples pertaining to resistance patterns in South Africa. It also provides information regarding antimicrobial stewardship and also the different strategies used for effective antimicrobial stewardship. This chapter also elaborates on the roles of individuals involved in antimicrobial stewardship programme (ASP). Lastly, intravenous to oral switch therapy is discussed in more detail as compared to other stewardship strategies as it was strengthened in the study. However, the latter was not the only strategy strengthened; education, antibiotic protocol reviews and treatment de-escalation were also addressed in this study.

2.2 INTRODUCTION TO ANTIMICROBIAL STEWARDSHIP

Over the years mortality due to infectious agents has decreased significantly ever since the development of antimicrobials, vaccines and improved sanitation (McDougall & Polk, 2005). In order for the available antimicrobials to be used optimally, prospective and formal strategies need to be developed so as to ensure that the available antimicrobials are used appropriately. According to Hornby (2005), stewardship is the act of taking care of or managing something, for example property, money or valuable objects. Based on this definition it is clear that antibiotic stewardship therefore refers to the process of taking care of or managing antibiotics. The type of strategies which were developed to ensure the appropriate use of the available antimicrobials are referred to as antimicrobial stewardship programmes. According to Gerding (2001) good antimicrobial stewardship is a practice which ensures the optimal selection, dose and duration of antimicrobial therapy leading to the best clinical outcome for treatment and/or prevention infections while minimizing side effects and with minimal risk for resistance to develop (Owens, 2008). Similarly, Fishman (2006) asserts that good antimicrobial stewardship involves selecting an appropriate drug and optimizing its dose and duration to cure an infection while
minimizing toxicity and conditions for selection of resistant bacterial strains. ASPs aim to achieve the best clinical outcomes while maintaining a low risk of developing resistance and toxic effects. Effective stewardship programmes integrate several strategic methods, including evaluation and feedback regarding the necessity and appropriateness of antimicrobial therapy, staff education, and formulary restrictions (Rybak, 2007). Also, for these programmes to work, multidisciplinary teams as well as institutional support are needed to form effective subcommittees to monitor them. There are many activities which can be considered to form part of antimicrobial stewardship, hence names like, antibiotic management programmes, antibiotic control programmes, etc., these names are sometimes used to describe this very same concept (McDougall & Polk, 2005). This may be due to the fact that the programme utilises a variety of strategies, which is fluent allowing direct antimicrobial use an institution.

Briceland et al. (1988) asserts that the first prospective audit and feedback was performed in Hartford Hospital, Hartford, in the late 1970s and 1980s by a team of an infectious disease physicians together with clinical pharmacists and was considered to be the first formal programme towards antimicrobial stewardship (Owens, 2008). Following this strategy, the team also introduced treatment de-escalation which was known as transitional therapy and streamlining. As a follow up on these strategies, research has been conducted to support their efficacy. So far there have been more strategies which are developed and are adopted by many institutions. Strategies used in antimicrobial stewardship all share one characteristic, which is, they have to be implemented continuously so as to optimize antimicrobial use and not on a temporary basis. For instance, the use of certain antimicrobials may be restricted following an outbreak of some multidrug resistant organisms in an institution and used again at a later stage, so this will not be referred to as an antimicrobial stewardship strategy because it is not continuous.

Antimicrobial resistance is one of the main subjects addressed by antimicrobial stewardship. As such, the following section addresses antimicrobial resistance and the involvement of antibiotic stewardship as means of prevention.
2.3 ANTIMICROBIAL RESISTANCE

The use of antibiotics has greatly improved patient care since the middle of 1900 and as such clinicians have always emphasized the importance of using these agents wisely (Fishman, 2006). Micro-organisms developing resistance to antibiotics, increase in drug costs, poor patient management, are amongst the detrimental effects that occur as a result of misuse or overuse of these agents. It was around the 1940s and 1950s where clinicians started to recognize that there was an increase in strains of bacteria which were developing resistance to the antimicrobial agents used (Owens, 2008). Over the years, as new antibiotics were developed to deal with resistant bacteria, their clinical use also increased, as such resistance or decreased susceptibility also started to occur. Nonetheless, this was not a huge problem around 1960 because the development of new chemical entities was at its peak. Around 1957 there were new discoveries, from the tetracyclines, microlides, aminoglycosides, glycopeptides, polyenes, polymyxims, even the penicillase-resistant penicillins (Owens, 2008).

Over the years, research has demonstrated that overuse of antibiotics does correlate with the reduction in susceptibility of micro-organisms. For instance, in Canada, there was a huge correlation identified between an increase in number of ciprofloxacin prescriptions and a reduction in susceptibility to this agent among pneumococci (Fishman, 2006). As a result, when the rate of fluoroquinolone containing prescriptions was 0.8 for every 100 patients per year in 1988, all the strains of Streptococcus pneumoniae were susceptible. However, the rate increased to 5.5 prescriptions per 100 patients by 1998, resulting in 1.7% of S. pneumoniae developing resistance to ciprofloxacin (Fishman, 2006). This is one example in which antibiotic resistance has been observed to emerge rapidly over the years and is now a big problem globally.

The increase in the development of multi-drug resistant (MDR) pathogens accompanied by the decline in the development of new antibiotics is linked to a lot of problems for patients with infections. These challenges include:

- Higher mortality and morbidity rates,
- Longer hospital stay,
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- Poor patient management,
- Increased risk of adverse effects due to the use of more toxic antimicrobials or combinations,
- Increased medical care costs (Wang et al., 2012).

It has been suggested that a possible reason for the decline in new chemical entities might be related to the latest complexity of drug development protocols in comparison with earlier years. This is because all the bacterial binding sites have been exploited, not to mention number of years and costs it takes to develop one chemical entity (Owens, 2008). During the last two decades, only two antimicrobials with a novel mechanism of action have been released, i.e. linezolid and daptomycin (Owens, 2008). Antibiotic use, whether it is considered to be appropriate or inappropriate, is associated with increase in the selective pressure for the emergence of resistance. Thus, proper care should be exercised when using these agents, to maintain their effectiveness.

“Appropriate antimicrobial use refers to prescribing antimicrobial therapy when and only when it is beneficial to the patient, targeting therapy to the desired pathogens, and using the appropriate drug, dose, and duration” (Owens et al., 2004). Many factors are involved in the emergence of resistance, thus the best way to combat it is through combining different strategies. There are a number of strategies to consider as a way of combating this resistance issue and one of the ways is through the use of ASPs. Strategies to reduce antibiotic resistance include:

- Developing strategies to reduce reservoirs for resistant organisms
- Improving diagnosis so as to help direct therapy
- Developing new antibiotics and vaccines
- Preventing the transmission of resistant strains through infection control measures and
- Education (Fishman, 2006).
2.4 STEWARDSHIP AS A MEANS TO COMBAT ANTIMICROBIAL RESISTANCE

ASPs have emerged throughout the United States in response to the global antibiotic resistance crisis (Rybak, 2007). Many studies have confirmed the relationship between the prevalent use of antibiotics and the development of resistant strains of bacteria (Rybak, 2007). The misuse/overuse of antimicrobials always comes out as the leading cause of resistance amongst other causes. ASPs are supposed to serve as a wake-up call to clinicians and health care administrators with regard to the appropriate use of antimicrobials. Furthermore, it is important to note that appropriate use of antimicrobials does not only refer to optimizing the prescribed dose but actually refers to prescribing antimicrobial therapy when and only when it is beneficial to the patient, targeting therapy to the desired pathogens, and using the appropriate drug, dose, and duration (Owens et al., 2004).

A survey performed by the South African Society of Clinical Microbiology (SASCM) in South Africa revealed that approximately 40% of *Staphylococcus aureus* causing bloodstream infections in patients in the major academic hospitals in the public sector are resistant to the first-line antibiotic, cloxacillin. Also, in the private sector, more than 20% of *Escherichia coli* isolated from the urine are resistant to ciprofloxacin. *E. coli* is the most common cause of urinary tract infections and ciprofloxacin is the first-line antibiotic most commonly used for treatment (SASCM, 2011). Other studies in South Africa over recent years have indicated high rates of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis in all provinces of South Africa and the emergence of resistance to fluoroquino lone in *Neisseria gonorrhoeae*.

In January 2011 a campaign called “Best Care Always” was started as a collaborative effort from healthcare organizations and stakeholders across South Africa to combat resistance and this resulted in the development of “An antimicrobial stewardship getting started guide”. A significant contribution towards developing the guide was made by professionals who had been involved in developing and implementing ASPs in certain hospitals around South Africa. This guide highlights antibiotic stewardship interventions featured in the literature and recommended by leading experts on antibiotic therapy in South Africa. The recommendations have
been tested in some South African hospitals and are thus intended to assist healthcare facilities in prioritizing and implementing various antibiotic stewardship efforts. Some of the strategies mentioned in the guide will be adopted in this study (Best care always, 2011).

In order for the ASPs to be a success, a multidisciplinary approach should be followed. Figure 2.1 below displays the key role players in a stewardship programme. It is clear from the diagram that an infectious disease trained physician and a clinical pharmacist with infectious disease training are the key health care members necessary to drive the stewardship programme and all the other health care members' forms the support system. Nonetheless, each of the team members plays a vital role towards successful implementation of the stewardship programme, refer to Figure 2.1.

Key: ID: Infectious disease, PTC: Pharmacy and Therapeutics committee

Figure 2.1: Players in the Multi-disciplinary team involve in ASPs
2.5 ROLES OF PEOPLE INVOLVED

The antimicrobial stewardship team is led by a physician who is trained in infectious diseases (ID) and partnered by a clinical pharmacist with infectious disease training (Suleman & Meyer, 2012; Wang et al., 2012). Antimicrobial stewardship is usually initiated by the pharmacy department in an attempt to save costs and reduce resistance for rational use of antimicrobials.

a) The responsibilities of the clinical pharmacist with infectious disease training, amongst other things would be;

- Providing cost-effective pharmaceutical care to patients in receipt of certain/targeted antimicrobials
- Discuss antimicrobial order changes with the infectious disease physician
- Monitor antimicrobial therapy so as to evaluate the appropriateness therefore
- Provide pharmacokinetic and pharmacodynamic services when required
- Provide in-service training to all staff members
- Provide presentations, publications at the local, state, regional and national level
- Conduct collaborative research to test the effectiveness of new methods of antimicrobial control/restriction/reporting that may increase the effectiveness of antimicrobial stewardship (Robert, n.a).

b) The Infectious disease physician ensures that all strategies introduced by the stewardship programme are based on clinical evidence and practice and also overlooks the overall running of the stewardship programme as a whole

c) The clinical microbiologist plays a huge role in supplying the stewardship team with surveillance data on resistance patterns followed by organisms in the particular hospital.

d) A hospital epidemiologist and a member of the infection control team are also required in a stewardship team because antimicrobial resistance emerges and spreads not only because of selective pressure due to antimicrobial use but also because of physical transmission, thus these individuals can supply that information.
d) The PTC is responsible for approving restriction policies and procedures, reviewing budgetary issues, approval pathways and reviewing annual antimicrobial usage.

e) There is no way that an institution can establish and implement an ASP without involving hospital administration because they give the overall authority for the programme and compensation when necessary.

f) Last but not least, the microbiology laboratory plays a very important role in collecting, analysing and distributing information on antimicrobial resistance patterns in an institution.

Also, helps identify pathogens and promote efficient diagnosing, which leads to early de-escalation of antimicrobial therapy (MacDougall & Polk, 2005; Wang et al., 2012).

2.6 STRATEGIES USED IN STEWARDSHIP

ASPs at various institutions select one or more strategies out of the many strategies which are available and employ them simultaneously. This selection is made based on the available resources, needs and programme goals of the particular institution. This therefore implies that each individual hospital may select the strategies which will meet their needs best. Figure 2.2 gives an overview of the strategies used in stewardship. These strategies can be grouped into a pre-prescription or post-prescription category (Wang et al., 2012). In other words, those strategies used to promote optimal antimicrobial use before they are administered to the patient and those that are used once antimicrobials have been initiated.
2.6.1 Prospective audit and feedback

As indicated above, prospective audit and feedback is one of the earlier strategies which were developed in the late 1970s (Owens, 2008). Prospective audit and feedback has proven to reduce costs and inappropriate use of antimicrobials (Wang et al., 2012). This strategy involves the review of patients who are receiving antimicrobials by the ID physician or the ID trained clinical pharmacist and thereafter giving feedback. The clinical pharmacist, infectious disease physician or another member of the stewardship team reviews antimicrobial usage and make recommendations in order to promote the appropriate use of these agents. Interventions made can either be based on the inappropriate selection, dosage, route or duration of an antimicrobial and these recommendations are made to the
prescriber in writing (by placing a written form in a patient’s file) or by direct conversation (Suleman & Meyer, 2012). Because this strategy does not restrict or negatively challenge prescribers, it is therefore generally more acceptable. Also, it does not take away the prescriber’s authority and may promote an educational atmosphere, nonetheless, it remains within the prescriber’s choice to take or reject these recommendations.

2.6.2 Education and guidelines

Provider education forms a very important part of any antimicrobial stewardship programme (Fishman, 2006). Educational means can range from conference presentations, drug utilization review, hospital-pharmacy committee newsletters, student and provider teaching sessions, to providing written clinical guidelines or via electronic means (Wang et al., 2012). Another integral part of providing education is formulating peer-reviewed clinical guidelines for certain infectious diseases to assist physicians when making decisions about their diagnoses and therapy. Nonetheless, these guidelines need to be reviewed and updated regularly and most importantly need to be combined with other educational efforts because they fail dismally when used alone to impact prescribers.

2.6.3 Computer-assisted programmes

Computer-assisted decision support programmes provide physicians with specific information about a patient, advice, and feedback with regards to antibiotics and drug-related side effects (Fishman, 2006). Furthermore, these computerized programmes are designed to provide real-time integrated patient and institutional data, which includes cultures, susceptibility results, laboratory measures of organ function, allergy history, drug-interactions, cumulative or customized location-specific antibiogram data and cost information (Owens, 2008). More importantly, these programmes assist physicians by suggesting antimicrobial choices in specific situations. According to Evans et al., 1998; 1999 and Pestotnik et al. (1996) research published from the LDS Hospital in Salt Lake City, UT, shows that this strategy is in-fact associated with reductions on drug doses, inappropriate orders, costs, treatment
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duration and associated side effects says (Owens, 2008). Nonetheless, the impact of the programme on antimicrobial resistance is still unclear (Fishman, 2006).

2.6.4 Formulary restriction

One of the best ways to determine which antimicrobials are utilised in an institution and contain drug costs is by controlling which drugs are included in an institution's formulary (Fishman, 2006). The motivating factor for this strategy is that prescribers usually do not adhere to policies or set guidelines, thus restricting which drugs are available in an institution enforces a certain level of control (MacDougall & Polk, 2005). Selecting antimicrobials to include in a formulary requires several factors to be considered. These factors include knowledge of local resistance patterns, avoiding agents with a similar spectrum of activity with no added benefits, drug costs, toxicity, etc. Formulary restriction allows the selection of less expensive drugs, thus saving the hospital money and helps restrict agents which are more prone to resistance. Nevertheless, this strategy does not restrict the overuse of available antimicrobials, not even the broad spectrum antimicrobials. It is therefore necessary to combine it with other strategies e.g. de-escalation strategies.

2.6.5 Prior approval

Prior approval strategies have been seen as the most difficult to adhere to by prescribers, even though they can be the most effective in decreasing antibiotic costs and improve antibiotic use (Fishman, 2006). In this programme approval has to be obtained before prescribing any of the restricted antimicrobials. This approval can be obtained in a number of ways including, telephonically, antibiotic order forms, direct interactions, implementation of control categories etc. The prescribers have to obtain approval from an infectious disease specialist before prescribing the targeted antimicrobials. When they do so, they need to justify the need for the agent and the ID specialist can either approve or suggest an alternative (Owens, 2008). In the 1970s a retrospective review of antibiotic use was conducted in Boston City Hospital and this demonstrated that prior approval strategies were effective in improving antibiotic use (Fishman, 2006). In cases where the ID specialist did not grant access for a particular agent, they would then suggest an alternative but in cases where the
requesting prescriber did not agree then the initial antimicrobial was dispensed. Even with all these challenges McGowan and Finland (1974) noticed a reduction in the use of the targeted antimicrobials after the programme was initiated (Paskovaty et al., 2005). This use was lower even when compared to similar hospitals.

2.6.6 Pharmacodynamic dose optimization

Dose optimization was usually applied to patients with organ failure (e.g. renal failure) so as to optimise therapy but is now receiving attention as one of the most important interventions in antimicrobial stewardship (Owens, 2008). Pharmacodynamic principles are used to maximize drug exposure in special or complicated cases e.g. organisms with elevated minimum inhibitory concentrations (MICs), patients with excess body mass indexes or infection sites which are difficult to penetrate etc. (Owens, 2008). This strategy is aimed at using the available antimicrobials fully and as such to achieve the best efficacy from them. Lately, there has been a growing interest in pharmacodynamic dose optimization, hence there are many studies being conducted regarding this strategy.

2.6.7 Antibiotic cycling

Antimicrobial cycling refers to the rotation of two or more antibiotic classes with similar spectrum or coverage over a certain period of time (Fishman, 2006). This rotation occurs in a scheduled fashion whereby you end up returning to the initial regimen after some time. Antimicrobial cycling emerged in the 1980s where studies were conducted to examine formulary restriction of aminoglycosides (McDougall & Polk, 2005). These studies looked at instances where amikacin was exchanged for gentamicin or tobramycin. These led to the conclusion that rotating antimicrobials might help in slowing down the development of resistance to a particular agent. The idea behind this strategy is to reduce the selective pressure to one antimicrobial class, by regularly switching antimicrobials, the resistance to a single agent will be reduced.
2.6.8  Intravenous-to-Oral Switch

It is ideal to administer antimicrobials via the intravenous route when a patient has a severe infection, cannot take anything orally or for patients with deep-seated infections which require intravenous drug administration so as to guarantee that the drug will reach the target site. Another reason for parenteral drug administration is where the agent to use does not have a formulation for oral delivery and this could be for several reasons, e.g. acid liability. Examples would include aminoglycosides. The ideal route of administration for any antimicrobial agent is one which ensures that the drug achieves serum concentrations high enough to produce the desired effect without producing undesired effects (Kuper, 2008).

2.6.8.1.  Benefits of early IV-to-Oral switch

The oral route provides many advantages when compared to the intravenous (IV) route, hence it is always recommended whenever possible. Advantages include:

- A reduced likelihood of hospital acquired infections and infected/phlebitis IV lines.
- Fewer delays in administration because there are no problems with setting up IV access.
- A reduction in the risk of adverse effects like preparation errors as they are more common with IV preparations than oral.
- A reduction in discomfort and improved mobility
- Facilitates early hospital discharge
- A reduction in pharmaceutical and consumables costs and also savings in medical and nursing time (NHS guide, 2010).

2.6.8.2.  Types of IV-to-Oral therapy conversions

There are three ways in which intravenous therapy can be converted to oral therapy (Kuper, 2008) refer to Table 2.1 below.
Table 2.1: Types of IV-to-Oral conversions

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequential therapy</td>
<td>Refers to replacing a parenteral agent with its oral counterpart e.g. switching from 500 mg IV metronidazole tds to 400 mg PO metronidazole tds. This is impossible with agents that do not have oral formulations.</td>
</tr>
<tr>
<td>Switch therapy</td>
<td>Refers to a conversion from an IV drug to an oral equivalent which may be within the same class and have the same level of potency but is a different compound. e.g. switching from benzylpenicillin 1.2 g qid IV to amoxicillin 500 mg tds PO.</td>
</tr>
<tr>
<td>Step-down therapy</td>
<td>Refers to converting from an IV formulation to an oral agent in the same or another class, where the frequency, dose and spectrum of activity may not be similar. e.g. Converting from piperacillin/tazobactam 4.5 g IV tds to amoxicillin/clavulanate 875 mg PO bd.</td>
</tr>
</tbody>
</table>

Key: bd; twice daily, tds; three times daily, qid; four times daily, PO; orally

2.6.8.3. Agents which can be considered for conversion therapy

Not all antimicrobials can be considered for conversion therapy, for a various reasons which may include the lack of therapeutic equivalence or pharmacokinetic differences. Bioavailability is another aspect to consider when dealing with conversion therapy. While some agents can attain a bioavailability of 100% from the oral route (e.g. Linezolid) some have low oral bioavailability profiles (e.g. Azithromycin) and this has to be considered before switching gents (van Niekerk, 2010). The following diagram shows some agents which may be considered for IV-to-oral conversion.
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Figure 2.3: Antimicrobials which can be considered for IV-to-oral conversion

B: Bioavailability (Diagram adopted from van Niekerk, 2010; SAMF, 2010; Kuper, 2008)
2.6.8.4. **Possible IV-to-Oral switches**

As noted in the section above, the conversion from IV-to-oral can take place in a variety of ways and it does not always have to be with the same IV compound. For instance, if culture results are available, any oral agent that the organism is susceptible to, can be used for switching even if the coverage is completely different with the initial IV agent. Some possible examples of IV-to-oral switches are displayed in Table 2.2.

<table>
<thead>
<tr>
<th>Suitable IV-to-oral switches</th>
<th>Amoxicillin 500mg tds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzylpenicillin 1.2g qid</td>
<td>Amoxicillin 500mg tds</td>
</tr>
<tr>
<td>Co-amoxiclav 1.2g tds</td>
<td>Co-amoxiclav 625mg tds</td>
</tr>
<tr>
<td>Clindamycin 450-600mg qid</td>
<td>Clindamycin 450-600mg qid (if severe infection)</td>
</tr>
<tr>
<td>Metronidazole 500mg tds</td>
<td>Metronidazole 400mg tds (or 1g par rectal bd)</td>
</tr>
<tr>
<td>Cefuroxime 750mg tds</td>
<td>Co-amoxiclav 625mg tds</td>
</tr>
<tr>
<td>Clarithromycin 500mg bd</td>
<td>Doxycycline 100mg-200mg d</td>
</tr>
<tr>
<td>Ciprofloxacin 200-400mg bd</td>
<td>Ciprofloxacin 500mg bd or 750mg bd</td>
</tr>
</tbody>
</table>

Key: d = once daily bd= twice daily tds= 3 times/day qid =4 times/day

2.6.8.5. **Indications for switching from IV-to-oral**

It is very important to note that not all patients can be switched from IV-to-oral drug delivery. Thus each patient should be reviewed every 24 to 48 hours for eligibility. A patient may be considered for conversion from IV-to-Oral if:

- There is clinical improvement
- Signs and symptoms of infection are improving e.g. fever, white cell count, etc.
- Able to eat a regular or modified diet
- Able to receive enteral nutrition by the oral, gastric or other enteral tube
- Able to receive other scheduled medication by the oral route
The oral route is not compromised e.g. by vomiting, severe diarrhoea, malabsorptive disorder, swallowing problems or unconsciousness.

Does not meet any of the exclusion criterion, (Kuper, 2008; NRH, 2005; Royal Devon and Exeter NHS Foundation Trust, 2008).

2.6.8.6. **Indications for prolonged IV antimicrobial therapy**

Any patient who meets any one of the following criterion requires continued intravenous antimicrobial therapy:

- Unable to swallow, loss of consciousness or are strictly Nil-per-os (NPO)
- Severe nausea, vomiting, diarrhoea, short bowel syndrome, gastrointestinal obstruction, malabsorptive syndrome or ileus
- Active gastrointestinal bleeding
- Continuous tube feedings that cannot be interrupted and the required medication is known to bind to enteral nutrition formulas (e.g. tetracycline and calcium ions)
- Experienced severe trauma within the last 72 hours
- Severely immunosuppressed
- Neutropenic
- High risk or have deep-seated infections which require IV antimicrobials to guarantee sufficient drug levels at the site of action. Examples include:
  - *Staphylococcus aureus* bacteremia
  - meningitis
  - necrotizing fasciitis
  - severe cellulitis and soft tissue infections like group A hemolytic streptococcal infections
  - intracranial abscess
  - liver abscess
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- infective endocarditis
- legionella pneumonia
- exacerbations of cystic fibrosis
- inadequately drained abscess
- empyema
- infections of implants/prostheses
- osteomyelitis
- septic arthritis, (Kuper, 2008; NRH, 2005; Royal Devon and Exeter NHS Foundation Trust, 2008).

2.6.9 De-escalation or Streamlining

De-escalation involves the administration of broad-spectrum empirical antibiotic therapy together with early patient assessment and then therapy is narrowed or discontinued based on clinical improvement and culture results (Gyssens, 2009). The term “de-escalation” was created in intensive care medicine, in other settings the term “streamlining” is used to describe this strategy (Gyssens, 2009). In other words, this is when you modify the initial empirical therapy, in accordance with the culture results from the microbiology laboratory (Fishman, 2006). Also, streamlining involves the replacement of an antibiotic by another antibiotic with a narrower spectrum but also active against the isolated microorganism (Gyssens, 2009). Furthermore, this can be achieved by reducing the dose, frequency of administration, number of antimicrobials in the regimen or some combination. Treatment de-escalation is not always followed by physicians for different reasons, but this could reduce the over use of broad spectrum antibiotics and probably contribute to reducing the emergence of resistance.
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2.7 SUMMARY

This chapter focused on the literature which was reviewed pertaining to this study. It gave an insight on antimicrobial stewardship as means to combat the growing problem of antibiotic resistance and the different strategies used to achieve this. The chapter also gave an in-depth overview of IV-to-Oral switching therapy. The next chapter will focus on the methods used in conducting this study.
3.1 INTRODUCTION

This chapter presents the methods used while conducting this study, which includes
the study site, design, also information about the sample selection including, the
inclusion and exclusion criteria. This chapter also looks at the data collection tools
used as well as the analysis of the data thereafter.

3.2 BACKGROUND TO THE METHOD

The aim of this study was to determine whether the stewardship programme exists at
DGMH, and if present to determine whether all stakeholders abide by the
programme, and what the stumbling blocks in abiding by this programme were, if
any. This was to be achieved by following the objectives stated in Chapter 1. It was
thus necessary to determine the knowledge of the physicians with regards to
antimicrobial stewardship and the strategies employed by these programmes as well
as determining which strategies are already in place in the hospital. Another
necessity was to determine antimicrobial use in patients while admitted in the
hospital.

3.3 STUDY DESIGN

This was a prospective and descriptive study, where data on prescribing patterns
were collected and analysed in comparison with pre-existing antimicrobial resistance
patterns. Knowledge of physicians regarding antimicrobial stewardship and antibiotic
policies was also collected using a self-administered questionnaire.

3.4 STUDY SITE

The study was conducted in the adult internal medicine wards at DGMH. This is a
tertiary hospital situated in Ga-rankuwa, next to the University of Limpopo (Medunsa
Campus), Pretoria. The internal medicine wards which were selected for the study
include:
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- Ward 33 (adult male ward)
- Ward 34 (adult male ward)
- Ward 36 (admission ward for both males and females),
- Ward 37 (adult female ward)
- Ward 38 (adult female ward)

3.5 STUDY POPULATION

The target population for the study included all adult patients (male and female) who were admitted to the internal medicine wards at DGMH and treated with antimicrobial agents during the study period. The study population also included the physicians in the internal medicine wards, so as to assess their knowledge about antimicrobial stewardship and the strategies used.

3.6 STUDY PERIOD

The study was conducted from November 2011, until the end of October 2012. A pilot study was conducted in November 2011; subsequent data were then collected in 2012. Baseline or Phase 1 began on the 5th of January 2012 and this was followed by the review of patient files, which took place from the 9th of January to the 9th of February 2012. Phase 2, which was the intervention phase, occurred from February 2011 to the end of September 2012. These interventions resulted from the discussions stipulated in the work plan in Section 5.4 of the research protocol. Phase 3 data were collected from the 1st of October to the 31st of October 2012 and only included patient file reviews.

3.7 PILOT STUDY

A pilot study was conducted at the paediatric wards (i.e. ward 22 and 23). The questionnaire to test prescriber’s knowledge (Appendix 3) on antimicrobial stewardship was administered to six prescribers at these wards. Three interns and three registrars participated in this pilot study. The data collection forms (Appendix 1 and Appendix 2) were also tested in the same wards. A total of fourteen paediatric
patients who were on antimicrobials were followed over two days and their prescriptions were reviewed accordingly.

A few minor suggestions were made on the questionnaire by the participants and were implemented accordingly. For instance, instead of using the word antimicrobial policy, the prescribers suggested antimicrobial protocol, as they were more familiar with this term (Question 2 in Appendix 3). Additions were also made to question 3, to add another tick box that will allow for the option, “sometimes” to be selected because most prescribers refer to policies neither all the times nor rarely, but sometimes. Overall the pilot study was a great precursor of the study to come and all the participants were excited and willing to support the study in any way necessary.

3.8 SAMPLE SELECTION

Convenience sampling was used for this study. In this sampling method, a sample is chosen purely on the basis of availability, i.e. respondents are selected because they are accessible (Struwig & Stead, 2009). The study sample comprised of all patients who received antimicrobials and were admitted to the internal medicine wards at DGMH during the study period. A self-administered questionnaire was also given to the physicians who were at the internal medicine wards during the study period.

3.8.1 Inclusion criteria

The following inclusion criteria applied:

- All patients who were receiving antimicrobials on admission or after being admitted to the wards
- All physicians who were attending to patients at the internal medicine wards during the study period

3.8.2 Exclusion criteria

The following exclusion criteria applied:

- All patients who were not on any antimicrobials
- All patients who only received antimicrobials on discharge
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3.9 DATA COLLECTION INSTRUMENTS

3.9.1 Patient identification forms

This form was used by the researcher as a working document in Phase 1 and Phase 3 of the study (Appendix 1). This form was used to identify the patients when following them on a daily basis and the researcher kept it separate from other data collection instruments. The following information was recorded onto this form:

- Patient names
- Patient’s hospital number
- Patient’s ward number
- Allocated study number

Two separate forms were used in the study, where the first was used when collecting data in Phase 1 of the study, while the second was used in Phase 3 data collection.

3.9.2 Data capturing form

The researcher employed the use of this form when collecting data from the patient files on a daily basis (Appendix 2). The following information was recorded in this form:

- The study number allocated to the patient
- Provisional or actual diagnosis
- Microbiological specimen if collected
- Microbiological culture results
- Prescribed antimicrobial
- Dosage instructions and maximum daily dose
- Route of administration
- Therapy duration
Only antimicrobials for systemic use were recorded in this form (excluding immunoglobulins and vaccines) and not all the drugs each patient was taking. That means analgesics, anti-inflammatories etc. were not included. Treatment duration was monitored on a daily bases and recorded and any antibiotics which were stopped or added onto the patient's medicine chart were updated.

3.9.3 Questionnaire

A self-developed, participant-administered questionnaire was used to obtain the physicians' views about antibiotic policies and antimicrobial stewardship strategies used in DGMH (Appendix 3). The questionnaire addressed the following:

- The physician’s position/ rank
- Length of practice
- Available protocols which prescribers are familiar with
- How often do physicians refer to current protocols
- Other reference sources used when prescribing
- Most prevalent infections conditions observed at DGMH
- Infectious diseases where physicians often collect specimens for
- If the physicians recommend that the current protocols be updated and if they would use the updated version

3.10 DATA ENTRY AND ANALYSIS

Data analysis was done in consultation with a statistician. All the raw data which were collected in the study was captured into a Microsoft Excel® 2010 spreadsheet. Data capturing was verified and validity checks were performed as part of the data cleaning process. Descriptive statistics were used to analyse the data. The data were then appropriately presented in graphs and in tables.

Prescriptions which did not adhere to the relevant guidelines were analysed in depth to explore the deviations from the guidelines e.g. antibiotics not prescribed correctly or not according to standard regimen, etc. in a form of descriptive statistics. The data
from the questionnaires were also used to make recommendations to protocol changes and strengthening stewardship strategies. The questionnaire was used to assess the knowledge of the physicians regarding the available antibiotic protocol, adherence to it, and assess their knowledge about antimicrobial stewardship strategies.

3.11 RELIABILITY AND VALIDITY

The researcher only recorded data that were available in the patient files, which means there were no alterations on the data obtained. The data collected from the patient files could be retrieved whenever necessary because a study number was allocated to each patient, thus making it possible to assess the reliability of the collected data by another researcher (see Appendix 1). The report on sensitivity and resistance patterns of micro-organisms that was obtained from the microbiology laboratory was not altered by the researcher and such reports are available at microbiology laboratory whenever required, therefore another researcher can obtain the same information. This therefore account for reliability of the data.

Validity refers to the extent to which a research design is scientifically sound or appropriate (Struwig & Stead, 2009). A pilot study was conducted in the paediatric wards at DGMH, this account for internal and external validity. Lastly, because seasonal changes play an important role in infectious diseases and this study was not conducted over the four seasons, the researcher kept this in mind when analysing the results. Well known statistical methods as indicated in the study protocol were used to analyse the data and this also accounts for reliability.

3.12 ETHICAL CONSIDERATIONS

This research was observational. The researcher did not interfere with patient therapy in any way. There was only a review of patient files and the authority for access to patient files was sought from the hospital superintendent. Therefore an informed consent from the patients was not necessary. Confidentiality was maintained at all times during the study because the data capturing forms mentioned in Section 3.9.2 only showed the unique study number allocated to each patient file. The patient identification forms containing the patient names, hospital file number
and the study number allocated to each patient were kept safe by the researcher in a locked cupboard in a separate room from the data capturing system and not accessible to anyone else. As mentioned in Section 3.9.1 the form with the patient details was only used by the researcher purely to identify the patients in the different wards. The details in this form were not captured into the computer and were not accessible to other people. Only the study number which also appeared on the data capturing form could be used to link the two forms.

An informed consent was obtained from the physicians before administering the questionnaire. This consent form was adopted from the one provided by Medunsa Research Ethics Committee (MREC) (Appendix 4). Approval and permission to conduct the study was sought from the School Research Ethics Committee, Faculty of Medicine, University of Limpopo (SREC), MREC, the hospital superintendent and the Head of Department of Internal Medicine.

3.13 SUMMARY

In this chapter, the methodology of the study was described. A background to the method used was discussed, followed by information on the study design and study site. The chapter also gives details about sample selection and data collection instruments used in this study. The chapter ended with a discussion of the ethical considerations which were taken into careful consideration throughout all the phases in the study.

The following chapter presents all the results obtained during data collection.
4.1 INTRODUCTION

The results, based on the data collected during the study period are presented in this chapter. As indicated in Section 3.6, this study was conducted in three phases and as such the results will be presented accordingly. Section 3.6 also indicates that Phase 1 data which was collected early January 2012 consists of patient files review and a self-administered questionnaire given to the physicians. Phase 2 includes interventions based on the results of Phase 1. On the other hand, Phase 3 only includes patient file reviews and no questionnaires were given to the physicians. Thus, data collection in Phase 3 followed the interventions which were implemented in Phase 2.

4.2 PHASE 1

4.2.1 Questionnaire results

A self-administered questionnaire was given to 11 prescribers in the department of internal medicine. Five were interns and six were registrars. The questionnaire contained 11 questions in total.

4.2.1.1 Existence of antimicrobial protocols at the internal medicine wards

When the participants were asked which antimicrobial protocols they were familiar with at the internal medicine department the responses were as depicted in Figure 4.1. The protocols which were asked were obtained from the antibiotic protocol available at the internal medicine department.
Chapter 4: Results

**Antimicrobial protocols available**

<table>
<thead>
<tr>
<th>Name of protocol</th>
<th>No. of responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TB drug induced liver injury</td>
<td>7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6, 7</td>
</tr>
<tr>
<td>Hospital acquired pneumonia</td>
<td>7</td>
</tr>
<tr>
<td>Hemodialysis catheter related sepsis</td>
<td>1</td>
</tr>
<tr>
<td>Amoebic liver abscess</td>
<td>1</td>
</tr>
<tr>
<td>Infective exacerbations of COPD</td>
<td>3</td>
</tr>
<tr>
<td>Meningitis (chronic)</td>
<td>5</td>
</tr>
<tr>
<td>Meningitis (acute)</td>
<td>7</td>
</tr>
<tr>
<td>Community acquired Pneumonia</td>
<td>9</td>
</tr>
</tbody>
</table>

Key: COAD: Chronic Obstructive Airway Disease

**Figure 4.1: Antimicrobial protocols which prescribers were familiar with in IM wards**

The protocol for community acquired pneumonia (CAP) was the most familiar protocol with nine out of the eleven prescribers, saying that they were familiar with it. The least known protocols were those for the treatment of amoebic liver abscess and haemodialysis catheter related sepsis, with only one response for each.

**4.2.1.2. Usage of antimicrobial protocols by physicians**

When prescribers were asked if they referred to an antibiotic protocol when prescribing, three responded that they used policies all the time, five said sometimes and two responded never. Refer to Table 4.1 below

**Table 4.1: How often prescribers referred to an antibiotic protocol**

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Rarely</th>
<th>All the time</th>
<th>Sometimes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>
Chapter 4: Results

4.2.1.3. Other resources used when prescribing antimicrobials

Figure 4.2 below shows that most prescribers (seven out of 11) referred to the South African Medicines Formulary (SAMF) when prescribing, when they do not use antimicrobial protocols. Other sources used included medical journals and South African National Health guidelines, and another prescriber used medical pharmacy programmes.

![Other sources used](image)

Key: STG/EDL: Standard Treatment Guidelines/Essential Drugs List, SAMF: South African Medicines Formulary

**Figure 4.2:** Other resources used when prescribing antimicrobials

4.2.1.4. Specimen collection

When the prescribers were asked for which medical conditions did they normally send specimens to the laboratory for culture and sensitivity, meningitis was the most common, with eight out of eleven prescribers selecting it. Pneumonia came second with seven prescribers followed by tuberculosis with six selections. Refer to Figure 4.3 below.
Key: DKA: Diabetic ketoacidosis, PVO: Pulmonary vein obstruction, TB: Tuberculosis, UTIs: Urinary tract infections

Figure 4.3: Conditions which specimens were normally collected

4.2.1.5. Turn-around time for laboratory results

The prescribers were asked how long did it normally take for the results of the specimens which were collected to come back from the microbiology lab. Figure 4.4 below shows that seven of them said it took more than five days and none of them said within 24 hours.
4.2.1.6. Need for updating of antimicrobial policies

When asked if there was a need to update the current antimicrobial protocol at the internal medicine department, all the participants (11/11) agreed. A follow up to the above question asked the prescribers to state if they were willing to use the updated policies if they agreed that they should be updated. Again, ten of them answered yes and one did not respond to the question.

4.2.1.7. Training on antimicrobial protocol guidelines

Prescribers were also asked if they had been trained in antimicrobial protocol guidelines at the internal medicine department and only two responded with a yes, the other nine said no.

4.2.1.8. Frequency of de-escalation of antimicrobial therapy

Figure 4.5 below shows that eight out of the eleven prescribers indicated that they rarely de-escalated, while two did not know what de-escalation meant and none of them selected never.
Chapter 4: Results

4.2.1.9. **Antimicrobial Cycling**

When the prescribers were asked how often antimicrobial cycling was performed, the majority (5) answered that they did not know what antimicrobial cycling was. Refer to Figure 4.6 below.

![Bar chart showing the number of times therapy is de-escalated](image)

**Figure 4.5:** The number of times therapy is de-escalated

![Bar chart showing how often antimicrobial cycling is performed](image)

**Figure 4.6:** How often is antimicrobial cycling performed?
4.2.2  Review of patient files

4.2.2.1.  Patient selection

Hundred and one patient files were randomly selected and reviewed for collecting baseline data, also referred to as Phase 1 data. Data collected from one patient was lost, thus 100 patient files were reviewed. The data for base line was collected from all patients (male and female) who were on an antimicrobial and were admitted in internal medicine wards during the study period. This data were collected over a period of one month (from 9 January to 9 February 2012). The 100 patients consisted of 45 adult females and 55 adult male patients.

4.2.2.2.  Diagnosis

Some patients presented with one condition while others presented with two or more conditions, hence the diagnoses encountered were much more than the number of patients encountered. Nonetheless, the different diagnoses are grouped accordingly in the following sections.

4.2.2.2 (a) Conditions of the central nervous system

The diagnoses encountered for the central nervous system (CNS) are displayed in Table 4.2 below.

Table 4.2:  Conditions affecting the CNS

<table>
<thead>
<tr>
<th>CNS conditions</th>
<th>Diagnosis</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Confusion</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Brain abscess, Space occupying lesion (SOL)</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
Table 4.2 above clearly shows that out of the CNS conditions encountered, meningitis was the most common diagnosis (30 patients out of the 100). On the other extreme, brain abscess was only encountered once.

4.2.2.2 (b) Conditions of the respiratory tract

Conditions affecting the respiratory tract, 27 of the 100 patients were diagnosed with tuberculosis and this diagnosis was followed by pneumonia (20 cases) whilst others were not so common, refer to Table 4.3.

**Table 4.3: Conditions affecting the respiratory tract**

<table>
<thead>
<tr>
<th>Respiratory conditions</th>
<th>Diagnosis</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tuberculosis</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Chronic Obstructive Airway Disease (COAD)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Lower Respiratory Tract Infection (LRTI)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Pulmonary oedema</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Pulmonary emboli</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Chronic cough</td>
<td>1</td>
</tr>
</tbody>
</table>

4.2.2.2 (c) Conditions of the gastrointestinal tract (GIT)

Table 4.4 below clearly shows that hepatic related conditions were the only documented diagnoses identified under the GIT whereby patients received antibiotics.
Table 4.4: Conditions affecting the gastrointestinal system (GIT)

<table>
<thead>
<tr>
<th>GIT conditions</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>No. of cases</td>
</tr>
<tr>
<td>Hepatitis, liver failure, liver failure on Highly Active Antiretroviral Therapy (HAART)</td>
<td>6</td>
</tr>
<tr>
<td>Jaundice</td>
<td>2</td>
</tr>
<tr>
<td>Massive hepatomegaly</td>
<td>1</td>
</tr>
</tbody>
</table>

4.2.2.2 (d) Conditions affecting the cardiovascular system

Of the 100 files reviewed where an antibiotic was prescribed anaemia, congestive cardiac failure and epistaxis were only noted twice amongst the cardiovascular conditions followed by deep vein thrombosis and congestive cardiac failure. Refer to Table 4.5 below.

Table 4.5: Conditions affecting the cardiovascular system

<table>
<thead>
<tr>
<th>Cardiovascular conditions</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>No. of cases</td>
</tr>
<tr>
<td>Anaemia</td>
<td>2</td>
</tr>
<tr>
<td>Congestive Cardiac Failure (CCF)</td>
<td>2</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>2</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
</tbody>
</table>

4.2.2.2 (e) Conditions affecting other organs or systems

Other conditions could not be classified into distinguishable groups thus they were put under the miscellaneous group. Refer to Table 4.6 below.
### Table 4.6: Miscellaneous conditions

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>No of cases</th>
<th>Diagnoses</th>
<th>No of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus type 1, Diabetic ketoacidosis</td>
<td>6</td>
<td>RVD on HAART, RVD not on HAART, RVD stage 4</td>
<td>34</td>
</tr>
<tr>
<td>HFV, disseminated kaposis sarcoma, herpes circine</td>
<td>2</td>
<td>Oral candida, Oesophageal candida</td>
<td>2</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>1</td>
<td>Renal failure, nephropathy</td>
<td>2</td>
</tr>
<tr>
<td>Hyperlactemia</td>
<td>1</td>
<td>Peripheral neuropathy</td>
<td>1</td>
</tr>
<tr>
<td>Drug overdose/intoxication</td>
<td>1</td>
<td>Immune Reconstitution Syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Malaria</td>
<td>1</td>
<td>Sepsis</td>
<td>1</td>
</tr>
<tr>
<td>Myopathy</td>
<td>1</td>
<td>Organophosphate poisoning</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe MVR, cardiac valve lesion</td>
<td>1</td>
</tr>
</tbody>
</table>

Key: RVD: Retroviral Disease, HAART: Highly Active Antiretroviral Therapy, HFV: Human Foamy Virus, MVR: Mitral Valve Replacement

Table 4.6 above shows that retroviral disease came up as the most occurring diagnosis, with 34 cases diagnosed with it, and was always accompanied by other comorbid conditions e.g. tuberculosis, liver failure, meningitis or pneumonia.

#### 4.2.2.3. Most common encountered conditions

Figure 4.7 below shows the top 10 most encountered diagnosis amongst the 100 patients selected. As stated above RVD was the most common diagnoses overall, followed by meningitis, TB then pneumonia.
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Key: RVD: Retroviral disease, CVA: Cerebrovascular accident, DM 1: Diabetes Mellitus type1, DKA: Diabetic ketoacidosis

Figure 4.7: Top 10 most common diagnoses encountered

4.2.2.4. Types of specimen collected

Sixty six of the 100 patient files had specimens collected for investigating the suspected diagnoses. Out of 66 patient files where specimens were collected, Cerebrospinal fluid (CSF) were collected the most followed by blood cultures as shown in Figure 4.8.
Figure 4.8: Types of specimen collected and the frequency of collection

4.2.2.5. **Microorganism identified**

The micro-organisms which were isolated in the cases where the specimen was sent to the microbiology laboratory are displayed in Table 4.7 which shows that *Cryptococcus neoformans* followed by *P. falciparum* were isolated the most. Two sputum specimens were rejected and are not included in the table.
### Table 4.7: Microorganism isolated

<table>
<thead>
<tr>
<th>Microorganism isolated</th>
<th>Number of times</th>
<th>Specimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klebsiella pneumonia</td>
<td>3</td>
<td>Blood culture</td>
</tr>
<tr>
<td>Coagulase negative Staphylococcus</td>
<td>2</td>
<td>Blood culture</td>
</tr>
<tr>
<td>Corynebacterium spp</td>
<td>1</td>
<td>Blood culture</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>1</td>
<td>Blood culture</td>
</tr>
<tr>
<td>Streptococcus intestasi</td>
<td>1</td>
<td>Blood culture</td>
</tr>
<tr>
<td>Plasmodium falciparum</td>
<td>3</td>
<td>Blood for malaria</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>6</td>
<td>CSF</td>
</tr>
<tr>
<td>Yeast non candida albicans (YNCA)</td>
<td>2</td>
<td>Urine</td>
</tr>
<tr>
<td>Coagulase negative staphylococcus</td>
<td>1</td>
<td>Pus</td>
</tr>
<tr>
<td>Klebsiella pneumonia</td>
<td>1</td>
<td>Pus</td>
</tr>
<tr>
<td>Streptococcus mitis/oralis</td>
<td>1</td>
<td>Pus</td>
</tr>
<tr>
<td>Klebsiella pneumonia</td>
<td>1</td>
<td>Sputum</td>
</tr>
<tr>
<td>Streptococcus viridans</td>
<td>1</td>
<td>Sputum</td>
</tr>
</tbody>
</table>

The majority of specimens which were collected were negative, refer to Table 4.8 which shows that out of the 27 blood cultures collected only 8 were positive and 19 were negative.
Table 4.8: Comparison between the collected specimen and the results

<table>
<thead>
<tr>
<th>Specimen type</th>
<th>No. of collections</th>
<th>No of negative results</th>
<th>No. of positive results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF</td>
<td>33</td>
<td>26</td>
<td>6</td>
</tr>
<tr>
<td>Blood culture</td>
<td>27</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>Sputum</td>
<td>14</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Urine</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Blood for malaria</td>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Pus</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Pleural fluid</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

4.2.2.6. Infection markers

White cell count (WCC), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were the infection markers used to assist in the diagnosis of the cases encountered. In 80 of the 100 patient cases reviewed, these infection markers were requested to assist with the diagnosis. Table 4.9 below shows that the white cell count was normal in majority of cases (40), while the ESR and CRP were elevated in majority of cases.

Table 4.9: Infection markers identified

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>Normal</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>White cell count (wcc)</td>
<td>19 cases</td>
<td>40 cases</td>
<td>15 cases</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (ESR)</td>
<td>3 cases</td>
<td>17 cases</td>
<td></td>
</tr>
<tr>
<td>C-Reactive Protein (CRP)</td>
<td>4 cases</td>
<td>23 cases</td>
<td></td>
</tr>
</tbody>
</table>

4.2.2.7. Antimicrobial prescribing

From the 100 patient files reviewed, there were 16 different antimicrobials prescribed as depicted in Figure 4.9 below. These were either in combination or prescribed
individually. The most prescribed antimicrobial was Rifafour® (Rifampicin, isoniazid, pyrazinamide and ethambutol) which appeared in 51 patients, followed by ceftriaxone which was prescribed 45 times, then metronidazole together with co-trimoxazole (trimethoprim and sulfamethoxazole) which were prescribed for 28 patients.

![Antimicrobials prescribed](image)

**Figure 4.9:** Antimicrobial usage at DGMH internal medicine

### 4.2.2.8. Proper documentation of diagnoses

The indication for the use of some of the antimicrobials discussed above was not always documented. Figure 4.10 below shows the number of times certain
antimicrobials were prescribed without any documented indication. Of the 51 cases where Rifafour® was prescribed, its indication was not documented in at least 21 (41 %) of the cases. Also, in 28 cases where metronidazole was prescribed; it was used without any documented indication in 13 (46 %) of the patients. Refer Figure 4.10.

![Antimicrobials prescribed without any documented indication](image)

**Figure 4.10:** Antimicrobials prescribed without any documented indication

### 4.2.2.9. Prescribing patterns of antimicrobials

The use of certain antimicrobials was not always in accordance with Standard Treatment Guidelines or any antimicrobial policies. This practice was most prevalent with prescriptions containing co-trimoxazole and erythromycin, with regards to dosing frequency and route of administration as given below.

#### 4.2.2.9 (a) Dosing frequency for co-trimoxazole

Table 4.10 below shows the dosage of co-trimoxazole used in the 28 cases where the drug was prescribed, together with the dosing frequency. 960 mg was prescribed
four times per day in 19 cases and the maximum allowable dose of 1920 mg was prescribed in four cases.

Table 4.10: Dosing frequency of co-trimoxazole

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Number of tablets</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>960 mg D</td>
<td>1 DS (160/800)tablet D</td>
<td>2</td>
</tr>
<tr>
<td>960 mg BD</td>
<td>1 DS tablet BD</td>
<td>2</td>
</tr>
<tr>
<td>960 mg QID</td>
<td>1 DS tablet QID</td>
<td>19</td>
</tr>
<tr>
<td>1920 mg QID</td>
<td>2 DS tablets QID</td>
<td>4</td>
</tr>
<tr>
<td>500 mg TDS</td>
<td>1 (80/400) tablet TDS</td>
<td>1</td>
</tr>
<tr>
<td>Total no. of cases</td>
<td></td>
<td>28</td>
</tr>
</tbody>
</table>

Key1: D: daily, BD: twice daily, TDS: three times daily, QID: four times daily

Key2: 1 Double strength (DS) tablet is equal to 2 (80/400) tables

4.2.2.9. (b) Route of administration of erythromycin

Of the 15 patients that had erythromycin as part of their prescription the majority were getting it via the intravenous (IV) route. Refer to Figure 4.11 below.

Figure 4.11: Routes of administration of erythromycin
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4.3 PHASE 2: INTERVENTIONS

The results of Phase 1 were presented to the clinicians, interns and final year medical students during the internal medicine departmental meeting. These were also joined by some staff members from the medical microbiology and the pharmacy department. All the results were discussed thoroughly and suggestions made were taken into consideration before commencing with Phase 2 and Phase 3 of the study. As such, the suggestions which resulted from this meeting together with the results formed the basis of the interventions made thereafter. Those interventions which were implemented included: educating the junior medical staff or prescribers about the importance of appropriate blood culture specimen collection, developing intravenous-to-oral switch guidelines and updating the existing antibiotic protocol at internal medicine department.

4.3.1 Education

On Tuesday 07 Aug. 2012, a bedside training session was organised for interns and final year medical students in the medical wards. In this session, the aseptic technique to be followed when collecting blood cultures from a patient was demonstrated. The people involved were the following:

- Dr MRB Maloba: Co-supervisor and microbiologist
- Dr BG Mashitisho: intern co-ordinator for internal medicine
- Ms P Maleka: Phlebotomist
- Interns and final year medical students
- Bala Tulani (the researcher)

Arrangements were made with a phlebotomist to perform this demonstration. The microbiologist worked together with the phlebotomist in giving this bedside training session. Blood culture specimens were collected from a newly admitted patient in ward 36 in DGMH to demonstrate the principles and steps involved. Some of the issues discussed include:
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- Different blood culture bottles and the circumstances under which they are to be used, for instance, the use of the charcoal containing bottles when a patient has already received antibiotics.

- Indications for blood culture collection

- The implications of not investigating patients with suspected infection or sepsis e.g. wrong antimicrobials prescriptions, or treatment not being de-escalated

- Collection of blood from a single patient for multiple laboratory investigations

- Recommendation was made to start with filling blood culture bottles aseptically first to avoid cross contamination when chemistry and other laboratory investigations are required.

4.3.2 Management of commonly encountered infections

A guideline on how to manage the most commonly acquired infections as identified in Phase 1 was designed. These guidelines were then presented to the internal medicine HOD and other physicians to consider using when managing patients. The document is attached as Appendix 5.

4.3.3 Iv-to-oral switch therapy

A poster was designed and presented to the physicians at the internal medicine department and thereafter displayed at internal medicine wards (i.e. wards 33, 34, 36, 37 and 38). The poster presents the reasons for switching from an IV to an oral formulation and also reasons for not switching. It also shows the different agents available for consideration in switch therapy. The poster is attached as Appendix 6.

A follow up study will be conducted by another student/researcher to monitor the use of the proposed poster in the wards.
4.4 PHASE 3: RESULTS FOLLOWING INTERVENTIONS

4.4.1 Patient selection

Hundred patient files were selected using convenience sampling and reviewed by the researcher so as to complete data collection for this phase. As stated in Section 3.6, data collection in Phase 3 was done following the interventions in Phase 2. Those interventions as stated above include, presentation and discussion of Phase 1 results with the physicians at internal medicine department, education of the interns and final year medicine students about collecting blood for cultures and implementing guidelines for IV-to-Oral switch therapy.

4.4.2 Diagnosis

4.4.2.1 Conditions of the CNS

The following table (Table 4.11) displays the CNS conditions identified in the 100 patient files reviewed. It is clear from the table that meningitis occurred the most amongst other CNS conditions, followed by cerebrovascular accident.

<table>
<thead>
<tr>
<th>CNS conditions</th>
<th>Diagnosis</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis, TBM, Cryptococcal, complicated</td>
<td></td>
<td>34</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Acute confusion</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Meningoencephalitis</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Cerebral oedema, cerebritis</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Epilepsy</td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

Key: TBM: Tuberculous Meningitis
4.4.2.2. Conditions of the respiratory tract

Pneumonia was the most occurring respiratory diagnosis and it was followed by pulmonary tuberculosis and Chronic Obstructive Pulmonary Disease (COPD), refer Table 4.12.

Table 4.12: Conditions affecting the respiratory tract

<table>
<thead>
<tr>
<th>Respiratory conditions</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia, CAP, multilobar, aspiration, PJP</td>
<td>22</td>
</tr>
<tr>
<td>Pulmonary TB, disseminated TB</td>
<td>16</td>
</tr>
<tr>
<td>COAD, COPD</td>
<td>4</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>2</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1</td>
</tr>
<tr>
<td>Lung malignancy</td>
<td>1</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary oedema</td>
<td>1</td>
</tr>
</tbody>
</table>

Key: CAP: Community Acquired Pneumonia, PJP: *Pneumocystis jiroveci* pneumonia, COAD: Chronic Obstructive Airway Disease, COPD: Chronic Obstructive Pulmonary Disease, TB: Tuberculosis

4.4.2.3. Conditions of the gastrointestinal tract

As shown in Table 4.13, each of the GIT conditions was only encountered once.
Table 4.13: Conditions affecting the GIT

<table>
<thead>
<tr>
<th>GIT conditions</th>
<th>Diagnosis</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Gastritis</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Chronic hepatobilary adenoma</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

4.4.2.4. Conditions of the cardiovascular system

Amongst the 100 files reviewed, hypertension and anaemia occurred most amongst the cardiovascular conditions followed by deep vein thrombosis and congestive cardiac failure. Refer Table 4.14.

Table 4.14: Conditions affecting the cardiovascular system

<table>
<thead>
<tr>
<th>Cardiovascular conditions</th>
<th>Diagnosis</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Congestive Cardiac Failure (CCF)</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Deep vein thrombosis, chronic Venous Thromboembolism (VTE)</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Biventricular failure</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Cardiomyopathy (CMO)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Ischaemic heart disorder</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

4.4.2.5. Conditions affecting other organs/systems

Other conditions could not be easily categorised hence they are grouped as miscellaneous conditions in Table 4.15. Retroviral disease (RVD) was the most
common, while malaria, sepsis, warfarin toxicity and dermatitis were the least common conditions.

**Table 4.15: Miscellaneous conditions**

<table>
<thead>
<tr>
<th>Cardiovascular conditions</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>No. of cases</td>
</tr>
<tr>
<td>----------------------------------------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>RVD</td>
<td>26</td>
</tr>
<tr>
<td>DKA</td>
<td>5</td>
</tr>
<tr>
<td>Diabetes mellitus type 2</td>
<td>4</td>
</tr>
<tr>
<td>Autoimmune vasculitis, SLE, SJS</td>
<td>3</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>3</td>
</tr>
<tr>
<td>Renal failure</td>
<td>3</td>
</tr>
<tr>
<td>Dermatitis, Seborrheic dermatitis</td>
<td>2</td>
</tr>
<tr>
<td>Immune Reconstitution Syndrome (IRIS)</td>
<td>2</td>
</tr>
<tr>
<td>Malaria</td>
<td>1</td>
</tr>
<tr>
<td>Oesophageal candida</td>
<td>1</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>1</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1</td>
</tr>
<tr>
<td>Warfarin toxicity</td>
<td>1</td>
</tr>
</tbody>
</table>

Key: RVD: Retroviral disease, DKA: Diabetic ketoacidosis, SLE: Systemic Lupus Erythematosus, SJS: Steven Johnson’s Syndrome

**4.4.3 Most commonly encountered medical conditions**

Figure 4.12 below shows the top 14 most encountered medical conditions amongst the 100 patient files which were reviewed. Figure 4.12 below, shows that meningitis was the most commonly encountered condition followed by RVD, then pneumonia and tuberculosis.
Chapter 4: Results

Figure 4.12: Top 14 most encountered conditions

4.4.4 Types of specimen collected

Sixty six of the 100 patient files had specimens collected for investigating the suspected diagnoses. Out of 66 patient files where microbiological specimens were collected, blood cultures were collected the most, followed by CSF as shown in Figure 4.13.

Key: RVD: Retroviral disease, PTB: Pulmonary tuberculosis, DTB: Disseminated tuberculosis, CVA: Cerebrovascular accident, DKA: Diabetic ketoacidosis, COAD: Chronic Obstructive Airway Disease, COPD: Chronic Obstructive Pulmonary Disease, DM 2: Diabetes Mellitus type 2, SLE: Systemic Lupus Erythematosus, SJS: Steven Johnson’s Syndrome
4.4.5 Micro-organisms identified

The micro-organisms which were isolated in the cases where the appropriate specimen was sent to the microbiology laboratory are displayed in Table 4.16. This shows that *Cryptococcus neoformans* and coagulase negative *Staphylococcus* were isolated the most, followed by *Corynebacterium* species.
Table 4.16: Microorganism isolated

<table>
<thead>
<tr>
<th>Microorganism isolated</th>
<th>Number of times</th>
<th>Specimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase negative staphylococci</td>
<td>4</td>
<td>Blood culture</td>
</tr>
<tr>
<td>Corynebacterium spp</td>
<td>3</td>
<td>Blood culture</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>1</td>
<td>Blood culture</td>
</tr>
<tr>
<td>Pneumococci</td>
<td>1</td>
<td>Blood culture</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>4</td>
<td>CSF</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>1</td>
<td>Tissues</td>
</tr>
<tr>
<td><em>Candida albicans</em></td>
<td>2</td>
<td>Urine</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>1</td>
<td>Urine</td>
</tr>
<tr>
<td><em>Mycobacterium complex</em></td>
<td>1</td>
<td>Sputum</td>
</tr>
<tr>
<td>Acid fast bacilli</td>
<td>1</td>
<td>Sputum</td>
</tr>
</tbody>
</table>

The majority of specimens which were collected were negative; refer to Table 4.17 which shows that out of the 12 sputum specimens collected only two were positive and ten were negative.
Table 4.17: Comparison between the collected specimen and the results

<table>
<thead>
<tr>
<th>Specimen type</th>
<th>No. of collections</th>
<th>No of negative results</th>
<th>No. of positive results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood culture</td>
<td>37</td>
<td>27</td>
<td>9</td>
</tr>
<tr>
<td>CSF</td>
<td>33</td>
<td>29</td>
<td>4</td>
</tr>
<tr>
<td>Sputum</td>
<td>12</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Urine</td>
<td>6</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Fluid/aspirate</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Tissues</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Malaria test</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>TB culture</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

4.4.6 Infection markers

WCC, CRP, ESR and CSF chemistry were the infection markers used to assist in the diagnoses of the cases encountered. In 73 out of the 100 patient cases reviewed, these infection markers were identified. Also, 14 cases in these 73 files also had CSF chemistry investigated. Table 4.18 below shows that in majority of the cases the infection markers were elevated.

Table 4.18: Infection markers identified to assist with the diagnosis

<table>
<thead>
<tr>
<th>Infection marker</th>
<th>Low</th>
<th>Normal</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>White cell count (WCC)</td>
<td>11</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (ESR)</td>
<td>0</td>
<td>4</td>
<td>27</td>
</tr>
<tr>
<td>C-Reactive Protein (CRP)</td>
<td>0</td>
<td>5</td>
<td>26</td>
</tr>
</tbody>
</table>

4.4.7 Antimicrobial prescribing

From the 100 patient files reviewed, there were 27 different antimicrobials prescribed. Figure 4.14 below shows that the most prescribed antimicrobial was
ceftriaxone which was administered to 38 patients, followed by Rifafour® which was prescribed 34 times, then cefuroxime prescribed 29 times.

**Figure 4.14: Antimicrobials prescribed**
4.4.8 Proper documentation

In Phase 3 Cefuroxime was found to be prescribed without any documented indication in most cases, and was followed by metronidazole. On the other extreme doxycycline and albendazole was prescribed only once and without documented indication. Refer to figure 4.15 below.

![Antimicrobials prescribed without a documented indication](image)

**Figure 4.15:** Antimicrobials prescribed with no documented indication

4.4.9 Prescribing patterns of antimicrobials

4.4.9.1. Dosage frequency of co-trimoxazole

It is shown from Table 4.19 below that co-trimoxazole had many dosing intervals and many dosages and it is clear from the table that it was prescribed at 960 mg four times daily in most (12) of the cases.
### Table 4.19: Dosing frequency of co-trimoxazole

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Number of tablets</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>960 mg D</td>
<td>1 DS (160/800)tablet D</td>
<td>2</td>
</tr>
<tr>
<td>960 mg BD</td>
<td>1 DS tablet BD</td>
<td>5</td>
</tr>
<tr>
<td>960 mg QID</td>
<td>1 DS tablet QID</td>
<td>12</td>
</tr>
<tr>
<td>960 mg TDS</td>
<td>1 DS tablet TDS</td>
<td>2</td>
</tr>
<tr>
<td>1920 mg QID</td>
<td>2 DS tablets QID</td>
<td>2</td>
</tr>
<tr>
<td>Total no. of cases</td>
<td></td>
<td>23</td>
</tr>
</tbody>
</table>

Key1: D: daily, BD: twice daily, TDS: three times daily, QID: four times daily

Key2: 1 Double strength (DS) tablet is equal to 2 (80/400) tables

#### 4.4.9.2. Route of administration of erythromycin

A total of 13 patient files reviewed had erythromycin prescribed and in the majority of the cases it was prescribed intravenously. Refer Figure 4.16.

![Route of administration of erythromycin](image)

**Figure 4.16:** Routes of administration of erythromycin
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4.5 SUMMARY

This chapter expressed all the results obtained from the study. The results from Phase 1 of the study, which consisted of self-administered questionnaires and patient file reviews are expressed followed by the results of Phase 2, which consists of the interventions implemented following the findings of Phase 1. Also results of Phase 3 which only consists of patient file reviews.

A discussion of the results is offered in the next chapter.
5.1 INTRODUCTION

The results presented in Chapter 4 will be discussed in this chapter. The chapter starts with a brief discussion of the study population involved in both Phases 1 and 3. This is followed by a discussion of the results according to the six main objectives of the study, as set out in Chapter 1. This discussion compares the results obtained in Phase 1 (baseline) which was before any interventions were made and results from Phase 3, which was done after the interventions were made.

5.2 STUDY POPULATION

5.2.1 Patient demographics

As indicated in Section 3.5 this study included both adult male and female patients who were admitted at the internal medicine wards and were on an antimicrobial agent. For the final analysis in this study 100 patient files were reviewed in Phase 1 and another 100 patient files were reviewed in Phase 3. Phase 1 had 10 more male patient files than females whereas Phase 3 had 12 more female patient files than males. The difference seen is attributed to the convenience sampling method used, which enables the inclusion of any available patient as long as they meet the inclusion criterion. Many studies have been conducted globally to determine gender differences in health seeking behaviour or the use of health services and the results clearly show that women consult services more than men (Vlassoff, 2008). The differences seen could be attributed to many things, for instance, sensitivity to symptoms, knowledge, socialization etc. A study by Green and Pope (1999) which was conducted in the United States over a period of 22 years showed that female sex and age were the predictors of higher health-care usage over the study period (Vlassoff, 2008). Nonetheless, in this study the difference in the number of female and male patients seen was minimal, thus does not support the idea that females have more health-service seeking behaviour than males.
5.2.2 Prescriber demographics

The prescribers at the internal medicine wards comprised interns, community service doctors, registrars and consultants. Because of availability and the convenience sampling, only interns and registrars participated in filling in the questionnaire. These self-administered questionnaires were administered to these prescribers while they were in the wards. The questionnaire was given to 11 prescribers and not to the entire medical staff at the internal medicine. This group does not represent a certain portion of the prescribers in internal medicine, as it is simply the number of those prescribers who were available at the wards during the day of data collection.

5.3 ANTIMICROBIAL USAGE

5.3.1 Prescribed antimicrobials

The most commonly prescribed antimicrobial agents in this study are shown in Figure 4.9 (for Phase 1) and Figure 4.14 (for Phase 3). Ceftriaxone and Rifafour® were the top two most prescribed antimicrobials before interventions were made i.e. in Phase 1 and after interventions were made i.e. in Phase 3. These results are contrary to those obtained by Tlali (2005) who conducted a study on antimicrobial usage in the internal medicine wards at DGMH and found that cefuroxime followed by co-trimoxazole, then erythromycin were the top three most commonly prescribed antimicrobials. Nonetheless, the number of times ceftriaxone and Rifafour® were used in Phase 3 (38%) is relatively lower than the number of times they were used in Phase 1 (45%). The usage of metronidazole in Phase 3 (14%) was half of that in Phase 1 (28%). This indicates a huge impact brought by the discussion of the findings obtained from Phase 1 with the physicians. The high usage of metronidazole was amongst the topics discussed when the results of Phase 1 were presented. There was no difference seen in the use of other agents like, erythromycin, amoxicillin and clavulanate, amikacin, ciprofloxacin between the two phases.

5.3.2 Prescribing patterns of antimicrobials

Erythromycin and co-trimoxazole came up as two agents which were not prescribed in accordance to standard treatment guidelines or protocols in most cases.
In both Phases 1 and 3 there were more prescriptions of erythromycin by the intravenous (IV) route than the oral. In Phase 1, out of 13 patients who had erythromycin prescribed via the IV route, nine (69%) had other drugs prescribed orally. On the other hand, in Phase 3 out of the nine patients receiving erythromycin via the IV route only five (55%) had other drugs prescribed orally. There is a minor difference observed between the IV usage of erythromycin in Phase 3 compared to Phase 1, meaning the intervention where this use was highlighted might have helped reduce the IV over usage. Apart from its use as an antimicrobial, erythromycin is also used as a prokinetic agent and both the oral and the IV form can be used (Hatton, 2010). Nonetheless, the patients in this study had erythromycin prescribed to them for its antimicrobial properties. To compare the over use of IV erythromycin to other institutions around South Africa would be ideal but no literature could be found.

*Pneumocystis jiroveci* pneumonia (PJP) is an Acquired Immunodeficiency Syndrome (AIDS) defining illness in patients who are in World Health Organization (WHO) clinical stage 4 (Cunha, 2011; National Department of Health, 2012b; WHO, 2004). The treatment is with co-trimoxazole 960mg (2 (80/400) tablets or 1 double strength (DS) tablet) four times daily for 21 days and the prophylaxis thereof is 960mg (2 tablets or 1 DS tablet) daily for at least six months and until the CD4 cell count is above 200 cells/mm$^3$ on antiretroviral therapy (National Department of Health, 2012b). The dosage frequency of co-trimoxazole in this study was also identified not to be in accordance to Standard Treatment Guidelines for South Africa. For instance, the treatment dose for PJP of 960mg four times daily was the most common dosage encountered in both Phases 1 and 3. Even though, the usage was lesser after the interventions were made. In Phase 1 only three patients were suspected to have PJP and would therefore be expected to get the dose of 960mg four times daily. In Phase 3 only one patient was diagnosed with PJP and would thus be expected to be on the 960mg four times a day dosage. Yet, the results of both Phases 1 and 3 showed that the treatment dosage of 960mg four times daily was the most commonly used dosage either as treatment or prevention of PJP. Refer to Tables 4.10 and 4.19.
Another dosage of co-trimoxazole noted in this study was 960mg (2 (80/400) tablets or 1 double strength (DS) tablet) given as a daily dose and this dose is intended as secondary prophylaxis for PJP (National Department of Health, 2012b). PJP is rarely encountered when a patient’s CD4 cell count is above 200 Cells/mm³ hence secondary prophylaxis is required after infection until the CD4 count is above 200 Cells/mm³ (Cunha, 2011). In both Phases of this study only two cases were encountered with the prophylactic dosage and these findings were contradictory since there were very few diagnoses of active PJP infection.

Four patients in Phase 1 received the maximum dosage of 1920 mg (4 (80/400) or 2 DS tablets) four times daily and two patients received this dose in Phase 3. This dosage of co-trimoxazole can be used as treatment of PJP in severe cases and would thus be given for 3 weeks (Rossiter, 2008). Another HIV-related opportunistic infection which occurs at low CD4 cell counts (<100 cells/mm³) is toxoplasmosis (Cunha, 2011). This is also treated and prevented with the use of co-trimoxazole. For instance, in cases of cerebral toxoplasmosis 1920 mg of co-trimoxazole is given twice daily for 4 weeks, then 960mg twice daily for 3 months (Rossiter, 2008). Nonetheless, no diagnoses of toxoplasmosis were identified in this study.

In the discussion of Phase 1 results with the prescribers, the dosing of co-trimoxazole was also discussed but no real difference or improvement is seen in Phase 3. The main reason why prescribers decide to give the 960mg dose four times a day even when they are not treating PJP is that “HIV positive patients always present with complicated infections, hence they don’t want to risk by using the lower doses” said one of the prescribers. Another reason noted by the physicians for using the treatment doses instead of the lower dose was because “it takes long to get confirmatory laboratory results thus the 960 mg four times daily would therefore be used empirically in such cases.”

5.3.3 Documentation of indications for antimicrobials

Table 4.10 shows antimicrobials which were used without any documented indications in Phase 1 (98 antimicrobials) of the study and Figure 4.15 shows antimicrobials which were prescribed without documented indications in Phase 3 (54 antimicrobials).
In general there was a noticeable reduction in the usage of antimicrobials without properly documenting the indication after the interventions were made, as noted in the two figures above. Metronidazole was the second most common antimicrobial prescribed with no indication in both phases but there was a reduction in the number of cases seen in Phase 3. A huge difference was also seen on the use of Rifafour®, which was the number one most commonly prescribed antimicrobial without any documented indication in Phase 1. Rifafour® was used without any indication in 21 cases seen in Phase 1 and was used with no indication in only five cases seen in Phase 3. This is an indication that the educational efforts including the presentation of Phase 1 results to the physicians helped improve Rifafour® usage. Cefuroxime was in third place with 12 cases where it was prescribed without indication in Phase 1 and was the number one most prescribed drug without indication in Phase 3 with 10 cases. This shows a minor improvement as compared with Phase 1. In general, it shows that discussing the results of Phase 1 with the physicians helped in improving documentation of patient’s diagnosis. Similarly, Mohamed Ibrahim and Sahrif (2012) conducted a study to determine the impact of clinical pharmacist interventions on drug and antibiotic prescribing in a teaching hospital in Cairo. The results of that study clearly showed that interventions like distribution of guidelines and giving workshops and seminars on rational drug use to prescribers can lead to significant improvement in prescribing behavior (Mohamed Ibrahim & Sahrif, 2012).

5.4 LABORATORY INVESTIGATIONS

5.4.1 Specimen collection

The type of microbiological specimen to be collected for investigation depends on the suspected infection and its location. For instance, cerebrospinal fluid (CSF) is collected to investigate meningitis or other CNS infections and sputum is the ideal specimen when diagnosing respiratory infections like, pulmonary TB. This concept was one of the topics covered in the presentation in section 4.3.2. A blood culture should always be collected when there is a clinical suspicion of a bloodstream infection (Ntusi et al., 2010). Standard blood culture bottles include an aerobic and anaerobic bottle but when a patient was on an antimicrobial prior to investigation, the bottles used have additives like charcoal or resins which inactivate the antimicrobial
to prevent false negatives (Ntusi et al., 2010). The use of blood cultures to detect bacteraemia in evaluating sick individuals still remains the standard of care (Connell et al., 2007). The advantages of isolating an organism includes optimizing the choice and the duration of antimicrobial therapy thereby help reduce hospital stay and unnecessary hospital costs as well as decreasing the development of resistance (Connell et al., 2007).

In this study blood cultures were requested more in Phase 3 (37 patients) as compared to Phase 1 (27 patients), the majority of the results were negative in both cases. These negative results could have been due to prior administration of antibiotics, the use of inappropriate culture bottles as some prescribers were not aware of the different types of bottles that exist during the discussion in the intervention Phase. There are many factors that might affect the yield form blood cultures but evidence from both adult and paediatric studies show that the rate of isolation from blood cultures increases with the quantity of blood submitted (Connell et al., 2007). Thus, blood volume is the most important factor to consider when culturing. Other reasons for negative results include:

- Organisms may no longer viable be present and the clinical signs being are due to by-products like endotoxins
- Somatic cells may have phagocytized the organism
- Antibiotics used prior the investigation may have killed or suppressed organism numbers to unrecoverable levels
- Storage may have reduced numbers of viable organisms to undetected levels
- The organism may require special cultural conditions other than those used during routine isolation, for instance, reduced temperature, prolonged incubation, special media, anaerobic conditions etc.

The fact that more blood cultures were collected in Phase 3 than in Phase 1 could imply that the educational interventions provided in Phase 2 worked. On the other hand, CSF was collected an equal number of times in both Phases 1 and Phase 3 and the majority of results were negative in both phases. The number of sputum cultures collected in Phase 1 (14) were just a little more than those in Phase 3 (12)
Chapter 5: Discussion

but only two were positive in both Phases (4 positives in total), as the majority of the results were negative, therefore the reasons for the negative results could be any of the ones stated above.

5.4.2 Infection makers

It is a well-known fact that the best way to diagnose bacterial infections is through culturing but this is not a quick process, thus infection and inflammation markers are used to guide treatment and improve patient outcomes (Simon et al., 2004). C-reactive protein (CRP), procalcitonin (PCT), white cell count and erythrocyte sedimentation rate (ESR) are markers which are normally used to confirm the presence of inflammation or infections. Elevated concentrations of these markers beyond the normal reference ranges are used to confirm infections or inflammation. In DGM only WCC, CRP and ESR are use and not PCT. Nonetheless, PCT concentrations are regarded as a better marker of infection as compared to CRP or leukocyte count (Hatherill et al., 1999; Simon et al., 2004). Also, CRP is a more specific marker than ESR. ESR concentrations do not change as rapidly as CRP concentrations and this also adds an advantage to CRP.

In both Phases 1 and 3, these markers were investigated in more than 70% of the patients who were put on an antimicrobial, even though a slightly higher number of patients were investigated in Phase 1 than in Phase 2. Ideally, one would expect that these were investigated in all the patients put on an antimicrobial. ESR and CRP were used in more cases seen in Phase 3 as compared to Phase 1 and were both elevated in a majority of cases as expected, in infectious conditions. CRP is usually increased in an HIV patient together with a range of other infections (Muthu et al., 2007). Since the majority of the patients in this study were found to be RVD positive and on WHO stage 4, it therefore makes sense why the majority of CRPs were elevated.

On the other hand, white cell count was requested in more cases in Phase 1 than in Phase 3. Majority of cases in Phase 1 the WCC was within range and an equal number of normal range and elevated levels was seen in Phase 3. High, normal and low WCC can still point to an infection because many types of infections can be accompanied by a completely normal WCC and differential (DiPiro et al., 2008).
5.4.3 Microorganisms isolated

The most isolated microorganism in both Phases, 1 and 3 of the study was Cryptococcus neoformans, appearing more in Phase 1 (6) than Phase 3 (4). These findings are similar to those obtained by Grootboom in 2010, where fungal meningitis was the most common type of meningitis observed at the internal medicine wards in DGMH. C. neoformans is the most common form of fungal infection in the CNS and a major cause of morbidity and mortality in immunosuppressed individuals (DiPiro et al., 2008). In the United States 85% of cases occur in HIV infected individuals.

In this study K. pneumoniae was the second most common organism isolated in Phase 1 yet no specimen were positive for K. pneumonia in Phase 3. The clinical presentation of K. pneumonia infections is different from all parts of the world. For instance, in South Africa it commonly causes severe Community Acquired Pneumonia (CAP) whereas it is uncommon for this microorganism to cause pneumonia in other parts of the world like, USA, Europe and Israel (Gordon & Feldman, 2010). It is therefore not surprising that this microorganism was amongst the prevalent microorganisms in Phase 1 of this study, and one of the reasons for this difference in Klebsiella cases seen in Phase 1 (in summer) and in Phase 3 (in spring) could be attributed to seasonal variations between the data collection which occurred in Phase 1 and in phase 3. A study conducted by Anderson et al. in 2008 showed that Klebsiella bloodstream infections were higher during warm months. Their study analysed surveillance data from 2001 to 2006 at four hospitals located on four continents and discovered that the incidence rates for Klebsiella infections was highest during the four warmest months (November, December, January and February) of the year as compared to the other eight months (Anderson et al., 2008). Similarly, in DGMH more cases of Klebsiella were identified in Phase 1 of this study which was conducted in two of the warmest months, January and February.

Klebsiella, Pseudomonas and S. aureus are the most common causative organisms for hospital acquired pneumonia in the critically ill patient in the United States (DiPiro et al., 2008). On the contrary, in South Africa K. pneumoniae has been found to be a common causative agent for community-acquired pneumonia, accounting for 15% of such cases and 32% of severe pneumonias which necessitates intensive care admission (Gordon & Feldman, 2010). Therefore providing a second reason why k.
Chapter 5: Discussion

*Pneumoniae* was amongst the most commonly isolated organisms in Phase 1 of this study, as this organism is common for causing CAP in South Africa.

Coagulase negative *Staphylococcus* (CNS) was the second most isolated organism in Phase 3 (4 isolates) but the third most isolated in Phase 1 (2 isolates). In both Phases these isolates were from blood cultures. Coagulase negative *Staphylococci* are most commonly isolated from blood cultures, where they may be just contaminants or a cause of bacteremia (Garcia, *et al.*, 2004). According to Huebner & Goldmann (1999) Coagulase negative *Staphylococcus* are the leading cause of bacteremia in patients with indwelling medical devices such as catheters, artificial heart valves, pace-makers etc. and other infections involving biofilm formation on implanted biomaterials (Garcia, 2004). Nevertheless, it is always very difficult to determine whether an isolate of Coagulase negative *Staphylococcus* represents a true bacteremia or contamination of specimen. In order to make this differentiation, indicators like determining the number of positive blood cultures, species of this organism and biotype, susceptibility testing etc. can be used (Garcia, 2004). In this study, no such tests were done to determine the nature of the Coagulase negative *Staphylococcus*.

*Plasmodium falciparum*, was identified in three cases in Phase 1 but no specimens were positive in the third Phase. Also, more blood specimens (six) were obtained to investigate malaria in the first Phase as compared to Phase 3 (two specimens). It is estimated that 95% of malaria infections in South Africa are caused by *P. falciparum* and the burden of malaria lies with Limpopo and Mpumalanga provinces, even though there is no local transmission in Gauteng, a number of cases are reported each year (DOH, 2008a). Therefore, the very low number of positive specimens for malaria in DGMH is a true reflection of Gauteng province cases. Malaria is seasonal in South Africa and is most prevalent during the wet summer months. Also, Phase 1 data were collected in summer which is why there were more positive blood specimens for *P. falciparum* than Phase 3 where the data were collected in spring.

More than 80% of sputum cultures for investigating TB were negative for Acid Fast Bacilli (AFB) even though TB came up on the top five most common acquired infections in the 200 patient files reviewed in both Phases. HIV infection increases susceptibility to infections including *M. tuberculosis* and the risk increases with
immunosuppression, which also causes the TB to disseminate (WHO TB/HIV, 2004). Since the majority of the patients in this study were HIV infected and were in WHO stage 4, it was therefore expected that their sputum results may be negative even though they are symptomatic for tuberculosis. These negative TB results are supported by a prospective study of pulmonary tuberculosis patients who also had HIV in Lusaka, Zambia which was conducted by Elliott et al. in 1993. This study compared sputum smear results from 72 patients who were HIV positive and 37 patients who were HIV negative. The results of this study showed that 43% of the HIV positive patients had a negative smear compared with 24% of the HIV negative patients and that there was a strong trend towards negative sputum smears in the HIV positive group (Elliott et al., 1993).

5.5 MOST PREVALENT INFECTIOUS DISEASES AT INTERNAL MEDICINE IN DGMH

In order to summarize the most encountered diagnoses in this study, in Phase 1 the top 10 most common encountered conditions were identified but in Phase 3, the top 14 most encountered diagnoses were identified. In Phase 3 the top 14 most common encountered were identified and not the top 10 because six diagnoses occurred the same number of times (three times) making it impossible to use the first 10. Refer to Figure 4.7 and Figure 4.12.

In both Phases, meningitis, RVD, pneumonia and TB came out as the top four most encountered diagnoses as depicted in Figures 4.7 and 4.12. RVD was never diagnosed alone in all the cases where it was identified; it was always diagnosed with either meningitis or TB, and Pneumonia. There were 34 cases of RVD in Phase 1 and 26 cases in Phase 3. It is not surprising that these conditions are the top four most encountered because global studies show a similar pattern. A study conducted by Tlali (2005) over a period of five months at the internal medicine wards in DGMH also displayed a similar disease pattern as this study. Also, pneumonia, followed by TB and then meningitis were the top three most common conditions encountered in internal medicine at DGMH. In 2010 Grootboom also conducted a study at the internal medicine department in DGMH to determine the prescribing patterns in adult
patients with meningitis. This study also revealed that the top four most commonly encountered infectious diseases at internal medicine wards were meningitis, followed by RVD, then TB and lastly, pneumonia.

HIV/AIDS is the largest cause of deaths in South Africa (26%), followed by ischaemic heart disease (7%), stroke (7%), TB (6%) and interpersonal violence (6%) (Crowther-Gibson et al., 2011). In other words 5.5 million cases of HIV/AIDS have been estimated in South Africa which therefore accounts for 17% of the global total (Jarvis et al., 2010). Even though, males usually die from interpersonal violence and TB than females, the latter have higher proportions of deaths due to HIV/AIDS, heart disease and stroke (Crowther-Gibson et al., 2011). When compared to other countries, South Africa has the highest number of people living with HIV/AIDS and it is estimated that 1000 of those die each day as a result of AIDS (Crowther-Gibson et al., 2011). This study also shows HIV/AIDS as the most common diagnosis encountered, which is in support of this fact.

According to van de Beek et al. (2006) in developed countries, the incidence of bacterial meningitis is estimated at 0.6 to 4 per 100 000 per year and could be ten times higher in other parts of the world (van de Beek & de Gans, 2008). In Phase 1 of this study meningitis was the second most common diagnosis but in Phase 3 it was the number one most common diagnoses encountered. These findings are similar to those obtained by Grootboom (2010), where meningitis was the number one most common diagnoses encountered.

The number of tuberculosis cases in this study were also very high in both Phases, 1 and 3 with Phase 1 having almost double the number of cases compared to Phase 3. These figures make sense because tuberculosis is highly prevalent in South Africa. India has the largest TB population in the world, followed by China at second place, then Indonesia and South Africa is at fourth place (Crowther-Gibson et al., 2011). 28% of this TB burden in South Africa is related to HIV/AIDS.

Pneumonia is the sixth most common cause of death in the United States (Bartlett et al., 1998). In the US the overall deaths due to pneumonia and influenza increased by 59% between the year 1979 and 1994 (Bartlett et al., 1998). CAP is the most common type of pneumonia and the incidence is different from country to country,
Chapter 5: Discussion

ranging from 1.6 to 11 per 1000 adults (Esperatti & Marti, 2008). It is therefore no surprise that in both Phase 1 and 3 of this study pneumonia was in the top four (20 cases in Phase 1 and 22 cases in Phase 3) most common diagnosis and majority of the cases were CAP as opposed to HAP.

5.6 PRESCRIBERS’ KNOWLEDGE ON ANTIMICROBIAL STEWARDSHIP

5.6.1 Questionnaire findings

5.6.1.1. Existence of antimicrobial protocols at the internal medicine wards

The antibiotic protocols which were used as reference when designing the questionnaire for the prescribers were obtained from the internal medicine department. Thus, the prescribers were expected to be familiar with all the protocols displayed in Figure 4.1. The protocols for the management of the top three most common infectious diseases in this study (Section 5.5), namely pneumonia, TB and meningitis were the most familiar to the majority of prescribers or physicians.

An antibiotic protocol is used to standardise prescribing patterns which will lead to a decrease in costs, resistance and improve quality of health care (Nathwani, 1999). Aly et al. (2012) conducted an audit of physician’s adherence to the antibiotic policy guidelines in government hospitals in Kuwait. The results of this study showed low adherence levels to the local antibiotic policy guidelines (Aly et al., 2012). Similarly, Table 4.1 shows that at DGMH the majority of the physicians did not adhere to local antibiotic policies as often as they were supposed to. In the discussion of the results of Phase 1 with the physicians, the most common reasons which the physicians gave for not using protocols all the time were that protocols are not usually up-to-date, not always specific to the hospital at hand and most patients do not come with disease presentations similar to the protocol, they come with much more complicated presentations. A study conducted by Essack et al. (2005) to determine antibiotic use and resistance in the public-sector hospitals in Kwazulu-Natal showed that resistance profiles amongst bacteria vary too much amongst different hospitals to allow a national antibiotic policy like the standard treatment guidelines to be used
Chapter 5: Discussion

across the different institutions. Some of the reasons provided by physicians at DGMH for not adhering to antibiotic protocols are similar to those provided by the physicians in the study by Aly et al. (2012), which included the lack of updated protocols.

The Standard Treatment Guidelines and Essential Medicines List (STG/EDL) for South Africa were developed by the South African National Department of Health to provide access to quality and needed health care to all citizens of this country (National Department of Health, 2012b). It is therefore expected that when treating patients in the South African context, these are used often by prescribers, but the results of this questionnaire revealed that the majority of the respondents do not use these guidelines. The lack of training on the use of guidelines like antibiotic protocols or STG/EML came up in the discussion of results with the prescribers as the leading reason why prescribers do not use guidelines as often as expected. The results of the questionnaire also revealed that when prescribers were asked if they have received any training on antimicrobial protocol guidelines, only two of the 11 respondents responded with a yes. The reasons stated by physicians in DGMH are similar to those provided by Aly et al. (2012), in government hospitals in Kuwait. The results of their study showed that poor implementation of the developed protocols, contributed substantially in the suboptimal adherence expressed by the physicians. Similarly, in a study conducted by Mol et al. (2004) on the adherence barriers to antimicrobial treatment guidelines in teaching hospital, in the Netherlands, physicians also suggested that more effort should be put into familiarizing them with the developed guidelines. The physicians suggested an electronic version of the guidelines to be made available to all of them (Mol et al., 2004).

Furthermore, another reason for the suboptimal use of antibiotic protocols was noted as the lack of current or updated guidelines, as all (100%) of the respondents of the questionnaire agreed that the antibiotic protocols at the internal medicine need to be updated and 10 out of the 11 agreed that they would use the updated protocols, should they be available.
5.6.1.2. Specimen collection, turnaround time of results and conditions where specimens were collected

It is expected that prior to prescribing an antibiotic to a patient, microbiological investigations should be done to confirm or exclude an infection. In this study, when the clinicians were asked as to which conditions they normally take specimens for microbiological investigations, Figure 4.3 shows the responses given by the clinicians. It would be expected that microbiological specimens for all the conditions listed in Figure 4.3 so as to optimize antibiotic therapy and also enable streamlining thereafter. Diabetic ketoacidosis (DKA) is usually precipitated by insulin omission in type 1 diabetes and intercurrent illness, particularly infection, therefore one would expect the investigation of infectious causes in a DKA diagnoses (DiPiro et al., 2008).

Once the appropriate microbiological specimen is collected and sent to the laboratory for investigations, the results have to come back timeously to have an impact on patient management. These results help the physician to either confirm or rule out an infection and they help narrow down empirical antibiotic therapy to more specific antimicrobials. The majority of respondents in this study revealed that it usually took more than 120 hours (5 days) for results to get back from the laboratory. This is because on routine cultures only preliminary results are usually available one day after request and susceptibilities would be available two days after receipt but cultures are held 2-14 days depending on the specimen source (Stanford University Medical Centre, n.a). Results from certain tests can be made available as quick as possible, e.g. 2 hours after receipt of the specimen and those include gram stain, India ink preparations and Cryptococcal latex test. On the other hand TB cultures usually take 10 days to 3 weeks to detect positive results whereas negative results are held for up to six weeks (Stanford University Medical Centre, n.a). A study conducted by Rogers et al. (1991) on the turn-around times in a microbiology laboratory showed that the longest interval was that between the specimen arriving in the laboratory and being signed out by the microbiologist than other intervals e.g. interval from collection until received by the laboratory.
5.6.1.3. **Antimicrobial stewardship strategies**

In the questionnaire, the physicians were only asked about two antimicrobial stewardship strategies namely, de-escalation and antimicrobial cycling. The majority of the prescribers rarely de-escalated antimicrobial therapy from empirical therapy and their reasons included the fact that it took long to receive specimen results from the laboratory, amongst other things. Two out of the 11 prescribers did not know what de-escalation strategies are all about and would therefore benefit from education. The majority of respondents did not know what antimicrobial cycling strategies were. One of the reasons for this lack of knowledge about antimicrobial stewardship strategies is that antimicrobial stewardship programme has not been implemented in DGMH. A pilot study on antimicrobial stewardship knowledge and attitudes was conducted by Le Saux (2012) at a paediatric tertiary care centre in Ottawa, Canada. In this study a survey was sent to the physicians in the paediatric care centre with the objective of determining if hospital based physicians had knowledge of fundamental principles of antimicrobial stewardship. The results of this study showed that the mean knowledge score of respondents was 50% and of all the respondents only 9% had had education in stewardship. The study also showed that discontinuing, narrowing the spectrum and decreasing the length of antimicrobial therapy were indicated as the most difficult aspect of modifying therapy by 39%, 28% and 20% of the respondents (Le Saux, 2012).

5.7 **RECOMMENDATIONS FOR STRENGTHENING STEWARDSHIP**

5.7.1 **Interventions introduced in Phase 2**

As indicated in section 4.3, the second phase of this study comprised of three interventions which came up as a result of a discussion which arose as a response to Phase 1 results.

The interventions which were implemented included: educating the junior medical staff or prescribers about the importance of appropriate blood culture specimen collection, developing intravenous-to-oral switch guidelines and updating the current antibiotic protocol at internal medicine. As discussed in section 2.6. education of healthcare professionals is one of the easiest antimicrobial stewardship strategies to
implement. Also, the development and implementation of guidelines/policies brings about a change in the prescribing patterns of prescribers which may lead to a reduction in costs, resistance and improve antibiotic prescribing. Between 1997 and 2003 Goossens et al. (2006) assessed the impact of antibiotic policies in two European countries which had a high antibiotic usage, namely, Belgium and France (Filippini et al., 2011). The authors compared results from these two countries to England, which had lower and persistent antibiotic consumption and the findings suggested evidence of reduced antibiotic prescribing in both Belgium and France. On the other hand, a study conducted by Filippini et al. (2011) in Europe to assess the impact of antibiotic policies revealed that national policies are likely to affect antibiotic consumption more in countries where levels of bacterial resistance are higher as compared to other countries (Filippini et al., 2011). It is therefore necessary to monitor the impact of the strategies employed by this study at DGMH.

5.8 SUMMARY

This chapter discussed all the results presented in Chapter 4 according to the objectives of the study and were compared to published literature and also unpublished studies conducted at DGMH. The results of Phase 1 (baseline) were compared and contrasted with those obtained in Phase 3 (after interventions). Differences and similarities between these results were thus explored. Based on the results of the study, a conclusion, recommendations and limitations of the study are offered in the next and final chapter.
CHAPTER 6
CONCLUSIONS, RECOMMENDATIONS AND LIMITATIONS

6.1 INTRODUCTION

In this chapter the conclusion of the results discussed in Chapter 5 is presented. Also based on the findings of the study, recommendations for practice and further research are offered. This Chapter also presents the limitations encountered while conducting this study.

6.2 CONCLUSIONS

This study included both adult female and adult male patients admitted at the internal medicine wards during the study period and in both phases the gender difference was very small. The clinicians who participated in the questionnaire were selected on the basis of availability and do not represent a particular percentage of the physicians in internal medicine.

This study revealed that ceftriaxone and Rifafour® were the top two most prescribed antimicrobials before and after interventions were made. Even though, after the interventions the number of prescriptions for these were relatively lower. On the other hand, the usage of metronidazole decreased by (50%) in Phase 3, signalling that discussing this over usage in Phase 2 with the physicians had an impact. In general, the usage of penicillin antibiotics was low in this study which is contrary to studies conducted in other teaching hospitals which display its high usage, with or without interventions made.

In both Phases 1 and 3 there were more prescriptions of erythromycin prescribed via the IV route as opposed to the oral route. After this use was discussed with the physicians, only a minor difference was noted.

In this study the dosing of co-trimoxazole in the treatment and secondary prophylaxis of PJP was noticed not to be in line with national guidelines e.g. EDL/EML.
In general there was a noticeable reduction in the usage of antimicrobials without properly documenting the indications in Phase 3 compared to Phase 1.

Blood cultures were collected more after the educational interventions were made as compared to Phase 1. Majority of microbiological investigations were negative.

WCC, CRP and ESR were the infection and inflammation markers investigated in more than 70% of the patients in this study and as expected the majority of ESR and CRP were elevated. On the other hand, WCC was either normal or low in the majority of case, nonetheless these levels can still point out to an infection (DiPiro et al., 2008).

This study revealed *C. neoformans* as the most isolated microorganism, similar to a study by Grootboom (2010), which revealed that fungal meningitis was the most common type encountered in the internal medicine wards at DGMH. *K. pneumonia* was the second most isolated microorganism in Phase 1 yet no specimens were positive in Phase 3. Similarly, *P. falciparum* was investigated more in Phase 1 than Phase 3 and positive results were only obtained in Phase 1. Coagulase-negative *Staphylococcus* was the second most isolated microorganism in Phase 3 and the third most isolated in Phase 1, yet it was not clear whether the cases represent true bacteraemia or contamination.

Meningitis, RVD, pneumonia and TB came up as the top four most encountered diagnoses at the internal medicine in both phases.

Prescriber’s knowledge on antimicrobial stewardship was investigated with the use of a self-administered questionnaire. The questionnaire results revealed that the majority of prescribers were familiar to antibiotic protocols for the top three most common encountered infectious diseases at internal medicine, namely pneumonia, TB and meningitis. Nevertheless, adherence levels to these protocols were very low and this is a global trend. The questionnaire results also revealed that physicians do not collect microbiologic specimens as often as they are supposed to. Majority of
respondents stated that when microbial specimens are sent to the laboratory, it takes longer than five days to receive the results.

The knowledge of prescribers on two antimicrobial stewardship strategies was also determined. Those strategies involve treatment de-escalation and antimicrobial cycling. The majority of the prescribers rarely de-escalate antimicrobial therapy and the most common reason amongst them was the delay noted with the return of microbiologic results. The majority of the respondents were not familiar with de-escalation strategies.

Based on the results of Phase 1 and the discussion with the physicians thereafter, three antimicrobial stewardship strategies were implemented in Phase 2. Those included, education of junior physicians and final year medicine students on blood culturing techniques, development of IV-to-oral antibiotic switch guidelines and updating the guidelines for managing the most common encountered conditions at the internal medicine wards.

6.3 RECOMMENDATIONS

The findings of this study lead to the following recommendations.

6.3.1 Antimicrobial use

There was a small difference observed in the top 3 most commonly prescribed antimicrobials between Phase 1 and Phase 3. Nonetheless, the use of penicillin antibiotics was observed to be very minimal at the internal medicine. A recommendation would be to gather reasons or sensitivity data to determine if microorganisms isolated at DGMH have developed resistance to penicillin.

There was overuse of IV erythromycin even after the educational interventions were made, thus a recommendation would be to further investigate the reasons why
physicians use IV erythromycin more than oral dosage forms even though other agents are prescribed orally.

In Phase 3 there was no real difference seen in the dosing of co-trimoxazole even though it was discussed with the prescribers on presentation of Phase 1 results, thus more education is necessary.

Antimicrobials were commonly prescribed without properly documenting the indication more reinforcement to prescribers about the importance of properly documenting their diagnoses is still necessary.

6.3.2 Laboratory investigations

Further investigations into the reasons why the majority of microbiological laboratory results were negative are highly recommended from either the microbiology laboratory or the internal medicine department.

More education is needed regarding the aseptic technique followed when collecting blood cultures to minimise the dominance coagulase Negative staphylococci isolates from originating from contamination.

Procalcitonin has been proven as a more accurate infection marker than CRP and WCC (Hatherill et al., 1999; Simon et al., 2004). Thus a recommendation would be for the laboratory at DGMH to include this test amongst other infection markers.

6.3.3 Prescribers’ knowledge on antimicrobial stewardship

The findings of this study show that prescribers don’t always use/adhere to national prescribing protocols even though these are designed to assess physicians in making diagnoses and therefore treatment decisions. Since the most common reason for non-adherence was noted to be the lack of up-to-date local policies, lack of training and availability of these guidelines to physicians, then a recommendation would be to update the antibiotic protocols at DGMH and to ensure that all physicians are properly trained on their use.
Chapter 6: Summary, Conclusion and Recommendations

Physicians also suggested that the delay in the turn-around time for specimens sent to the laboratory is amongst the reasons why they rarely de-escalate/ streamline empirical antibiotic therapy and therefore an investigation into the turn-around time for specimens is necessary. This investigation can be done by assessing the process followed by a specimen from collection until the results are available.

The study also revealed that physicians had very little knowledge about antimicrobial stewardship strategies and would therefore require more presentations or focus group discussions about these strategies.

6.3.4 Recommendations for strengthening stewardship

Three interventions for strengthening antimicrobial stewardship in DGMH were introduced. Nonetheless, suboptimal efficacy has been shown post intervention.

Secondly, a poster was designed which presents the guidelines for IV-to-oral antibiotic switch. Yet, the use of these guidelines was not apparent in the results post intervention. Therefore, more presentations and more discussions with the clinicians are still necessary to ensure more awareness of the guidelines and to also make the guidelines available electronically for all the physicians.

Thirdly, guidelines on the management of the most commonly encountered infectious disease at internal medicine have been designed as part of Phase 2 and presented to the HOD of internal medicine to consider using them. Refer Appendix 5.

6.4 LIMITATIONS OF THE STUDY

Limitations of the study include the following:

- The study was conducted in the internal medicine department at DGMH and not in other wards therefore the results obtained cannot be applicable to other departments in the hospital e.g. Paediatrics or Intensive Care Unit.

- Convenience sampling was used to select the participants in this study, while this method was correct for selecting the patient files, it did not help selecting the
prescribers for the questionnaire. A formal sampling method was necessary to ensure that the physicians selected for the questionnaire are a true representative sample of the total physicians at internal medicine, in terms of the different ranks as their knowledge, experience, duties and responsibilities differ.

- Any patient who was admitted and was put on an antibiotic was admitted in the study regardless of their diagnosis and only patient files which were available on the patient beds were included, so this might have introduced some bias.

- Antibiotic prescriptions made on discharge of patients were not included in the study and this could have influenced the number of IV to Oral erythromycin prescriptions, as IV dosage forms are rarely prescribed on discharge.

- The period to monitor the change made by the interventions was too short to observe any real difference in the prescribing patterns; hence a follow up study could be beneficial at least 12 months post intervention.
REFERENCES


References


Owens, R.C., Fraser, G.L., Stogsdill, P. 2004. Antimicrobial Stewardship Programs as a Means to Optimize Antimicrobial Use; Insights from the Society of Infectious


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[Accessed 04/07/11].


APPENDICES

Appendix 1: Patient identification form

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<th>Patient names</th>
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Appendix 2: Data capturing form

Study number: 001

Diagnosis:

Microbiological specimen collected: Yes ☐ No ☐

<table>
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<tr>
<th>Date of initiation of drug</th>
<th>Prescribed antibiotic</th>
<th>Total daily dose</th>
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<th>Duration of therapy in days (✓ = administration)</th>
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Appendix 3: Questionnaire for the prescriber

Questionnaire to assess prescriber’s knowledge about antibiotic policies and antimicrobial stewardship at DGMH’s internal medicine wards.

1. Prescriber’s rank/position: (please tick the appropriate box)

Intern  
Community service  
Medical officer  
Registrar  
Consultant/Specialist  
Other (please specify)

2. Which of the following antibiotic protocols are you familiar with in this department? (Please tick the appropriate box)

Community acquired Pneumonia  
Meningitis (acute)  
Meningitis (chronic)  
Infective exacerbations of COPD  
Amoebic liver abscess  
Hemodialysis catheter related sepsis  
Hospital acquired pneumonia  
Diarrhea  
Anti-TB drug induced liver injury
3. Do you refer to an antibiotic policy when prescribing? (Please tick the appropriate box)

Never □  Rarely □  All the time □  Sometimes □

4. If not, what do you refer to when prescribing? (Please tick the appropriate box)

Standard Treatment Guidelines/Essential Drugs List □
South African Medicines Formulary □
DGMH guidelines □
Other □
Please specify other sources……………………………………………………………………………………………………

5. For which infectious conditions do you normally send specimens to the lab, for culture and sensitivity?

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6. Thereafter, how quick do you get the results? (Please tick the appropriate box)

Within 24 hours □  in 48 hours □  More than 120 hours □
Never □

7. Do you think there is a need to update the current antibiotic policies at internal medicine? (Please tick the appropriate box)

Yes □  No □

8. If yes, would you be willing to use the updated version? (Please tick the appropriate box)

Yes □  No □
Appendices

9. Have you been trained in policy guidelines in this department?
   Yes ☐   No ☐

10. How often do you de-escalate antibiotic therapy?
    Never ☐ Rarely ☐ All the time ☐ I don’t know what is that ☐

11. When do you do antimicrobial cycling?
    Never ☐ Rarely ☐ All the time ☐ I don’t know what is that ☐

Thank you very much for participating in this questionnaire and I guarantee that privacy/confidentiality will be maintained and that the information obtained will only be used for the purpose of this study only.
Appendices

Appendix 4: Consent form for prescribers

Statement concerning participation in a Research Project

Name of Study: Antimicrobial stewardship at DGMH

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

I understand that participation in this Study is completely voluntary and that I may withdraw from it at any time and without supplying reasons.

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

I hereby give consent to participate in this Study.

............................................................  ..............................................................
Name of volunteer  Signature of volunteer

Place…………………………………… Date

Statement by the Researcher

I provided verbal information regarding this Study

I agree to answer any future questions concerning the Study as best as I am able.
I will adhere to the approved protocol.

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<tr>
<th>Name of Researcher</th>
<th>Signature</th>
<th>Date</th>
<th>Place</th>
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Appendices

Appendix 5: Guidelines for the management of common infectious diseases at internal medicine (DGMH)

MANAGEMENT OF COMMON INFECTIOUS DISEASES OCCURRING AT INTERNAL MEDICINE DGMH

1. Introduction

Antimicrobial stewardship involves the optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance Owens et al. (2004). One of the essential strategies employed by antimicrobial stewardship programs is provision of guidelines for antimicrobial prescribing in the form of an antibiotic policy. This is a pre-prescription strategy which greatly impact antimicrobial prescribing when implemented and followed properly. The development of antimicrobial resistance over the years is a growing health problem as it influences patient management, especially in the hospital setting. The overuse together with irrational use of antimicrobials has been noted amongst the contributing factors to this development of resistance. Thus providing guidelines for antimicrobial prescribing is the starting point in preventing this problem.

NB: Prior to initiating antibiotics, microbiological specimens are to be collected, bearing in mind that empirical therapy should be given while awaiting the results thereof.

2. Purpose

These guidelines are meant to assist clinicians when deciding on a treatment plan for their patients. It is designed for adult patients managed in a hospital setting and is formulated based on local and commonest infectious disease treatment guidelines, sensitivity patterns and evidence based literature.
3. Meningitis

3.1. Acute bacterial meningitis

This is a medical emergency, blood culture together with CSF (if there intracranial pressure is not raised) should be collected and empirical therapy should be started immediately.

**NB: do not await results before initiating empirical therapy**

<table>
<thead>
<tr>
<th>Common pathogen/s</th>
<th>Suggested empirical therapy</th>
<th>Alternative therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>N. meningitidis</em></td>
<td>Ceftriaxone 2g IV q12h for 2 weeks</td>
<td>Cefotaxime 3g IV q6h for 2 weeks</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
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<td></td>
</tr>
</tbody>
</table>

3.2. Chronic meningitis

Past medical history is very important in aiding the diagnosis process. Blood culture should be done for both bacteria and tuberculosis. Also, CSF should be obtained for investigating Cryptococcus, Syphilis and tuberculosis.

<table>
<thead>
<tr>
<th>Common pathogen/s</th>
<th>Suggested therapy</th>
<th>Alternative therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>M. tuberculosis</em>, <em>Brucella</em>, <em>T. pallidum</em>, <em>Cryptococcus</em>, <em>Toxoplasmosis</em>, <em>Enterovirus</em>, <em>Histoplasmosis</em></td>
<td>Treat pathogen after confirming the diagnosis. Do not treat empirically.</td>
<td></td>
</tr>
</tbody>
</table>
3.2.1 Cryptococcal meningitis

<table>
<thead>
<tr>
<th>Common pathogen/s</th>
<th>Suggested therapy</th>
<th>Alternative therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. neoformans</td>
<td>Amphotericin B IV 0.7 mg/kg/d for 2 weeks Followed by Fluconazole 400 mg daily Oral for 10 weeks then 200 mg daily for life (unless CD4 count is improving)</td>
<td>Fluconazole 800 mg daily IV or Oral for 10 weeks</td>
</tr>
</tbody>
</table>

3.2.2 Tubercular meningitis

<table>
<thead>
<tr>
<th>Common pathogen/s</th>
<th>Suggested therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. tuberculosis</td>
<td>use standard combination tuberculosis therapy for 12 months</td>
</tr>
</tbody>
</table>
4. Pneumonia

4.1. Community acquired pneumonia in an HIV negative patient

4.1.1 Community acquired pneumonia in patients who are admitted without comorbidities and are less than 65 years

<table>
<thead>
<tr>
<th>Common pathogens</th>
<th>Suggested therapy (MILD CASES)</th>
<th>Alternative therapy (SEVERE CASES)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. pneumoniae</td>
<td>Amoxicillin 1g q8h Oral for 5-7 days / cefuroxime 500 mg bd (or Higher)</td>
<td>Amoxicillin/Clavulanic acid 875mg (Amox/clav 375mg + 500mg amoxicillin (to make 625mg)) or Cefuroxime 750mg q12h in penicillin allergy give Ofloxacin 400 bd (confirm) if poor response after 48-72 hours add the same agents as for mild cases in the second column</td>
</tr>
<tr>
<td>H. influenzae</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. aureus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical pathogens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Legionella spp. (falls under other not atypical)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4.1.2 Community acquired pneumonia in patients who are admitted with comorbidities and are above 65 years (e.g. COPD, diabetes mellitus, renal disease, cardiac failure etc.)

<table>
<thead>
<tr>
<th>Common pathogen/s</th>
<th>Suggested therapy</th>
<th>Alternative therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same community pathogens</td>
<td>Amoxicillin/Clavulanic acid 1.2g IV q8h or Cefuroxime 1.5g IV q8h or Ceftriaxone 1g IV q12h or Cefotaxime 1g q8h plus Erythromycin 500mg q6h oral</td>
<td>if allergic to penicillin give Moxifloxacin 400mg IV q24h (Based on availability)</td>
</tr>
</tbody>
</table>

Ofloxacin
4.1.3 Community acquired pneumonia and HIV infection

<table>
<thead>
<tr>
<th>Common pathogen/s</th>
<th>Suggested therapy</th>
<th>Alternative therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pneumocystis jiroveci</em> (PCP)</td>
<td>Co-trimoxazole 160/800 oral q6h for 21 days followed by 160/800 oral daily for at least 6 months and until CD4 count increases to greater than 200 cells/mm³ if one is on HAART or give it lifelong if they are not on HAART</td>
<td>Dapsone 100mg Oral q24h (in case of allergy)</td>
</tr>
</tbody>
</table>

Key: HAART, Highly active antiretroviral therapy

4.1.4 Mycobacteria avium pneumonia

<table>
<thead>
<tr>
<th>Common pathogen/s</th>
<th>Suggested therapy</th>
<th>Alternative therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>M. Avium complex</em></td>
<td>Ofloxacin/ Ciprofloxacin Clarithromycin Ethambutol</td>
<td>Alt Rx Pg 53 antibiotic essentials</td>
</tr>
</tbody>
</table>

4.2. Hospital /ventilator acquired pneumonia

<table>
<thead>
<tr>
<th>Common pathogen/s</th>
<th>Suggested therapy</th>
<th>Alternative therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. aureus</em> (especially MRSA) <em>Enterobacteriaceae</em> <em>P. aeruginosa</em> <em>Acinetobacter spp</em></td>
<td>Piperacillin/tazobactam 4.5g q8h Plus or Minus Vancomycin if MRSA is suspected</td>
<td>Cefepime 2g q8h or Ertapenem 1g q24h or ciprofloxacin 400mg q8h or Levofloxacin 500mg q12h (for sensitive <em>S. aureus</em>) or 750mg q24h or Imipenem 500mg IV q6h or Meropenem IV 1g q8h</td>
</tr>
</tbody>
</table>
5. References


Appendices

Appendix 6: Guidelines for IV-to-Oral switch therapy

### IV-to-Oral Switch Guideline (2012)

#### REASONS FOR CONTINUING WITH IV THERAPY
- Patient is unable to swallow, unconscious or is strictly NPO
- Patient has severe nausea, vomiting, diarrhoea, short bowel syndrome, GI obstruction, mal-absorptive syndrome or ileus
- Patient has active gastrointestinal bleeding
- Patient has continuous tube feedings that cannot be interrupted & the required medication is known to bind to enteral nutrition formulas (e.g. Tetracycline & Divalent cations)
- Patient has experienced severe trauma within the last 72 hours
- Severely immunosuppressed patients
- Neutropenic patients
- High risk patients or have deep-seated infections which require IV antimicrobials to guarantee sufficient drug levels at the site of action, e.g.:  
  - S. aureus bacteraemia
  - Meningitis
  - Neurosurgical fasciitis
  - Severe soft tissue & soft tissue infections e.g. group A haemolytic streptococcal infections
  - Intracranial abscess
  - Liver abscess
  - Infective endocarditis
  - Legionella pneumonia
  - Infections of cystic fibrosis
  - Inadequately drained abscesses
  - Empyema
  - Infections of implants/prostheses
  - Osteomyelitis
  - Septic arthritis

#### REASONS FOR SWITCHING
- There is clinical improvement
- Signs and symptoms of infection are improving e.g. fever, white cell count, CRP, PCT etc.
- Patient is able to eat a regular or modified diet
- Patient is able to receive enteral nutrition by the oral, gastric or other enteral tube
- Patient is able to receive other scheduled medication by the oral route
- The oral route is not compromised e.g. by vomiting, severe diarrhoea, mal-absorptive disorder, swallowing problems or unconscious
- Patient does not meet any of the exclusion criteria

#### Continuous IV therapy and review for switching criteria every 24 hours.

#### Does the patient meet the above criteria for switching?

**N** =

**Y** =

Use this table to select the appropriate oral agent to switch to.

<table>
<thead>
<tr>
<th>IV agents</th>
<th>ORAL agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin 000mg – 2g 4-6 hourly</td>
<td>Amoxicillin 000mg – 1g 6 hourly</td>
</tr>
<tr>
<td>Cefuroxime 1.2g 2-4 hourly</td>
<td>Cefuroxime 000mg – 1g 8 hourly</td>
</tr>
<tr>
<td>Cefonicid 1.2g 4 hourly</td>
<td>Cefonicid 000mg – 2g 6 hourly (Co-amoxiclav 975mg + Amoxicillin 500mg)</td>
</tr>
<tr>
<td>Clindamycin 600mg – 1.2g 8 hourly</td>
<td>Clindamycin 000mg – 1g 8 hourly (000mg in severe cases)</td>
</tr>
<tr>
<td>Cefotaxime 750mg 8 hourly or 1.5g 8 hourly in severe cases</td>
<td>Cefotaxime 000mg – 1g 8 hourly (Co-amoxiclav 000g 8 hourly)</td>
</tr>
<tr>
<td>Clarithromycin 500mg 12 hourly</td>
<td>Clarithromycin 000mg – 1g 12 hourly</td>
</tr>
<tr>
<td>Co-trimoxazole 000g 24 hourly PCP prophylaxis, 000mg 12 hourly in acute infections and 000mg 24 hourly in PCP treatment for 21 days</td>
<td>Co-trimoxazole 000mg 24 hourly PCP prophylaxis, 000mg 12 hourly in acute infections and 000mg 24 hourly in PCP treatment for 21 days</td>
</tr>
<tr>
<td>Ciprofloxacin 000mg 12 hourly</td>
<td>Ciprofloxacin 000mg 12 hourly</td>
</tr>
<tr>
<td>Cefazolin 1.5g 8 hourly (maximum 15g daily)</td>
<td>Cefazolin 000mg 1g 8 hourly</td>
</tr>
<tr>
<td>Amoxicillin 150mg 24 hourly (maximum 1.5g 24 hourly)</td>
<td>Amoxicillin 000mg 1g 12 hourly</td>
</tr>
<tr>
<td>Sulfamethoxazole 200mg 12 hourly (or 500mg/800mg in combination with a penicillin)</td>
<td>Sulfamethoxazole 000mg 8 hourly</td>
</tr>
<tr>
<td>Metronidazole 500mg 8 hourly</td>
<td>Metronidazole 000mg 8 hourly</td>
</tr>
<tr>
<td>Erythromycin 1g 6 hourly</td>
<td>Erythromycin 000mg 6 hourly</td>
</tr>
</tbody>
</table>

### Resources: