

Using hospital data to generate facility-specific antibiogram for a private hospital in the Western Cape

HM Snyman

 orcid.org/0000-0002-7560-5595

Dissertation submitted in partial fulfilment of the requirements for the degree *Master of Pharmacy* in *Advanced Clinical Pharmacy* at the North-West University

Supervisor: Dr JM du Plessis

Co-supervisor: Prof JR Burger

Graduation May 2018

Student number: 20249330



ACKNOWLEDGEMENTS

I would like to thank all the people who contributed and assisted in the completion of this research project. The study would not have been possible without the support and help of several people. The following people deserve special acknowledgement:

- I give my praise to the Lord my God for all my talents, opportunities, and strength that He gave me and for carrying me through this amazing life journey. Thank You for all Your Grace and for the wonderful people You have surrounded me with throughout this period of my life.
- To Dr Jesslee du Plessis, as supervisor of this study, for your advice, guidance, and insights in this study. I do appreciate all the effort and time you devoted to me.
- To Prof Johanita Burger, as co-supervisor of this study, for your assistance throughout this study.
- To Ms Marike Cockeran, for your expertise in the statistical analysis of the data.
- To Ms Helena Hoffman for assistance with the referencing of the study.
- To Ms Engela Oosthuizen, for the administrative support of the mini-dissertation.
- To Prof Annette Combrink for the language editing of the dissertation.
- To Mr Pietie and Mrs Hester Snyman, my parents, for all your prayers, support, motivation, and love.
- To Mr Gerhardt and Mr Wikus Snyman, my brothers, for all your love and support.
- My friends, for all your support and understanding.

Isaiah 44:4

“And they will spring up among the grass like poplars by streams of water.”

LIST OF DEFINITIONS

Adipose tissue	A collection of fat cells (Driskell et al., 2014:630; Mosby's Dictionary of Medicine, Nursing & Health Professions, 2006:44).
Adverse event	Harm caused when a drug was administered, but the drug is not necessarily the cause (Nebeker et al., 2004:796).
Antibiogram	Described by The National Committee for Clinical Laboratory Standards (NCCLS, 2002:1) as the overall profile of antimicrobial susceptibility results of an organism to a panel of antimicrobial agents.
Antibiotics	An agent produced by a semi-synthetic substance or derived from a micro-organism used to inhibit or cause death of another micro-organism (Merriam-Webster's Medical Dictionary, 2015a).
Antimicrobial	A substance or agent that kills or inhibits the growth or replication of a micro-organism (Dorland's Illustrated Medical Dictionary, 2012:107; Mosby's Dictionary of Medicine, Nursing and Health Professions, 2006:119).
Antimicrobial stewardship	Designed ordered interventions in order to improve and measure appropriate antimicrobial usage (Kelkar & Galwankar, 2013:43).
Azotaemia	An excess of urea or other nitrogenous compounds in the blood (Dorland's Illustrated Medical Dictionary 2012:188; Mosby's Dictionary of Medicine, Nursing and Health Professions, 2006:179).
Bacteria	Prokaryotic, unicellular micro-organisms that multiplies by cell division and whose cell is typically contained within a cell wall (Dorland's Illustrated Medical Dictionary, 2012:191).
Cephalosporinases	Beta-lactamases that inactivate cephalosporins (Gallagher & MacDougall, 2013:70).
Colonisation	A state in which the micro-organism might be present in the host in a setting in which the level of damage is insignificant (Casadevall & Pirofski, 2000:6516).
Commensal	Refers to a microbe-human host interaction where the micro-organism is a normal inhabitant of the human body. Either the microbe or the host benefits in a commensal relationship (Relman & Falkow, 2014:1).
Comorbid	An existing condition and usually dependent of another medical condition (Meghani et al., 2013:1).
Cumulative antimicrobial susceptibility report	Described by the NCCLS (2002:2) as the report generated from a particular institution by analysis of isolates that reflects the percentage of first isolates per patient of a given species that is susceptible to the antimicrobial agents routinely tested.
Effective regimens	Described by Fox et al. (2008:S58) as dual combinations where the isolate was susceptible to at least one or two antimicrobials.

Empiric therapy	Treating a disease based on observations and experience without understanding the cause or mechanism of the disorder or in what way the therapeutic agent or procedure will affect the improvement (Mosby's Dictionary of Medicine, Nursing & Health Professions, 2006:637).
Empiric treatment	Described by Mosby's Dictionary of Medicine, Nursing and Health Professions (2006:1887) as a method of treating a disease based on observations and experiences without an understanding of the cause or mechanism of the disorder or the way the therapeutic agent or procedure effects improvement or cure.
Genera	The major subdivision of organisms of a biological family (The Free Dictionary, 2016a).
Intermediate susceptibility	When the bacterial strain is inhibited in vitro by a concentration of the drug, but the therapeutic effect is uncertain (Rodloff <i>et al.</i> , 2008:658).
Isolate	Explained by Mosby's Dictionary of Medicine, Nursing and Health Professions (2006:1021) as a pure culture of a micro-organism derived from any source.
Minimum (minimal) inhibitory concentrations	The lowest concentration of an antimicrobial agent that is effective against a bacterial infection, determined by inoculation of the bacteria into a culture medium containing various concentrations of a proposed antimicrobial (Mosby's Dictionary of Medicine, Nursing and Health Professions, 2006:1207; Wiegand <i>et al.</i> , 2008:163).
Neutropenia	A condition when the circulating neutrophils in the non-marginal pool decreases. When the absolute neutrophil count (ANC) falls to the severely neutropenic range (< 500/ μ L) the risk for serious infection increases (Braden, 2016).
OmpF porin	The outer membrane protein structure of the bacteria <i>Escherichia coli</i> (Kefala <i>et al.</i> , 2010:1117-1118).
Pathogen	A specific bacterial or viral agent that can cause a disease (Merriam-Webster's Medical Dictionary, 2015b).
Penicillinases	Beta-lactamases that are active against penicillins but inactive against cephalosporins (Gallagher & MacDougall, 2013:70).
Pharmacodynamics	The science of the action of the drug on the body or on micro-organism; e.g. the rate and extent of bactericidal action and post-antibiotic effect (Levison & Levison, 2009:791).
Pharmacokinetics	The study of the absorption, distribution, metabolism, and excretion of drugs (Bauer, 2008:3).
Plague	A virulent infectious disease caused by the bacterium <i>Yersinia pestis</i> . Bubonic and pneumonic is the two main clinical forms of plague that exists. The most common form is bubonic and is characterised by painful enlarged lymph nodes (WHO, 2017).
Polypharmacy	The use of multiple different medications by a patient who might have one or several health problems (Mosby's Dictionary of Medicine, Nursing & Health Professions, 2006:1492). Multiple medications usually refer to six or more concurrent medications (Bushardt <i>et al.</i> , 2008:384).

Prevalence	The number of cases of a disease or event occurrence expressed as a ration during a particular period (Mosby's Dictionary of Medicine, Nursing and Health Professions, 2006:1523; The Free Dictionary, 2017a).
Prokaryotic	Unicellular micro-organism that lack a nucleus and membrane-bound organelles (Merriam-Webster's Medical Dictionary, 2016a).
Red man syndrome	A specific reaction to vancomycin that is infusion-related (Sivagnanam & Deleu, 2002:119).
Resistant	Defined by Mosby's Dictionary of Medicine, Nursing and Health Professions (2006:1617) as the capacity of an organism to remain unaffected by an antimicrobial agent.
Sensitivity	Defined by Dorland's Illustrated Medical Dictionary (2012:1692) as the susceptibility to a substance. It refers to the organism or sense organ's capacity to respond to stimulation (Merriam-Webster's Medical Dictionary, 2017).
Specimen	A small sample of something, intended to show the nature of the whole, obtained for testing (The Free Dictionary, 2017b).
Susceptible	Vulnerability of a micro-organism strain to the effects of an antimicrobial agent; lacking immunity (Dorland's Illustrated Medical Dictionary, 2012:1809).
Thrombocytopenia	An abnormal drop in the number of platelets (Gauer & Braun, 2012:612; The Free Dictionary, 2016b).
Torsade de Pointes	A French term meaning "twisting of the points". It is a form of ventricular tachycardia that can rapidly change to ventricular fibrillation and end in cardiac arrest. Torsade de Pointes is characterised by a gradual change in the amplitude and twisting of the QRS complexes around the isoelectric line on the ECG and is associated with a prolonged QT-interval (Smith, 2012:125).
Transient	Microbe-human-host interaction where the micro-organism is only "passing through" and has little consequences for the host (Relman & Falkow, 2014:1).
Transposome	Genetic element that is able to move from one location in a chromosome to another (Muñoz-López & García-Pérez, 2010:115).
Tularaemia	An infectious disease also called deerfly fever or rabbit fever caused by a gram-negative bacterium, <i>Francisella tularensis</i> . The bacteria may be transmitted by insect vectors or direct contact. Six major clinical forms of tularaemia are recognised and depends mainly on the site of entry of the bacteria ulcerations (Maurin & Gyuranecz, 2016:113-115). Clinical presentation include fever, headache and ulcerated skin lesions with localised swollen lymph nodes or by eye infection, pneumonia or gastro-intestinal (Mosby's Dictionary of Medicine, Nursing & Health Professions, 2006:1907).
Virulence	Relative ability of an organism to cause damage in a host (Martínez & Baquero, 2002:647).

LIST OF ABBREVIATIONS AND ACRONYMS

ALT	Alanine transaminase
AmpC	Class C Betalactamase
ANC	Absolute neutrophil count
ATP	Adenosine triphosphate
AUC	Area-under-the-concentration-time curve
CA-MRSA	Community-acquired Methicillin-resistant <i>Staphylococcus aureus</i>
CCU	Critical care unit
CDCP	Centres for Disease Control and Prevention
CK	Creatinine kinase
CLSI	Clinical and Laboratory Standards Institute, United States of America
Cmax	Maximum concentration
DNA	Deoxyribonucleic acid
DRESS	Drug reaction with eosinophilia and systemic symptoms syndrome
ECG	Electrocardiography
EPIC	European Prevalence of Infection in Intensive Care
ESBLs	Extended spectrum beta-lactamases
HA-MRSA	Hospital-acquired methicillin-resistant <i>Staphylococcus aureus</i>
HIV	Human immunodeficiency virus
HREC	Health Research Ethics Committee
ICU	Intensive Care Unit
IDSA	Infectious Diseases Society of America
INR	International normalised ratio

IV	Intravenous
KPC	<i>Klebsiella pneumoniae</i> carbapenemase
MBC	Minimum bacterial concentration
MDR	Multi-drug resistant
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
MRSE	Methicillin-resistant <i>Staphylococcus epidermidis</i>
MSSA	Methicillin-susceptible <i>Staphylococcus aureus</i>
MU	Million units
MUSA	Medicine Usage in South Africa
n	Sample size/number of units in a subgroup of the study sample
N	Population size/total number of units in the study sample
NCCLS	National Committee on Clinical Laboratory Standards, United States of America
NHSN	National Healthcare Safety Network
NWU	North-West University
Omp F protein	Outer membrane protein F
Penicillin VK	Penicillin V Potassium
PO	Per os
PD	Pharmacodynamic parameters
PK	Pharmacokinetic parameters
RNA	Ribonucleic acid
Sp.	Singular species / Genus name
Spp.	Plural or several species

VRE	Vancomycin-resistant enterococci
WHO	World Health Organization

PREFACE

This study is presented as an article-format mini-dissertation, with Chapter 3 containing the results in the form of a manuscript. The manuscript was submitted for publication to the following journal: *Infection control and hospital epidemiology*. The manuscript was written in accordance with author guidelines provided by the journal which are included as Annexure E.

The study is divided into four chapters:

- Chapter 1 provides a short background on the study, along with the objectives, the methodology and statistical methods used, as well as the ethical considerations applicable to this research study.
- Chapter 2 offers a literature review that provides information of antimicrobial therapy and the development and usage of antibiograms in the hospital setting.
- The results and discussions of this study are presented in the form of a manuscript and a poster presentation in Chapter 3.
- Chapter 4 includes the limitations, conclusions, strengths, and recommendation for further studies.
- References and annexures for the study are incorporated at the end.

The co-authors in the manuscript included in Chapter 3 are the supervisor and co-supervisor of this study. They approved this study as well as the manuscript to be included in the results chapter. The following page provides an outline of the respective contributions made by each author to the study.

AUTHORS' CONTRIBUTIONS (STUDY, MANUSCRIPT AND POSTER)

The contribution of each author of the study, entitled “Using hospital data to generate a facility-specific antibiogram for a private hospital in the Western Cape”; the manuscript, entitled “Prevalence and facility-specific antibiogram of pathogens isolated at a private hospital in the Western Cape, South Africa” and poster presentation, entitled “Development and presentation of a facility-specific antibiogram for a private hospital in the Western Cape” are stipulated in the following table:

<i>Author</i>	<i>Role in the study</i>
Ms HM Snyman	Planning and designing of the study project and research presented in the manuscript Writing of literature review Planning of statistical analysis plan Interpretation of results Planning, writing and compilation of the poster presentation Writing the final mini-dissertation and manuscript
Dr JM du Plessis (Supervisor)	Supervision of concept and design of the study and manuscript Supervision in writing of literature review and manuscript Reviewing of the manuscript and poster presentation for academic content and approval of version to be published
Prof JR Burger (Co-supervisor)	Supervision of the concept and design of the study and manuscript Supervision in the writing of the literature review and manuscript Reviewing of the manuscript and poster presentation for academic content and approval of the version to be published
Ms M Cockeran	Statistical analysis of data Verification of the research design Guidance in the interpretation of the results

The co-authors confirmed their different roles in this study, manuscript and poster presentation, as well as their permission that the manuscript may form part of the dissertation in the following statement:

I declare that I have approved the above-mentioned manuscript and poster presentation and that my role in this study, as indicated above, is a representation of my actual contribution, and I hereby give my consent that it may be published as part of the Master of Pharmacy degree in Advanced Clinical Pharmacy of Ms HM Snyman.

Dr JM du Plessis

Prof JR Burger

Ms M Cockeran

ABSTRACT

Title: Development of a facility-specific antibiogram for a private hospital in the Western Cape using hospital data

Fundamental information for a facility can be provided by identifying the prevalent pathogens and their susceptibility profile to antimicrobial agents. The aim of this study was to provide information about the prevalence and local susceptibility patterns of pathogens presented in the form of a cumulative antibiogram.

Two databases, viz. PathProvider® V.1.4.2 and ICNet® Clinical Surveillance Software was used in order to perform a quantitative, observational, descriptive, cross-sectional study by collecting retrospective data from existing medical data records. The study took place at a private facility positioned in Worcester in the Inland and Coastal District of the Western Cape of South Africa. The study population consisted of all patients aged 18 years and older admitted to the critical care, medical, orthopaedic and surgical units of the hospital during the study period of 1 January 2014 to 31 December 2015.

A total of 1424 pathogens were isolated in the hospital of which 63.7% (n = 908) represented gram-negative organisms and 36.2% (n = 516) gram-positive organisms. *Escherichia coli* (34.5%) was the most prevalent organism among gram-negative and methicillin-susceptible *Staphylococcus aureus* (MSSA) (31%) the most prevalent among gram-positive organisms. A total of 192 pathogens were isolated in the critical care unit; the three most prevalent organisms were *Escherichia coli* (n = 34), *Klebsiella pneumoniae* (n = 15) and *Enterococcus faecalis* (n = 13). In the medical unit a total of 408 pathogens were isolated, where *Escherichia coli* (n = 93), *Haemophilus parainfluenzae* (n = 40), and *Klebsiella* species (spp.) (n = 27) were the most prevalent. In the orthopaedic- and the surgical units a total of 288 and 536 organisms were isolated, respectively. *Escherichia coli* (n = 55 for orthopaedic and n = 104 for surgical), MSSA (n = 55 for orthopaedic and n = 78 for surgical) and *Enterococcus faecalis* (n = 22 for orthopaedic and n = 43 for surgical) were the most prevalent organisms.

The cumulative antibiogram generated for the facility included pathogens that were isolated 30 times or more in total in the specific units of the hospital and were presented in separate tables for gram-negative and gram-positive organisms as recommended by the Clinical and Laboratory Standards Institute (CLSI). Species that had fewer than 30 isolates, i.e. *Acinetobacter* spp., coagulase-negative *Staphylococcus* spp. and methicillin-resistant *Staphylococcus* spp. were morphologically grouped together in the antibiogram. *Escherichia coli* had enough isolates to separate urine isolates from non-urine isolates.

The study demonstrated resistance among multi-drug resistant organisms for the hospital. Carbapenem resistance among *Pseudomonas aeruginosa* and *Acinetobacter* spp. was confirmed. Surveillance studies should be done continually in order to monitor resistant patterns of these pathogens.

Key words: antimicrobials, pathogens, susceptibility, resistance, empiric treatment/therapy, antibiotics, combination antimicrobial treatment

OPSOMMING

Titel: Ontwikkeling van 'n fasiliteitspesifieke antibiogram vir 'n privaathospitaal in die Wes-Kaap deur die gebruik van hospitaaldata

Die identifisering van die algemeenste patogene en hul sensitiviteitsprofile ten opsigte van antimikrobiese middels kan fundamentele inligting aan 'n fasiliteit verskaf. Die doel van hierdie studie was om inligting oor die voorkoms en plaaslike sensitiviteitspatrone van patogene, in die vorm van 'n kumulatiewe antibiogram, te verskaf.

Twee databasisse, nl. PathProvider® V.1.4.2 en ICNet® “Clinical Surveillance Software” is gebruik om 'n kwantitatiewe, waarnemings-, beskrywende, deursneestudie uit te voer deur retrospektiewe data uit bestaande mediese data-rekords te versamel. Die studie het by 'n privaatspasient in Worcester in die binnelandse en kusdistrik van die Wes-Kaap van Suid-Afrika plaasgevind. Die studiepulasie het uit alle pasiënte 18 jaar en ouer wat gedurende die studietydperk van 1 Januarie 2014 tot 31 Desember 2015 in die kritieke sorg-, mediese-, ortopediese- en chirurgiese eenhede van die hospitaal opgeneem is, bestaan.

Altesame 1424 patogene is in die hospitaal geïsoleer, verteenwoordigend van 63.7% (n = 908) gram-negatiewe organismes en 36.2% (n = 516) gram-positiewe organismes. *Escherichia coli* (34.5%) was die algemeenste organisme onder die gram-negatiewe organismes en Metisillien sensitiewe *Staphylococcus aureus* (MSSA) (31%) die algemeenste onder die gram-positiewe organismes. Altesaam is 192 patogene in die kritieke sorg-eenheid geïsoleer. Die drie algemeenste organismes was *Escherichia coli* (n = 34), *Klebsiella pneumoniae* (n = 15) en *Enterococcus faecalis* (n = 13). In die mediese eenheid is altesaam 408 patogene geïsoleer, waarvan *Escherichia coli* (n = 93), *Haemophilus parainfluenzae* (n = 40), en *Klebsiella* spesies (spp.) (n = 27) die algemeenste was. In die ortopediese en chirurgiese eenhede is onderskeidelik 288 en 536 organismes geïsoleer. *Escherichia coli* (n = 55 vir ortopediese en n = 104 vir chirurgie), MSSA (n = 55 vir ortopediese en n = 78 vir chirurgie) en *Enterococcus faecalis* (n = 22 vir ortopediese en n = 43 vir chirurgie) was die mees geïsoleerde organismes vir die eenhede.

Die kumulatiewe antibiogram wat vir die fasiliteit gegenereer is, sluit in patogene wat 30 keer of meer in totaal in die spesifieke eenhede van die hospitaal geïsoleer is, en word in aparte tabelle vir gram-negatiewe en gram-positiewe organismes voorgestel, soos aanbeveel deur die Instituut vir Kliniese en Laboratoriumstandaarde (CLSI). Spesies wat minder as 30 isolate gehad het, d.i. *Acinetobacter* spp., koagulase-negatiewe *Staphylococcus* spp. asook metisillien-weerstandige *Staphylococcus* spp. is morfologies saam in die antibiogram groepeer. *Escherichia coli* het genoeg isolate gehad om urine-isolate van nie-urine-isolate te skei.

Die studie het bewys dat weerstandigheid onder veelvuldige middelweerstandbiedende organismes vir die hospitaal getoon word. Karbapenem-weerstand onder *Pseudomonas aeruginosa* en *Acinetobacter* spp. is bevestig. Waarnemingstudies moet deurlopend uitgevoer word om die weerstandigheidspatrone van hierdie patogene te monitor.

Sleutelwoorde: antimikrobiese middels, patogene, ontvanklik vir, weerstandigheid, empiriese behandeling/terapie, antibiotika, kombinasie antimikrobiese behandeling

TABLE OF CONTENTS

ACKNOWLEDGEMENTS	I
LIST OF DEFINITIONS	II
LIST OF ABBREVIATIONS AND ACRONYMS	V
PREFACE	VIII
AUTHORS' CONTRIBUTIONS (STUDY, MANUSCRIPT AND POSTER)	IX
ABSTRACT	XI
OPSOMMING	XIII
CHAPTER 1: INTRODUCTION	1
1.1 Background to study	1
1.2 Problem statement and research questions	4
1.3 Research aims and objectives	5
1.3.1 Research aim	5
1.3.2 Specific research objectives	5
1.4 Research methodology	6
1.4.1 Literature review	6
1.4.2 Empirical investigation	6
1.4.2.1 Study setting	6
1.4.2.2 Target and study population	6
1.4.2.3 <i>Inclusion criteria</i>	7
1.4.2.4 <i>Exclusion criteria</i>	7
1.4.3 Study design	7
1.4.4 Sampling	8
1.5 Data-collection tool	8

1.5.1	Development of data-collection sheets	8
1.5.2	Validity and reliability of data-collection sheets	9
1.6	Data-collection process	10
1.7	Data analysis.....	10
1.7.1	Study variables	10
1.7.2	Statistical analysis	12
1.7.2.1	Descriptive statistics	12
1.8	Ethical considerations	12
1.8.1	Permission and informed consent.....	12
1.8.2	Anonymity.....	13
1.8.3	Confidentiality	13
1.8.4	Anticipated risks and precautions	13
1.9	Chapter summary	13
CHAPTER 2:	LITERATURE REVIEW	14
2.1	Overview of antimicrobial therapy	14
2.1.1	Background to microbiology.....	15
2.1.1.1	Viruses	15
2.1.1.2	Bacteria	16
2.1.1.3	Fungi	17
2.1.1.4	Parasites	18
2.1.2	Prophylactic, empiric and definitive antimicrobial therapy	18
2.1.3	Pharmacological considerations involved in antimicrobial therapy	19
2.1.3.1	Pharmacokinetics involved in antimicrobial therapy	20

2.1.3.2	Pharmacodynamics involved in antimicrobial therapy	22
2.1.3.3	Pharmacokinetic/Pharmacodynamics (PK/PD) parameters	23
2.1.4	Adverse effects of antimicrobial usage	25
2.1.5	Factors in selection of antimicrobial agents	26
2.1.6	Other considerations of antimicrobial therapy	26
2.1.6.1	Bacteriostatic vs. bactericidal characteristics	26
2.1.6.2	Monotherapy vs. combination therapy	27
2.1.6.3	Intravenous therapy vs. oral therapy	27
2.1.7	Factors influencing dosing of antimicrobial agents	28
2.1.7.1	Renal impairment	28
2.1.7.2	Hepatic impairment	28
2.1.7.3	Critical illness/Sepsis	28
2.1.7.4	Obesity	29
2.1.7.5	Burns	29
2.2	Antimicrobial agents	29
2.2.1	Beta-lactam antimicrobials	32
2.2.1.1	Beta-lactamase sensitive penicillins: natural penicillins	33
2.2.1.2	Beta-lactamase sensitive penicillins with extended spectrum: aminopenicillins	34
2.2.1.3	Beta-lactamase inhibitor combinations	36
2.2.1.4	Beta-lactamase resistant penicillin: antistaphylococcal penicillins	37
2.2.1.5	Other beta-lactam antibacterials: cephalosporins and related substances	39
2.2.1.5.1	First-generation cephalosporins	44
2.2.1.5.2	Second-generation cephalosporins and loracarbef	45

2.2.1.5.3	Third-generation cephalosporins	46
2.2.1.5.4	Fourth-generation cephalosporins	48
2.2.1.5.5	Fifth-generation cephalosporins	48
2.2.1.6	Carbapenems	49
2.2.1.7	Monobactams	52
2.2.2	Glycopeptides	53
2.2.3	Fluoroquinolones	54
2.2.4	Aminoglycosides	59
2.2.5	Tetracyclines and glycylcyclines	61
2.2.6	Macrolides and ketolides	64
2.2.7	Oxazolidinones	66
2.2.8	Nitro-imidazoles	67
2.2.9	Nitrofurans and fosfomycin	68
2.2.10	Cyclic lipopeptides	69
2.2.11	Folate antagonists	70
2.2.12	Lincosamides	72
2.2.13	Polymyxins	73
2.3	Antifungal drugs and antimycobacterial drugs	74
2.3.1	Antifungal drugs	75
2.3.1.1	Polyenes	75
2.3.1.2	Azoles	76
2.3.1.2.1	Ketoconazole	76
2.3.1.2.2	Fluconazole	77

2.3.1.2.3	Itraconazole	78
2.3.1.2.4	Voriconazole.....	79
2.3.1.3	Echinocandins	80
2.3.2	Antimycobacterials	81
2.3.2.1	Rifampicin.....	81
2.3.2.2	Isoniazid	82
2.4	Pitfalls and considerations in antimicrobial prescribing	83
2.4.1	Contra-indications and drug-interactions.....	83
2.4.2	Duration of therapy	84
2.5	Resistance	85
2.6	Special patient groups	90
2.7	Antimicrobial combinations.....	91
2.8	Antibiograms	91
2.8.1	Use and necessity of antibiograms	91
2.8.2	Guidelines and decoding of antibiograms	92
2.8.3	Hospital cumulative antibiograms	96
2.8.4	Limitations of antibiograms	96
2.9	Antimicrobial stewardship	97
2.10	Empiric regimens for multi-drug resistant (MDR) organisms.....	98
2.10.1	Multi-drug resistant gram-positive bacteria	98
2.10.1.1	Enterococcus sp.	98
2.10.1.2	Staphylococcus aureus.....	99
2.10.1.3	Streptococcus pneumoniae	100

2.10.2	Multi-drug resistant gram-negative bacilli.....	100
2.10.2.1	Acinetobacter baumannii	100
2.10.2.2	Extended spectrum beta-lactamase producing Escherichia coli, Klebsiella pneumoniae or other Enterobacteriaceae	101
2.10.2.3	Carbapenemase producing aerobic gram-negative bacilli or Pseudomonas aeruginosa.....	101
2.11	Chapter summary	102
CHAPTER 3: RESULTS AND DISCUSSION.....		103
3.1	Introduction	103
3.2	Manuscript	104
3.3	Poster presentation	131
3.4	Chapter summary	135
CHAPTER 4: CONCLUSIONS AND RECOMMENDATIONS		136
4.1	Introduction	136
4.2	Conclusions from the study	136
4.2.1	Conclusions from the literature review	136
4.2.1.1	Review antimicrobial agents	136
4.2.1.2	Investigate resistance trends of pathogens.....	136
4.2.1.3	Determine the development and use of antibiograms in the hospital setting ...	137
4.2.1.4	Determine empirical treatment suggestions for multi-resistant gram-negative organisms	137
4.2.2	Conclusions from the empirical study objectives.....	138
4.2.2.1	Identification of pathogens isolated more than ten times during the study period in the hospital in order to identify the most prevalent pathogens in each unit of the hospital.....	138

4.2.2.2	Determination of susceptibilities of pathogens isolated 30 times or more in the hospital to antimicrobial agents.....	139
4.2.2.3	Generation of a cumulative antibiogram using the local data of pathogens isolated 30 times or more and their susceptibilities to antimicrobial agents.....	140
4.2.2.4	Analysis of the susceptibility of hospital-specific pathogens in order to predict antibiotic combinations that would provide adequate empiric therapy when a multidrug-resistant organism is suspected.....	140
4.3	Limitations of the study	141
4.4	Strengths of the study.....	142
4.5	Recommendations.....	142
4.6	Chapter summary	143
4.7	Study reflection	143
REFERENCES.....		144
ANNEXURE A: ELECTRONIC DATA COLLECTION SHEET A.....		193
ANNEXURE B: ELECTRONIC DATA COLLECTION SHEET B.....		194
ANNEXURE C: TABLE OF STATISTICAL ANALYSIS		195
ANNEXURE D: GOODWILL PERMISSION		196
ANNEXURE E: AUTHORS' GUIDELINES		199
ANNEXURE F: PROOF OF SUBMISSION		214
ANNEXURE G: AUTHORS GUIDELINES.....		215
ANNEXURE H: LETTER OF ACCEPTANCE FOR SASOCP CONFERENCE POSTER PRESENTATION		217
ANNEXURE I: CERTIFICATE OF LANGUAGE EDITING.....		219
ANNEXURE J: CERTIFICATE OF TECHNICAL EDITING.....		220

LIST OF TABLES

Table 2-1:	General classification of fungi	17
Table 2-2:	Classification of beta-lactam antimicrobials	31
Table 2-3:	Classification of other antibacterial agents	32
Table 2-4:	Spectrum of activity for cephalosporin antimicrobial agents	40
Table 2-5:	Classification of antifungals	74
Table 2-6:	Classification of antimycobacterials	75
Table 2-7:	Drug-drug interaction scale rating	84
Table 2-8:	Mechanisms of bacterial resistance	87
Table 2-9:	Example of the presentation of an antibiogram	95

LIST OF FIGURES

Figure 2-1:	Basic bacterial cell shapes	17
Figure 2-2:	General approach to infectious disease therapy.....	19
Figure 2-3:	Representation of the relationship between the patient, pathogen and antimicrobial agent	20
Figure 2-4:	Pharmacokinetic phases and parameters	21
Figure 2-5:	Pharmacokinetic/Pharmacodynamic indices associated with antimicrobial efficacy.....	24
Figure 2-6:	Activity of cephalosporin by generation	39
Figure 2-7:	Genetic exchange of antimicrobial agent resistance among organisms.....	88

CHAPTER 1: INTRODUCTION

1.1 Background to study

Resistance against antimicrobials is currently one of the greatest challenges when treating an infection. There is an indication that resistance against antimicrobials will become an even greater challenge in the future (Karlowsky & Sahm, 2002:487; Ventola, 2015:277). Prosperous drug development, in the early days of antimicrobials, meant that when drug resistance developed, a new antimicrobial agent was always available to treat the increasingly resistant bacteria. Between 1935 and 2003 fourteen new classes of antimicrobials were introduced. With the rapid development of antimicrobials came the development of antimicrobial resistance (Doron & Davidson, 2011:1113). Resistance is one of the reasons why initial empiric antimicrobial treatment could be inadequate and can be associated with therapeutic failure (Fox *et al.*, 2008:S57).

The development of antimicrobials has slowed down over the past thirty years, with limited options for treating the increasingly resistant infections (Coates *et al.*, 2011:184; Doron & Davidson, 2011:1113). Patients die every day because of bacterial infections for which no antimicrobial agent is available (Conly & Johnston, 2005:159; Doron & Davidson, 2011:1113). Since 1998 only two new antimicrobial agents have been approved that have new targets of action, namely linezolid and daptomycin (Conly & Johnston, 2005:159; Doron & Davidson, 2011:1113; So & Shah, 2014:176). The reasons for this are due to the fact that drug development is risky and expensive, and drugs used to treat chronic conditions are more profitable than those indicated to treat infections (Doron & Davidson, 2011:1113; Spellberg *et al.*, 2004:1279). Until antimicrobials in newer classes are developed, those available have to be conserved (Doron & Davidson, 2011:1113-1114; Mouton *et al.*, 2011:107).

According to the World Health Organization (WHO, 2011:2), strategies to prevent the emergence and spread of healthcare associated antimicrobial-resistant organisms are essential. These strategies include the development and implementation of an antimicrobial policy and standard treatment guidelines (WHO, 2011:4). In hospitals, antimicrobial stewardship teams are charged with the task to conserve the antimicrobial agents (Doron & Davidson, 2011:1114). The primary goal of antimicrobial stewardship programmes includes the optimisation of clinical outcomes while minimising unintended consequences of antimicrobial usages. These unintentional consequences include toxicity of antimicrobials, the development of collateral damage (such as *Clostridium difficile* infections) due to overuse of antimicrobials and the increase of resistance (Dellit *et al.*, 2007:159). Therefore, the appropriate use of antimicrobials is a crucial part of patient safety and deserves careful oversight and guidance (Dellit *et al.*,

2007:159). Inappropriate treatment can be described as the wrong choice of antimicrobial agent for treatment of the specific infection or the use of an antimicrobial agent to which a pathogen is resistant (Davey & Marwick, 2008:S15). The use of inappropriate therapy can be used as the predictor of antimicrobial resistance (Dellit *et al.*, 2007:159).

Effective empiric antimicrobial treatment has become very challenging due to the increase in antimicrobial resistance (Ventola, 2015:282-283). The use of incorrect empirical treatment may affect the outcome of the patient, especially in critical ill patients (Kuster *et al.*, 2008:1452). Knowing one's local microbiology data is more relevant to the empiric treatment of an infection (Ting & Miles, 2002:1194). According to Ting and Miles (2002:1194), tables that contain empiric treatment suggestions can be found in the literature but these tables usually represent nationwide data and may not reflect regional epidemiological information. In patients with a suspected acute infection, initial empirical antimicrobial therapy should be selected based on the individual patient characteristics, clinical differential diagnosis, place of infection (i.e. community *versus* hospital-acquired), and non-patient-related epidemiological data such as local susceptibility rates of bacteria (Kuster *et al.*, 2008:1451).

Susceptibility testing of antimicrobials involves the measuring of the ability of a specific organism to grow in the presence of a particular antimicrobial agent *in vitro* and is performed by using the guidelines of the Clinical and Laboratory Standards Institute (CLSI) (Leekha *et al.*, 2011:157; Pathcare, 2007). The ultimate goal of the antimicrobial susceptibility testing is to predict the clinical success or failure of the antimicrobial agent being tested against a specific organism. Data are reported in the form of minimum inhibitory concentrations (MIC), which is the lowest concentration of an antimicrobial agent that inhibits the micro-organism's visible growth (Leekha *et al.*, 2011:157). An annual summary of susceptibility rates, known as a cumulative antibiogram, is used in healthcare facilities to monitor the antimicrobial resistance trends (Hindler & Stelling, 2007:867).

Cumulative antibiograms are primarily used for the selection of appropriate empiric therapy. The cumulative data are produced from the individual results of clinical isolates that are tested against a series of antimicrobial agents. Generally the development and presentation of an antibiogram is initiated by the clinical microbiology laboratory in collaboration with physicians, pharmacists and infection control personnel (Horvat, 2010:S6).

In the antibiogram the cumulative data should be organised into separate tables for gram-positive and gram-negative bacteria, so that the data are easily accessible for the user. For each pathogen the total number of isolates found must be listed and the susceptibility data expressed as the percentage of strains susceptible to the specific antimicrobial agent (Horvat,

2010:S7). An antibiogram usually consists of the most common isolated pathogens in that specific institution along with susceptibilities of the pathogens to the antimicrobial agents that are regularly tested and prescribed in the specific setting. The antibiogram provides an essential tool for clinicians by illustrating the local *in vitro* microbial data. The clinician can use it as a tool in selecting empirical treatment for patients before patient-specific susceptibility reports become available. Some hospitals may further categorise antibiogram data into different areas (e.g. inpatients, outpatients, surgery, intensive care units (ICU)) or sources (e.g. urine, sputum) when sufficient number of isolates are attainable (Ting & Miles, 2002:1190). More accurate assessment of antimicrobial susceptibility is provided by antibiograms and include a larger number of isolates for particular bacteria, because the impacts of unusual isolates are minimised. Cumulative antibiograms are therefore generated on an annual basis (Horvat, 2010:S8).

The CLSI has developed consensus guidelines to standardise methods used in constructing antibiograms (Hindler & Stelling, 2007:868). The recommendations for the cumulative antibiogram preparation include that only species with at least 30 isolates should be included. If fewer than 30 isolates of a species are encountered during a one-year period, it is acceptable to include these isolates only if it is stated in a footnote. Only the first isolate per patient per period should be included, irrespective of the bodily site of the specimen. The percentage of susceptibility of isolates should be calculated. Isolates with intermediate susceptibility should not be included. For *Streptococcus pneumoniae* and *Viridans streptococci* the percentage susceptibility of isolates with intermediate susceptibility for penicillin should also be calculated (Hindler & Stelling, 2007:868; NCCLS, 2002:6-10).

Institution-specific cumulative antibiogram reports that guide the choice of empirical antibacterial therapy in hospital patients are compiled from other patients previously treated at the same institution (Kuster *et al.*, 2008:1451-1452). Microbiological test results are only available after 24 to 72 hours; initial therapy for infections is therefore often empirical and guided by clinical presentation (Leekha *et al.*, 2011:157). Broad-spectrum antimicrobials are used by clinicians to ensure adequate antimicrobial treatment while awaiting microbiology culture and susceptibility results that will facilitate the treatment regimen to the identified pathogen(s). Overuse of broad-spectrum antimicrobials may encourage antimicrobial resistance (Randhawa *et al.*, 2014:1).

The development of a cumulative antibiogram is needed for the construction of a hospital antibiogram policy (WHO, 2011:5). At local level the surveillance for antimicrobial resistance and preparation of a cumulative antibiogram support clinical decision-making, forecast infection control interventions, and support development of antimicrobial-resistance control strategies

(WHO, 2011:18). Antibigrams are recommended to be used as a quality indicator to provide useful information when deciding where to focus educational efforts (WHO, 2011:20).

The Society of Critical Care Medication strongly recommends the use of two antimicrobials of different classes for empirical treatment of neutropenic patients with severe sepsis and patients with suspected multi-drug resistant bacterial pathogens such as *Acinetobacter* and *Pseudomonas* spp. in its “Surviving Sepsis Guideline” (Dellinger *et al.*, 2012:177). The American Thoracic Society and Infectious Disease Society of America (Kalili *et al.*, 2016:e64-e65) joint guideline for the treatment of healthcare-associated pneumonia also support this concept of a combination empiric antimicrobial regimen for suspected multi-drug resistant bacterial pathogens. Together with site of infection, prior knowledge of bacteria and antibigrams available for important pathogens, clinicians can select empiric therapy (Leekha *et al.*, 2011:157). The National Committee on Clinical Laboratory Standards (NCCLS) (currently known as the CLSI), recommends that antibigrams be prepared on an annual basis to allow for proper trend-interpretation without confounders of seasonal variations (Zapantis *et al.*, 2005:2632). Provided the background, it is a necessity that a cumulative antibigram should be compiled for each and every hospital setting.

1.2 Problem statement and research questions

A rise in the multi-resistance of pathogens is limiting the availability of therapeutic options for infections. National antibigrams do not necessarily provide adequate information for specific hospital settings. Since the susceptibility of pathogens varies among institutions it is optimal to base empiric treatment on local susceptibility data (Beardsley *et al.*, 2006:791). Little is known about the susceptibility of pathogens in the Inland Coastal District of the Western Cape and investigation of these local susceptibility data and formulation of a cumulative antibigram supported empiric selection of antimicrobial treatment.

From the above discussion the following research questions were formulated:

- What are the most prevalent pathogens in a specific private hospital in the Western Cape Province of South Africa and what is their susceptibility to antimicrobial agents; and
- What is the best dual-combination therapy for a suspected infection by a pathogen using the susceptibility data?

1.3 Research aims and objectives

The research aims and specific research objectives necessary to conduct this study are discussed next.

1.3.1 Research aim

The general aim of this study was to develop a cumulative antibiogram for a private hospital positioned in Worcester in the Inland and Coastal District of the Western Cape of South Africa, using hospital data. The most prevalent pathogens in each unit of the hospital were identified initially. Hereafter, the susceptibility of pathogens to antimicrobials and most effective combination therapy were determined.

The study consisted of a literature review and an empirical investigation. Specific research objectives were developed for each stage.

1.3.2 Specific research objectives

The objectives of the literature review were to:

- Review antimicrobial agents.
- Investigate resistance trends of pathogens.
- Determine the development and usage of antibiograms in the hospital setting.
- Determine empirical treatment suggestions for multidrug-resistant gram-negative organisms.

The objectives of the empirical investigation were to:

- Identify the most prevalent pathogens that were isolated more than ten times during the study period in the hospital in order to identify the most prevalent pathogens in each unit of the hospital.
- Determine the susceptibilities to the antimicrobial agents of the most prevalent pathogens that were isolated 30 times or more in the hospital.
- Generate a cumulative antibiogram using the local data of pathogens isolated 30 times or more and their susceptibility to antimicrobial agents.
- Analyse the susceptibility of hospital-specific pathogens in order to predict antimicrobial combinations that would provide adequate empiric therapy when a multidrug-resistant organism is suspected.

1.4 Research methodology

1.4.1 Literature review

Literature and research articles that were included in the literature review of this study were selected by the researcher. Using appropriate databases such as EBSCOhost®, Google Scholar™, ScienceDirect® and PubMed the literature review was conducted during 2016-2017. Key words that were used in the internet search to conduct a literature research on a database include: antibiogram, empiric antimicrobial treatment, antimicrobial stewardship, resistance to antimicrobial treatment, dual-combination empiric antimicrobial treatment, cumulative antibiograms, resistance to antimicrobials, antimicrobials, antibiotics, pathogens, pathogen susceptibility, resistance, and colonisation.

1.4.2 Empirical investigation

The empirical study was performed by collecting retrospective data from existing medical data records (refer to paragraph 1.4.3). The steps followed during the empirical investigation are discussed in paragraph 1.6.

1.4.2.1 Study setting

The study took place at a 173-bed private hospital positioned in Worcester in the Inland and Coastal District of the Western Cape of South Africa. The reason for choosing the specific study setting was that it is a private hospital in the area and it provides health services to a large population. Units included in the hospital consist of critical care, obstetrics and neonatal unit, orthopaedic unit, surgical unit, medical unit, theatre, emergency care and a paediatric unit. The average bed occupancy statistics for the hospital for the financial year 1 April 2014 to 31 March 2015 was 73.7% (Wagenstroom, 2015).

1.4.2.2 Target and study population

The target population of this study was all adult patients (≥ 18 years) admitted to the hospital setting from which a pathogen was isolated from 1 January 2014 to 31 December 2015. The target population was estimated at 14 028 (average number of patients admitted as inpatients for the financial year 1 April 2014 to 31 March 2015), since it depends on the number of first pathogens isolated during the period of twelve months. Inpatients were regarded as a patient who occupies a hospital bed for at least one night in the course of treatment, examination, or observation (The Free Dictionary, 2018). Only patients who met the inclusion criteria formed part of the study population.

1.4.2.3 Inclusion criteria

The inclusion criteria used for the study population comprised:

- All male and female patients aged 18 years and older.
- Only patients admitted to the medical unit, orthopaedic unit, surgical unit, and critical care unit (CCU) with a positive cultured pathogen from 1 January 2014 to 31 December 2015.
- Only the first isolate of a pathogen per patient per year that was obtained irrespective of the source of specimen.

1.4.2.4 Exclusion criteria

The exclusion criteria used for the proposed study included:

- Any positive culture that was only a colonisation of organisms according to the Pathcare® laboratory report of the patient. A colonisation is a false positive result and not an indication of a true infection (Hall & Lyman, 2006:788).
- Multiple blood cultures that yielded the same pathogen.

1.4.3 Study design

The study made use of a quantitative, observational, descriptive, cross-sectional research design, collecting retrospective data from existing medical data records.

The design belongs to the category of the non-experimental design methods since the researcher did not attempt to influence the patients (participants) or their surroundings through manipulation or intervention (Mann, 2003:54). Observational studies are done when the investigator observes the natural relationship between factors and outcomes and does not act upon study participants (Thiese, 2014:200). The study design was suitable for this study since data were collected from laboratory information from patients previously admitted to the hospital. The goal was achieved through observing and collecting data on characteristics of interest without influencing the participant. The study was mainly a descriptive retrospective study since data were collected from past events from existing medical data records (Mann, 2003:54). Descriptive research studies examine the situation in its current state and are limited to the description of the occurrence which may be prevalence or incidence (Joubert & Ehrlich, 2012:78). Retrospective designs measure variables from past events (Thiese, 2014:200).

A quantitative research approach focuses on logical concepts within the research and on measurable aspects of human behaviour (Brink, 2011:10). The research can be used in response to questions of variables within the research and involves the collection of data

(Williams, 2011:66). The study design was a quantitative approach since variables were measurable in the study. The independent variables were the wards/units, age, antimicrobials being tested and pathogens and the dependent variables included the susceptibility and resistance to antimicrobials. Cross-sectional studies can be retrospective and consist of assessing a population, as represented by the study sample, at a single point in time (Thiese, 2014:202). The susceptibilities to antimicrobial agents were studied at a point in time in order to assess the susceptibility of pathogens to antimicrobials of the population.

1.4.4 Sampling

All patients who met the inclusion criteria during the study period (1 January 2014-31 December 2015) were included in the study. There was no estimated number of participants for the study since the prevalence of organisms and risk factors of patients admitted to the hospital varies throughout the years. Risks associated with increased infection include hospital days, age, catheters and ventilators (Balkhy *et al.*, 2006:328). Other factors responsible for the varying of prevalence of organisms include facility construction and renovation, maintenance of infection control programmes, hand hygiene, education of staff in infection control practices and disinfection and sterilisation of medical devices, and surgical instruments (Sydnor & Perl, 2011:159-164). Based on the target population estimate of 14 028 patients, it was foreseen that at least 100 patients' data would be included in the study.

1.5 Data-collection tool

Data in this study were obtained from information available on two databases, viz. PathProvider® V.1.4.2 and ICNet® Clinical Surveillance Software. The goals were to collect information on pathogens isolated from a specimen and their susceptibility to antimicrobials and to supply reliable information for the prescribing of antimicrobials in the hospital.

It was the responsibility of the researcher to use the data-collection tool and to collect the data. The data-collection tool consisted of two datasheets (Annexures A and B). Each datasheet was in the format of a Microsoft® Office Excel® spreadsheet. Only data necessary to conduct the cumulative antibiograms were included in the data-collection sheets.

1.5.1 Development of data-collection sheets

The information necessary to be collected on the data sheets were selected based on the recommendations of the NCCLS stated in document M39-A (NCCLS, 2002:3-6). Data needed for the research project were collected retrospectively from the databases (PathProvider® V.1.4.2 and ICNet® Clinical Surveillance Software). The data-collection sheet A (Annexure A)

was designed to collect each patient's information such as patient number, age and the unit/ward admitted to. Clinical information sought was the source of specimen, date of specimen collection, organism cultured, colonisation or infection and susceptibility to antimicrobials. Data-collection sheet B (Annexure B) was developed to capture the susceptibilities of the identified pathogens to the antimicrobial agents tested. The susceptibility of the organism was marked as resistant (R), intermediate (I) or sensitive (S) (NCCLS, 2002:3-6).

1.5.2 Validity and reliability of data-collection sheets

Data used in this study were obtained from the only laboratory used by the hospital, namely Pathcare®. Data were assumed to be valid and reliable since all tests done at Pathcare® complied with the specifications and regulations of laboratory testing. The laboratory data were imported in the ICNet® Clinical Surveillance Software programme by the Information Technology (IT) team of the hospital group. Measurements taken from laboratory tests were seen as more objective, since the reliability and validity was known (Kimberlin & Winterstein, 2008:2277).

Reliability and validity are key indicators of the quality of a measuring instrument. Reliability estimates the stability of measures (test-retest reliability) or internal consistency of measurement instruments (Kimberlin & Winterstein, 2008:2276-2277). The administrative data-capturing sheets ensured reliability as the research can be repeated in any other facility using the ICNet® Clinical Surveillance Software programme. Validity is defined as the extent to which an instrument measures what it intended to measure (Kimberlin & Winterstein, 2008:2276-2277). The administrative capturing sheets included all the variables that needed to be measured in order to generate a cumulative antibiogram according to the guidelines of the NCCLS (2002:3-6). Validity was insured by double-checking all data for accuracy by repeating the capturing process and comparing two sets of data using Excel®. Electronic data collection decreased the opportunity for error in data entry, which resulted in more reliable data collection (Gregory & Radovinsky, 2012:111).

To collect the data an organism for a specific location (ward/unit) was chosen on the ICNet® Clinical Surveillance Software programme. The specific date range (e.g. 1 January 2014 to 31 December 2015) was entered to generate a report, which was then transferred to the datasheets. PathProvider® was only used to clarify any data about a specimen, date of specimen collection, organism, colonisation of organism or any sensitivity to antimicrobial agents where needed.

1.6 Data-collection process

Pathogens isolated and their susceptibilities were retrospectively collected from 1 January 2014 to 31 December 2015 from the private hospital, using the ICNet® Clinical Surveillance Software programme of the hospital.

All data were collected electronically and no hard copies of the data were used. The collection of data took place from 1 April 2016 until 31 December 2016.

ICNet® Clinical Surveillance Software was used to identify all the pathogens in the hospital. These data were captured on data-collection sheet A. Ordered numeric numbers were allocated to the different patients starting from one. All the susceptibility data of the identified pathogens were captured on the data-collection sheet B. PathProvider® V.1.4.2 and ICNet® Clinical Surveillance Software were used to determine the patient's admission number, ward, source of specimen, date of specimen collection, organism/pathogen cultured, infection or colonisation and sensitivity to antimicrobials. The data were transferred to the data sheets and values were correlated to ensure accuracy. A cumulative antibiogram was then generated for the hospital using the collected data.

The susceptibility of the bacterial isolates to the antimicrobial agents was expressed as a percentage (%). It was calculated by summing the number of times the isolate was sensitive to a specific antimicrobial agent (x) divided by the total number of times it was tested against the specific antimicrobial (y). The quotient was then multiplied by 100 to express the value in a percentage (e.g. $\frac{x}{y} \times 100 = \%$) (Adorka *et al.*, 2013:1031). All the susceptibility percentages were reported in a document known as a cumulative antibiogram.

1.7 Data analysis

The susceptibility of an isolated pathogen was expressed as a percentage to each antimicrobial tested. Intermediate susceptibility was categorised as resistant. Each patient had one isolate that contributed to the data. The study variables are discussed in the next section and a summary of the statistical analysis were tabulated and included as Annexure C.

1.7.1 Study variables

Variables can take on more than one possible value and are defined as the qualities, properties or characteristics of persons, things or situations that can change or vary (Brink, 2011:84). To investigate the study population certain study variables were used which are discussed next.

- **Age**

Age can be referred to as a period of human life measured by years from birth (Dictionary.com, 2016a). The patients included in the study from which the data were used were all 18 years and older. The age was calculated by using the date of birth of the patient and their date of treatment.

- **Pathogen**

A pathogen is defined as any micro-organism that is capable of producing a disease (Mosby's Dictionary of Medicine, Nursing and Health Professions, 2006:1410). The names of the pathogens that were isolated were documented. Only the first isolate per patient per year was documented irrespective of the source of specimen.

- **Specimen**

A specimen is defined as a sample of a substance or material for examination or study (Dictionary.com, 2016b). The source of specimens collected from different body sites were documented for each isolate.

- **Drug susceptibility**

The ability of a specific organism to grow *in vitro* in the presence of a particular drug is measured by antimicrobial susceptibility testing (Leekha *et al.*, 2011:157). Resistant (R), intermediate (I) or sensitive (S) were used to document the susceptibility of the isolated pathogen to antimicrobial agents.

- **Wards/Units**

A ward/unit is a division in a hospital for the care of a particular group of patients. The patients generally experience similar medical conditions or are receiving similar treatment (Farlex Partner Medical Dictionary, 2012). Only data were reported of patients admitted to the medical unit, orthopaedic unit, surgical unit and CCU of the hospital.

- **Antimicrobial combinations**

Antimicrobials can be used in combinations of two or more. If the combined effect of the agents is greater than the sum of their independent activities then it is called synergy (Leekha *et al.*, 2011:158). The susceptibility results of hospital-specific pathogens were analysed together with literature in order to predict antimicrobial combinations that would provide adequate empiric therapy.

1.7.2 Statistical analysis

The data of this study were analysed by using the programme IBM® SPSS® Statistics for Windows®, Version 24.0. and Microsoft® Office Excel 2007 was used to assist with general calculations (Cockeran, 2017). Descriptive statistics are used to describe and summarise data (Brink, 2011:171).

1.7.2.1 Descriptive statistics

It is customary to define a study population in descriptive studies and then make observations on a sample taken from it (Banerjee & Chaudhury, 2010:61). Descriptive statistics are used to organise, summarise and display the data collected in a study (Hightower & Scott, 2012). Frequency was used in the study to assist in describing the characteristics of the study populations.

Frequency is the number of times something occurs and is usually expressed as a percentage of the sample size (Maree, 2014:184). The occurrence is normally measured in a unit of time (Merriam-Webster's Medical Dictionary, 2016b).

1.8 Ethical considerations

1.8.1 Permission and informed consent

Admission to the private hospital was subject to terms and conditions as part of the admission contract. This agreement required patient's acknowledgement that the company that owns the hospital and other third parties, were allowed to process personal information for the purposes of providing services. The researcher as an employee of this company at the time of the study had access to information required in the study on a daily basis as part of normal responsibilities as a pharmacist in the hospital. According to the National Health Act 61 of 2003 (Chapter 2 number 16) it is not necessary to obtain informed consent from the patient if the healthcare provider access patient records for research purposes and obtains no information in order to identify the participants (South Africa, 2004:25-26).

The contract between the researcher and the employer had a non-disclosure clause regarding confidential information, which included patients admitted to the hospital. Goodwill permission (Annexure D) to use the data retrospectively was obtained from:

- The Hospital manager
- Pathcare® Laboratory

- Chief clinical officer of the hospital group.

The research commenced after final approval from the Health Research Ethics Committee (HREC) (Ethics number: NWU-00355-15-S1). All goodwill permissions were subject to approval of HREC.

1.8.2 Anonymity

The participants' anonymity was maintained since no names were captured or recorded. It was not possible to link data to the patient's identity. The name of the hospital was kept anonymous in the mini-dissertation, manuscript and poster presentation.

1.8.3 Confidentiality

The confidentiality of the patients was assured during the collection and analysis of the data. All data were kept confidential. It was not possible to link data to the patient's identity since the data were completely unidentifiable at this stage of the study.

The study only commenced after approval of HREC. Confidentiality was ensured since patients' information was kept anonymous.

1.8.4 Anticipated risks and precautions

Anticipated risks associated with this study were classified as medium risk therefore the benefits outweighed the risks for this study. The data and name of the hospital were kept anonymous.

1.9 Chapter summary

In this chapter the background, motivation and ethical considerations for this study were discussed. The chapter that follows will entail a literature review on antimicrobial therapy and antibiograms.

CHAPTER 2: LITERATURE REVIEW

2.1 Overview of antimicrobial therapy

Antimicrobials are known as the “miracle drugs of medical discovery” because they can cure people of potentially fatal infectious diseases (Carlet *et al.*, 2011:369). Antimicrobial, antibiotic and anti-infective terminology includes a variety of pharmaceutical agents that consist of antibacterial, antifungal, antiviral, and antiparasitic drugs (Leekha *et al.*, 2011:156). The terms ‘antibiotic’ and ‘antimicrobial agents’ can be used synonymously (Leekha *et al.*, 2011:156; Sefton, 2002:557).

Antimicrobials are seen as unique drugs, since they act on the bacteria responsible for causing the infection as well as a myriad of commensal bacteria which can create a reservoir of resistant organisms (Carlet *et al.*, 2011:369). Bacteria are pathogenic micro-organisms that invade tissues, damage cells, trigger systemic inflammatory response, and release toxins (Medical Dictionary for the Health Professions & Nursing, 2012). In medical terms a pathogenic organism is any micro-organism that has the capacity to cause a disease (Pirofski & Casadevall, 2012). An infection is normally caused by the establishment of a micro-organism on, or within, a host which could be transient (acute) or persistent (chronic) and may result in harm. Infectious diseases are caused when the interaction between the micro-organism and the host causes damage to the host, resulting in clinical signs and symptoms of a disease due to the associated damage or altered physiology (Relman & Falkow, 2014:1). Opportunistic pathogens on the other hand are microbes that live on, and in, the human body. Usually they do not cause any healthcare problems, but have the potential to cause a disease when gaining access to a part of the anatomy where they do not belong (Engelkirk & Duben-Engelkirk, 2008:4).

Accurate diagnosis of a bacterial infection in clinical practice is difficult (Heuker *et al.*, 2016:253; Klugman, 2003:S27). It is therefore made by applying in-depth knowledge of medical and laboratory science together with principles of epidemiology, pharmacokinetics of antimicrobials and host-parasite interactions (Baron *et al.*, 2013:2; Leekha *et al.*, 2011:156). Eradication of bacteria is the process of completely removing or destroying the bacteria (Medical Dictionary for the Health Professions and Nursing, 2012:668) without destroying the host and is the primary goal of antimicrobial therapy (Bill, 2017:213; Song, 2003:S3).

Infections can be classified into two main categories namely community-acquired and hospital-acquired (nosocomial) infections. Community-acquired infections are infections developed outside of the hospital. When an infection is detected within the first 48 hours of hospitalisation without previous contact to a healthcare service it is also regarded as a community-acquired

infection. Nosocomial infections are infections acquired during hospitalisation. Any localised or systemic condition that results from an adverse reaction due to the presence of an infectious agent(s) or its toxin(s), which occur 48 hours after hospital admission and not incubating at hospital admission time is regarded as a nosocomial infection (Cardoso *et al.*, 2014:1-2; Yarden *et al.*, 2002:1431).

The success of any antimicrobial therapy is determined by complex interactions between the administered drug, the host and the infecting agent (Mueller *et al.*, 2004:369; Rogers *et al.*, 2011:388). The minimum inhibitory concentration (MIC) of a drug against the susceptible organism, the pharmacodynamics (PD) and pharmacokinetics (PK) are needed to identify the dose and dosing interval that would provide adequate blood concentrations to inhibit bacterial growth without causing unnecessary side effects (Roberts *et al.*, 2012:187).

2.1.1 Background to microbiology

Microbiology can be referred to as the study of microbes (Sharma *et al.*, 2009:1169). Microbes can be divided into four general groups, namely viruses, bacteria, fungi, and parasites (Murray *et al.*, 2015:2). Viruses are acellular microbes and are not composed of cells. Bacteria, fungi and parasites, on the other hand, are cellular microbes that are composed of cells and are referred to as micro-organisms (Sharma *et al.*, 2009:1169). The total number of bacteria species across all habitats may alone exceed one million (Woolhouse *et al.*, 2015).

2.1.1.1 Viruses

Viruses, the smallest of all infectious particles, can contain either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) and can infect all living cells. They are parasitic in nature and cannot multiply without living cells since they depend solely on the host cells to carry their metabolic activities for replication. Infections caused by viruses can lead to rapid replication of the cell which leads to an immediate infectious cycle or to a chronic integration of the viral genetic information into the host genome which remains dormant in the cellular site of the host until an etiological agent triggers them to produce (Murray *et al.*, 2015:2). Diseases caused by viruses are determined by the virus and can range from common colds to fatal conditions such as rabies. The survival of the host depends on its immune response, as well as the severity and type of the infection (Murray *et al.*, 2015:2; Sethi, 2002:952-953).

2.1.1.2 Bacteria

Bacteria are simple unicellular organisms that contain no nuclear membrane, mitochondria, Golgi apparatus or endoplasmic reticulum (Murray *et al.*, 2015:2-3). The wall of the bacterial cell is complex and has one of two basic forms, namely gram-positive cell wall or gram-negative cell wall (Silhavy *et al.*, 2010:1-2). The difference between the two basic forms is that a gram-positive cell wall has a thick peptidoglycan layer and a gram-negative cell wall has a thin peptidoglycan layer with an overlying outer membrane (Murray *et al.*, 2015:2; Silhavy *et al.*, 2010:9-10). Some bacteria lack the cell wall structure and they survive only in host cells or in a hypertonic environment (Murray *et al.*, 2015:2). They are atypical organisms resembling organisms of the genera *Mycoplasma*, *Micrococcus* and *Bacillus* (Onwuamaegbu *et al.*, 2005:2-14).

Macroscopic morphology, microscopic morphology, stain characteristics (Gram staining), environmental requirements, nutritional requirements, and resistant profiles are only a few phenotypic characteristics of bacteria that can help to identify and classify the organism (Tille, 2014:2-3). Gram staining (crystal violet) is used to differentiate between the two varieties of bacterial cells. It is a substance that selectively stains cell walls of the gram-positive bacteria. The gram-positive bacteria retain the initial crystal violet due to the thick layer of peptidoglycan. The outer membrane of gram-negative bacteria blocks the stain from adhering to the peptidoglycan within the cell. Those bacteria that are decolorised when stained with red carbol fuchsin or safranin are considered as gram-negative bacteria (Beveridge, 2001:111; Gallagher & MacDougall, 2013:6). *Mycoplasma* is bacteria with no cell walls (Parija, 2014:18). The basic cell shapes of bacteria (refer to Figure 2-1, adapted from Engelkirk & Duben-Engelkirk, 2008:194) are round, or spherical known as cocci, rod-shaped known as bacilli and curved and spiral-shaped bacteria that are referred to spirilla (Young, 2006:674). Bacteria can be divided further into five categories: gram-positive cocci, gram-positive bacilli, gram-negative bacilli, anaerobes, and Candida species (Perez-Jorge & Burdette, 2014). Most medically important gram-positive pathogens are cocci rather than bacilli. The bacilli predominate among gram-negative pathogens (Gallagher & MacDougall, 2013:8-12). Gram-negative cocci rarely cause bacteraemia except for *Neisseria meningitides* (Perez-Jorge & Burdette, 2014).

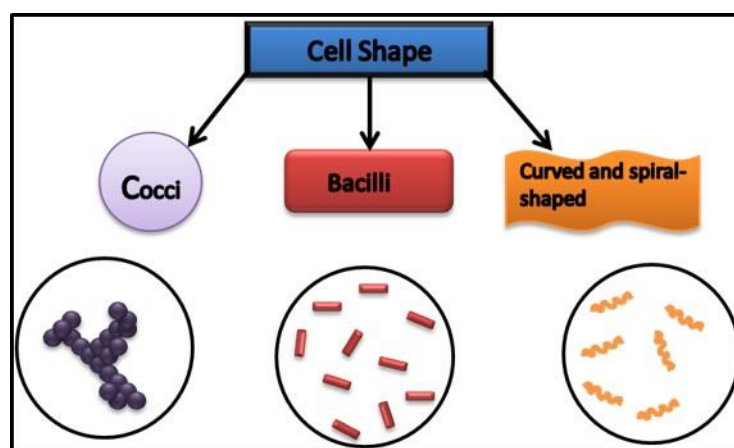


Figure 2-1: Basic bacterial cell shapes

Depending on the particular species and manner in which cells divide, cocci may be seen as being singly or in pairs (diplococci), chains (streptococci), clusters (staphylococci), packets of four (tetrads) or packets of eight (octads) (Engelkirk & Duben-Engelkirk, 2008:194-195). Bacilli may be single, in pairs (diplobacilli), in chains (streptobacilli), branched or in long filaments and spiral-shaped bacilli are also known as spirochetes (Pommerville, 2012:113). *Mycoplasma* bacteria are pleomorphic bacteria which are cell wall-deficient and exist in various shapes (Engelkirk *et al.*, 2011:55).

Bacteria can be classified into aerobes and anaerobes depending on their atmospheric requirements. Aerobes require oxygen to grow and multiply; and anaerobes usually do not require oxygen to live and reproduce (Ellis & Wackett, 2012:3).

2.1.1.3 Fungi

Fungi are eukaryotic organisms with a more complex cellular structure when compared to bacteria. These organisms contain a well-defined nucleus, mitochondria, Golgi apparatus and an endoplasmic reticulum (Murray *et al.*, 2015:3). Fungi can be divided into yeast, dimorphic fungi and moulds (refer to Table 2-1, adapted from Gallagher & MacDougall, 2013:167).

Table 2-1: General classification of fungi

Yeasts	Dimorphic fungi	Moulds
<i>Candida</i>	<i>Histoplasma</i>	<i>Aspergillus</i>
<i>Cryptococcus</i>	<i>Blastomyces</i>	<i>Fusarium</i>
	<i>Coccidioides</i>	<i>Scedosporium</i>
	<i>Paracoccidioides</i>	<i>Zygomycetes</i>

2.1.1.4 Parasites

Parasites can be regarded as the most complex microbes and are all classified as eukaryotic. They are much bigger in size than viruses, bacteria and fungi (Murray *et al.*, 2015:3). Parasites can be differentiated into unicellular parasitic protozoa or parasitic helminths (worms) (Helms *et al.*, 2015:449).

2.1.2 Prophylactic, empiric and definitive antimicrobial therapy

Antimicrobial therapy is the treatment of micro-organisms with chemical agents (Gallagher & MacDougall, 2013:16). All antimicrobial agents have the potential to cause public health consequences since they affect the bacterial ecology by exerting selective pressure and thereby driving resistance whether used appropriately or inappropriately (Deresinski, 2007:S177).

Inadequate therapy against infections in patients who are hospitalised and critically ill are associated with increased morbidity and mortality (Boyd & Nailor, 2011:1077; Leekha *et al.*, 2011:157).

Antimicrobial therapy can be categorised as prophylactic, empiric or definitive therapy (Gallagher & MacDougall, 2013:16). Antimicrobial prophylaxis is used to prevent an infection in patients and its use should be limited to avoid excess cost, toxicity and antimicrobial resistance (Enzler *et al.*, 2011:686). Optimally it should only be given to patients at risk of developing an infection such as patients with weakened natural defences. These are generally the patients using immunosuppressive therapy, cancer patients and patients undergoing surgery (Gallagher & MacDougall, 2013:16). Primary prophylaxis is the prevention of an initial infection and secondary prophylaxis is the prevention of the recurrence or reactivation of an infection. Prophylaxis may also be used to prevent infection by eradicating a colonising organism (Enzler *et al.*, 2011:686). Empiric antimicrobial therapy is described as the initial antimicrobial regimen started within 24 hours of admission when an infection is suspected (Mettler *et al.*, 2007). Because microbiological results may only become available after 72 hours, initial therapy is often empiric and guided by clinical presentation of the patient (Leekha *et al.*, 2011:157; Zur Wiesch *et al.*, 2014:1). A common approach is to use a broad-spectrum antimicrobial agent for initial therapy followed by a narrow spectrum antimicrobial agent once the microbiological results are known (Leekha *et al.*, 2011:157; Mandel *et al.*, 2007:S29-S30). Combinations of antimicrobial agents can also be used empirically with the aim of covering multiple possible pathogens commonly associated with a specific clinical syndrome (Boyd & Nailor, 2011:1081; Leekha *et al.*, 2011:157). Definitive treatment can be described as any treatment acknowledged normally as a specific cure for a disease (Mosby's Dictionary of Medicine, Nursing & Health Professions, 2006:522). It can be seen as "fine tuning" therapy when identification of the

pathogen is completed and susceptibility test results have been obtained (Paterson, 2008:S18). The general approach to antimicrobial treatment of infectious disease can be seen in Figure 2-2 (adapted from Gallagher & MacDougall, 2013:18). Response to antimicrobial treatment can be assessed by the use of clinical and microbiological parameters, such as signs and symptoms, laboratory values and radiological findings (Leekha *et al.*, 2011:162).

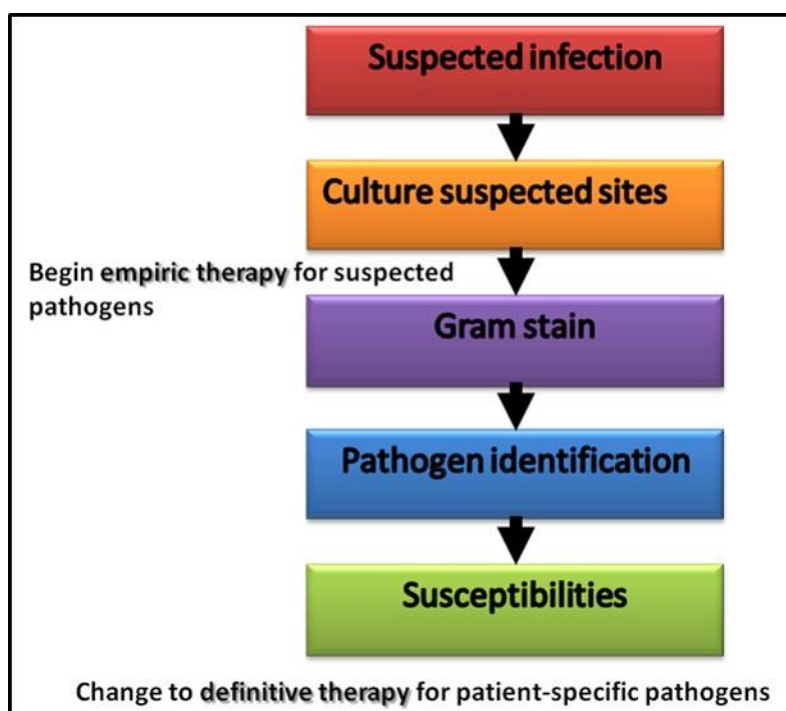


Figure 2-2: General approach to infectious disease therapy

2.1.3 Pharmacological considerations involved in antimicrobial therapy

Drug characteristics, host factors and the infecting pathogen all have an impact on the selection of the antimicrobial agent and dose (McKinnon & Yu, 2004:231). The most comprehensive assessment of the interactions between the pathogen (organism), host (patient) and antimicrobial agent (drug) as schematically illustrated in Figure 2-3 (adapted from Gallagher & MacDougall, 2013:16; McKinnon & Davis, 2004:272) is best provided by the principles of antimicrobial pharmacology and pharmacokinetic parameters of an individual patient. Patient characteristics include those that affect the interaction between the patient and the infection such as comorbid factors, the immune status and patient-specific factors (such as organ function and weight) which will impact again the pharmacokinetic factors of the antimicrobial agent. Considerations of the bacteria include its role as a pathogen in causing the infection at the site, pattern of susceptibility to antimicrobial agents and consequences of resistance. The

selection of the antimicrobial agent includes antibacterial activity, clinical efficacy, safety and potential for drug interactions (McKinnon & Davis, 2004:271). Pharmacokinetic and pharmacodynamic principles are important to assist in optimising efficacy while minimising the risk of drug-related toxicity (Filho *et al.*, 2007:183; McKinnon & Yu, 2004:231).

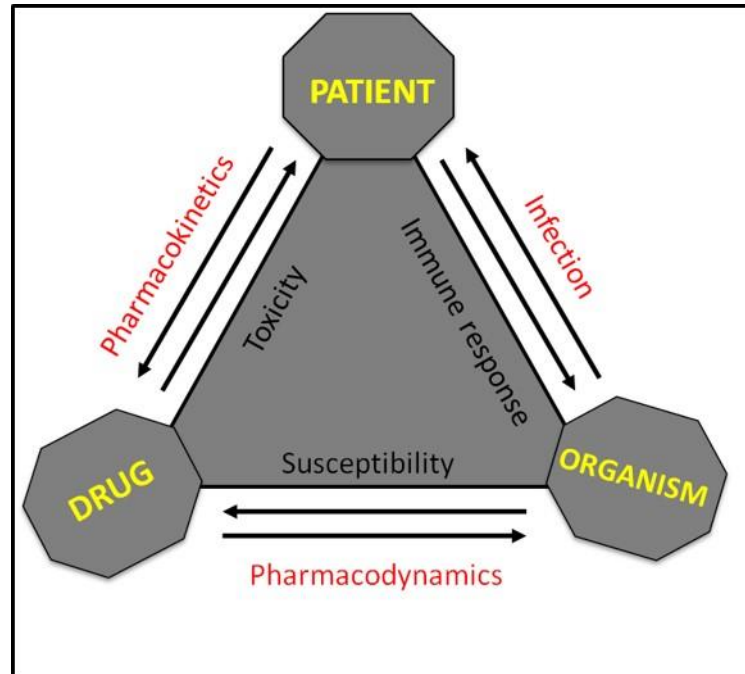


Figure 2-3: Representation of the relationship between the patient, pathogen and antimicrobial agent

2.1.3.1 Pharmacokinetics involved in antimicrobial therapy

Pharmacokinetics is the study of the processes of absorption, distribution, metabolism and elimination and represents the concentration-versus-time profile of an agent when administered *in vivo* (Levison & Levison, 2009:793; McKinnon & Davis, 2004:272). This is the key to effectiveness of drugs since these agents need to reach the right site of infection at a high enough concentration to be effective (Gallagher & MacDougall, 2013:23). Bioavailability of a drug best describes its absorption. It is defined as the percentage of a drug's dose that reaches systemic circulation (Levison & Levison, 2009:791-793). Only medication that is administered IV has a 100% bioavailability because it can directly reach blood circulation (Cyriac & James, 2014).

Pharmacokinetic studies describe parameters such as peak concentration, serum half-life and cumulative exposure to an agent (area-under-the-concentration-time curve (AUC)) for a 24-hour period as illustrated in Figure 2-4 (adapted from Gallagher & MacDougall, 2013:24).

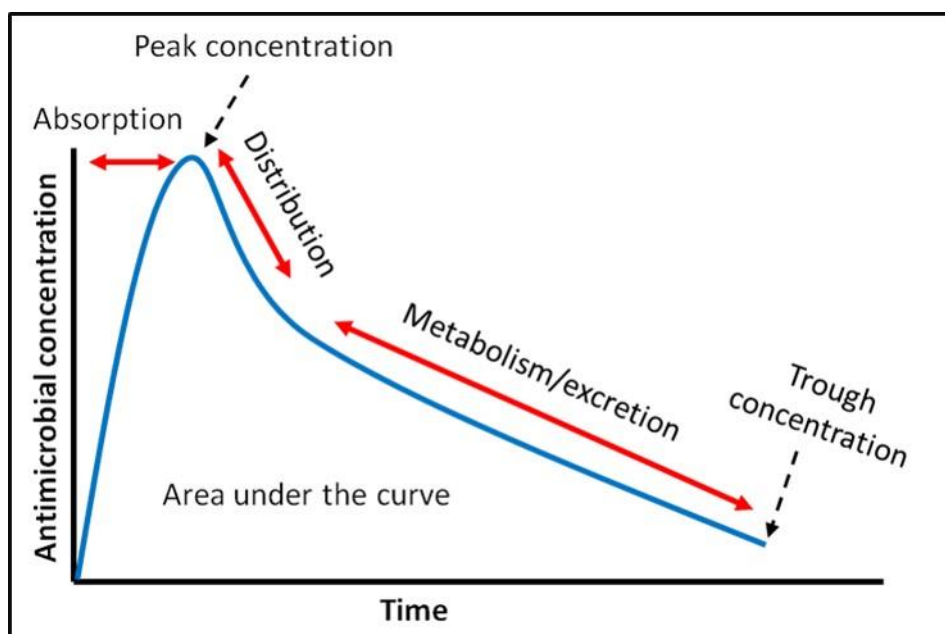


Figure 2-4: Pharmacokinetic phases and parameters

The height of the peak plasma level is determined by the drug's IV infusion rate, dosage, volume of distribution and the elimination rate. Only a few antimicrobial agents have good bioavailability when administered orally. The peak plasma levels of orally administered drugs can be delayed and are usually not as high as those achieved by IV infusion due to absorption and distribution after oral administration (Levison & Levison, 2009:793). Absorption of orally administered antimicrobials can be substantially influenced by food, gastric acidity, poor circulation, and drug interactions (Gallagher & MacDougall, 2013:25; Levison & Levison, 2009:793). Well-absorbed oral antimicrobial agents are preferred for mild to moderate infections in patients with normal gastro-intestinal function who are hospitalised for other reasons (e.g. dehydration, pain control, and cardiac arrhythmias) (Leekha *et al.*, 2011:160).

Distribution is best described by the drug's volume of distribution and is the process by which a drug diffuses from the intravascular fluid space to extravascular fluid spaces (Levison & Levison, 2009:795). The drug diffuses through tissues according to the supply of blood and the drug's water (hydrophilic) or lipid (lipophilic) solubility. Lipophilic drugs enter lipid-rich tissues, whereas hydrophilic drugs remain in the plasma. Drugs that are bound to plasma protein are inactive and cannot interact with receptors. Only free, unbound drugs are active and distribute

into extravascular space and are responsible for the pharmacological activity and/or side effects (Schmidt *et al.*, 2008:3994). Protein-bound drugs are less often removed by dialysis (Bateman & Eddleston, 2008:340). Protein-binding plays an important role in antibacterial drugs, due to the effects on pharmacokinetics and bioactivity (Gurevich, 2013; Nix *et al.*, 2004:3419).

Drugs undergo two distinct phases during metabolism and elimination. Phase I reactions are functionalising reactions that result in activation or deactivation of the drug. Phase II is conjugated reactions where the metabolised derivative combines with glucuronic acid, sulphate or acetyl groups to form highly polar compounds that can be readily excreted in faeces or urine (Sahoo *et al.*, 2015:297). Metabolism is the chemical conversion of the drug molecule into another chemical entity referred to as a metabolite usually by an enzymatic mediated reaction. The irreversible removal of the drug from the body (i.e. excretion) commonly occurs via the kidney or biliary tract (Bauer, 2008:3).

Plasma half-life reflects the duration of action of a drug and is one of the most important factors that determine the selection of a dosage regimen since a drug with a short half-life needs more frequent dosing. The half-life of a drug is determined by volume of distribution and elimination clearance (Alavijeh *et al.*, 2005:559; Golan *et al.*, 2008:44).

2.1.3.2 Pharmacodynamics involved in antimicrobial therapy

Pharmacodynamics describes the relationship between measurements of drug concentration in serum, tissues and body fluids and the pharmacological and toxicological effects of the drugs (Burke & Cunha, 2011:563; McKinnon & Davis, 2004:272).

Parameters used to measure *in vitro* activity of antimicrobials against various pathogens are known as MIC and minimum bactericidal concentration (MBC). They are excellent predictors of the potency of the antimicrobial agent against the infecting organism (Levison & Levison, 2009:792). Bacteriostatic antimicrobials inhibit growth of organisms without destroying the organisms. The agents are usually successful when treating infections due to the assistance of the host's immune system (Gallagher & MacDougall, 2013:37). Bactericidal antimicrobials destroy the organism without any assistance of the immune system (Kohanski *et al.*, 2010:423). Antimicrobials only inhibit growth of the organisms at MIC levels. A drug is seen as bactericidal when the MBC/MIC ratio is four or less. When the ratio is greater than four the drug is seen as bacteriostatic (Gallagher & MacDougall, 2013:37).

Concentration-dependent killing and time-dependent killing are the two primary patterns of microbial killing. With concentration-dependent killing higher drug concentrations results in a greater rate and extent of microbial killing (Leekha *et al.*, 2011:160). Examples of concentration-

dependent antimicrobials are aminoglycosides, fluoroquinolones, metronidazole, colistin, daptomycin, and possible ketolides and azithromycin. Time-dependent killing on the other hand is dependent on the duration of exposure of the organism to the antimicrobial. Higher concentrations will not kill microbes faster or more extensively. Examples of time-dependent antimicrobials include β -lactams and vancomycin (Levison & Levison, 2009:801).

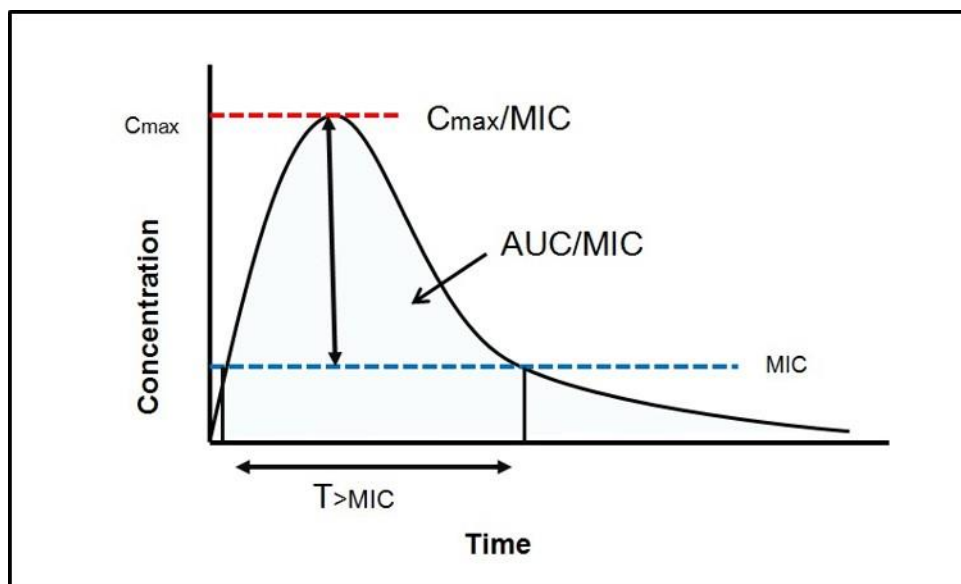
The optimisation of duration of exposure is the goal of time-dependent killing. To maximise antimicrobial concentration and attain the highest possible concentration at the site of infection is the goal of concentration-dependent killing (Septimus, 2012).

Persistent effects of antimicrobials are also known as the postantibiotic effect which is the continuation of suppression of bacterial growth following antimicrobial exposure. In other words, it is the time it takes for an organism to recover from the effects of antimicrobial exposure and to resume normal growth (Smith *et al.*, 2003:1081; Wakshlak *et al.*, 2015). The postantibiotic effects are minimal with time-dependent killing and are prolonged with concentration-dependent killing even when concentrations are below the MIC (Lehman, 2007).

2.1.3.3 Pharmacokinetic/Pharmacodynamics (PK/PD) parameters

The concentration-effect relationship of a drug is called the pharmacokinetic/pharmacodynamic (PK/PD) parameters that can be used for dosage and dosing interval adjustments of antimicrobial agents (Mueller *et al.*, 2004:369). Pharmacokinetic/pharmacodynamic targets are needed for optimal antimicrobial dosing in order to achieve maximal bactericidal effect (Udy *et al.*, 2013:2070).

A PK/PD index is the quantitative relationship between a pharmacokinetic parameter and a microbiological parameter. The three main PK/PD indices that are associated with the effect of antimicrobials and the prediction of the antimicrobial efficacy include: the timing during which the concentration of the drug was over the MIC ($T_{>MIC}$), the peak concentration and the MIC ratio (C_{max}/MIC), and the ratio of the 24-hour area under the concentration-time curve divided by the MIC (AUC/MIC) (Asín-Prieto *et al.*, 2015:320; Mouton *et al.*, 2005:601). See Figure 2-5 for illustration of PK/PD indices (adapted from Asín-Prieto *et al.*, 2015:321), T referring to time and C_{max} to peak/maximum concentration.



(C_{max}/MIC = maximum concentration / minimum inhibitory concentration; AUC/MIC = area under the curve / minimum inhibitory concentration; $T>MIC$ = time above the MIC)

Figure 2-5: Pharmacokinetic/Pharmacodynamic indices associated with antimicrobial efficacy

The PK/PD indices describe antimicrobial efficacy the best depending on the activity pattern of each antimicrobial. Three major groups of antimicrobial activity exist. The first group of antimicrobial activity reveals concentration-dependent killing along with prolonged persistent effects. The bacterial killing rate of this group escalates with an increase in concentration of the antimicrobial, therefore the drug concentration should be maximised. The second group includes the antimicrobials that reveal time-dependent (concentration-independent) killing and none or very short persistent effects. The third group includes the antimicrobial agents that show concentration-independent killing and prolonged persistent effects. For group two and three their effect depends on the length of time that the drug is in contact with the bacteria. As the concentration increases their effects will increase up to a fixed point where a maximum killing rate is reached. Increasing concentrations after that point will not produce a corresponding increase in the effect and therefore high peak concentrations will not produce a better effect. Concentrations of approximately three to five times the MIC have shown maximum killing (Asín-Prieto *et al.*, 2015:321; Mueller *et al.*, 2004:369-370).

The PK/PD indices for the first group of antimicrobial activity which reveal concentration-dependent killing along with prolonged persistent effects are C_{max}/MIC or the AUC/MIC ratios, because the prolonged persistent effects protect against regrowth when the concentration of the active drug falls below the MIC. Aminoglycosides, fluoroquinolones, polymyxins, daptomycin and metronidazole are examples of this group. The PK/PD index for the second group of

antimicrobial activity which reveal time-dependent killing and no or very short persistent effects is the duration of time that the active antimicrobial concentration exceeds the MIC. Usually it is expressed as the percentage of the dosing interval and only the fraction of the drug not bound to proteins is considered. Examples of this group include β -lactam antimicrobials such as penicillins, cephalosporins, carbapenems, and monobactams. The best PK/PD indexes to describe the third group of antimicrobial activity which reveal concentration-independent killing and prolonged persistent effects are C_{max}/MIC or the AUC/MIC. Antimicrobials of this group include tetracyclines, tigecycline, macrolides, azithromycin, clindamycin, linezolid and other oxazolidinones, chloramphenicol, trimethoprim, sulphonamides and vancomycin (Andes & Craig, 2002:262-267; Asín-Prieto *et al.*, 2015:321; Burgess, 2005:S99-S100-S102; Mueller *et al.*, 2004:369-370).

2.1.4 Adverse effects of antimicrobial usage

An understanding of the mechanism of action, and the mechanism of toxicity is needed when selecting optimal antimicrobial therapy (McKinnon & Davis, 2004:283). The ideal antimicrobial agent would target microbes without affecting mammalian cells. Unexpected or undesirable non-antimicrobial effects are inevitable due to man and microbes sharing many essentials of life including DNA, adenosine triphosphate (ATP) and other biochemical pathways (Pasquale & Tan, 2005:127). Adverse effects are undesirable effects that vary from minor common side-effects to life-threatening anaphylaxis (Smith, 2013:12).

Adverse effects include allergies/hypersensitivity, drug interactions (alteration in hepatic metabolism, intestinal flora and impaired absorption), direct toxicity, cardiac effects, renal effects (McKinnon & Davis, 2004:283), and superinfection (infection occurring during antimicrobial therapy for another infection due to the change in the normal tissue flora) (McKinnon & Davis, 2004:283; Mosby's Dictionary of Medicine, Nursing and Health Professions, 2006:1793). These adverse effects can limit the choice of antimicrobial therapy and/or the doses that may be tolerated (McKinnon & Davis, 2004:283).

A true penicillin allergy is an IgE-mediated reaction. According to the Centres for Disease Control and Prevention (CDCP) less than 1% of the reported penicillin allergies were found as true penicillin allergies. Characteristics of an IgE-mediated (Type 1) reaction are: immediately occurring reactions (or usually within one hour), hives, angioedema, wheezing and shortness of breath, and anaphylaxis (CDCP, 2017a).

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a severe form of drug reaction and can be caused by antimicrobial agents. The DRESS syndrome is a potentially life-threatening idiosyncratic cutaneous reaction to drugs characterised by extensive

mucocutaneous eruption, fever, hematologic abnormalities, and extensive involvement of internal organs (Sriratanaviriyakul *et al.*, 2014).

Effects associated with prolonged antimicrobial treatment include increased risk of developing *Clostridium difficile*-associated diarrhoea and superinfections with resistant bacteria and *Candida* organisms (Deresinski, 2007:S180).

2.1.5 Factors in selection of antimicrobial agents

Important drug-related factors to consider when choosing antimicrobial therapy are knowledge about the spectrum of antimicrobial activity, its adverse effect profiles, pharmacokinetic disposition and dosage (Adorka *et al.*, 2013:1030; Peterson, 2008:35). Several host-related factors also need to be considered when selecting appropriate antimicrobial therapy, such as patient characteristics, pathogen characteristics and antimicrobial properties (Leekha *et al.*, 2011:159). Other pharmacokinetic factors that need to give thought to when selecting the most appropriate antimicrobial therapy include tissue penetration and the patient's individual tolerance to drugs (Darley & MacGowan, 2004:928).

Timing of initial therapy is crucial in critically ill patients, such as those with septic shock (Kumar *et al.*, 2006:1594), febrile neutropenia (Freifeld *et al.*, 2011:e84), bone and joint infections (Darley & MacGowan, 2004:928), and in patients with bacterial meningitis (Leekha *et al.*, 2011:157; Tunkel *et al.*, 2004:1267). Antimicrobial therapy should normally be withheld in patients with more stable clinical circumstances until appropriate specimens have been collected and submitted to the microbiology laboratory (Baron *et al.*, 2013:4; Leekha *et al.*, 2011:157).

A drug's safety profile, resistance to antimicrobials and cost of therapy must also be taken into consideration when choosing antimicrobial therapy (Burke & Cunha, 2011:2-3).

2.1.6 Other considerations of antimicrobial therapy

2.1.6.1 Bacteriostatic vs. bactericidal characteristics

Antimicrobials can be classified based on the cellular component of bacteria they affect together with their bactericidal or bacteriostatic effect (Kohanski *et al.*, 2010:423). Bactericidal drugs induce bacterial cell death (Lobritz *et al.*, 2015:8173), whereas bacteriostatic agents inhibit bacterial cell growth (Leekha *et al.*, 2011:158; Lobritz *et al.*, 2015:8173). In the case of serious infections bactericidal agents are preferred in order to achieve a rapid cure (Leekha *et al.*, 2011:158). The maximum tolerable antimicrobial dosage is needed to improve the therapeutic outcome and prevent resistance from developing therefore bactericidal agents may be preferred

over bacteriostatic agents. The administrated dosage of bactericidal agents must be sufficient to achieve bactericidal activity since some antibacterials have concentration-dependent bacterial killing effects (Silva *et al.*, 2011:321).

2.1.6.2 Monotherapy vs. combination therapy

In both community and hospital-acquired infections, a combination of antimicrobial agents can be considered for empiric therapy (Leekha *et al.*, 2011:157; Mandel *et al.*, 2007:S29). Combination therapy is mostly used due to the following reasons (Ahmed *et al.*, 2014):

- To broaden the antimicrobial spectrum (especially in the critically ill patient).
- For polymicrobial infections to cover all the bacterial pathogens.
- For antimicrobial synergy (proven advantageous in animal models).
- To lower the emergence of resistance (limited evidence).

The antimicrobial spectrum should be narrowed once microbiology results are available to assist in identifying the etiologic pathogen and the antimicrobial susceptibility data (Kollef, 2006:91; Leekha *et al.*, 2011:157). This is important to reduce cost and toxicity and to prevent further resistance of pathogens against antimicrobials (Leekha *et al.*, 2011:157).

2.1.6.3 Intravenous therapy vs. oral therapy

The ideal route of administration of any medication is the route that achieves serum concentrations of the drug sufficient to produce the desired effect without producing any unwanted effects (Cyriac & James, 2014). Intravenous injection of a drug is preferred when rapid absorption of drugs is needed, when medication cannot be given orally or when medication administered subcutaneously or intramuscular causes too much irritation (Jin *et al.*, 2015:924). Intravenous antimicrobial therapy is often the choice of administration in hospitalised patients (Leekha *et al.*, 2011:160).

Switching to an oral agent reduces the incidence of catheter-related infections and can reduce hospital stay (Mertz *et al.*, 2009:189). The oral route provides the safest and convenient way of medication administration. There is little therapeutic difference between intravenous and oral medications if the given oral medication achieves tissue and blood concentrations to the same extent as the intravenous medication (Cyriac & James, 2014). Antimicrobial properties such as bioavailability, patient tolerance and cost and the availability of an oral agent with an appropriate antimicrobial spectrum can influence the initiation of switching therapy (Scheinfeld, 2015).

2.1.7 Factors influencing dosing of antimicrobial agents

2.1.7.1 Renal impairment

Dosage adjustments are important in patients with a pre-existing renal disease, patients receiving antimicrobial therapy with a narrow toxic-to-therapeutic ratio and patients receiving other nephrotoxic medication (Burke & Cunha, 2011:3-4). The effects of many drugs are altered by renal disease causing a decrease in its effects or more often causing an increase in its effects thus increasing the toxicity potential. These changes are normally predictable and can be managed by changing drug dosages (Doogue & Polasek, 2011:69). Normally the initial dosage remains unchanged and the maintenance dosage or dosage interval are modified proportionally to the predicted reduction in clearance of the drug (according to creatinine clearance) (Burke & Cunha, 2011:3-4; Doogue & Polasek, 2011:69).

2.1.7.2 Hepatic impairment

Maintaining homeostasis is an important function of the liver (Büdingen *et al.*, 2014:17). For most drugs the liver plays a central role in the absorption, distribution and elimination and activation or inactivation of drug metabolite. It is the most important site of biotransformation (Singh *et al.*, 2011:2; Verbeeck, 2008:1147). Liver disease and factors such as liver flow, binding to plasma proteins and biliary excretion can all potentially influence the pharmacokinetic characteristics of the drugs (Büdingen *et al.*, 2014:17-18). Patients with hepatic dysfunction may be more prone to the desired as well as adverse effects of several drugs (Verbeeck, 2008:1147). In practice, dosing adjustments are usually only recommended for severe hepatic dysfunction and not for mild or moderate hepatic insufficiency. Dosage adjustments are made for antimicrobials with hepatotoxic potential. Considering an antimicrobial that is eliminated by the renal route can be an alternative for therapy (Burke & Cunha, 2011:5).

2.1.7.3 Critical illness/Sepsis

Sepsis is the term for the systemic response to infection. Septic shock occurs when this syndrome results in hypotension and organ dysfunction and is characterised haemodynamically by a hyperdynamic stage and occasionally a hypodynamic stage (De Paepe *et al.*, 2002:1136).

Pathophysiologic conditions that alter drug absorption, distribution, clearance and elimination may be present in patients that are critically ill (Blot *et al.*, 2014:4; McKinnon & Davis, 2004:279). The pharmacokinetic and pharmacodynamic characteristics of drugs are altered in these patients and they show significant inter-individual variation which makes empirical drug administration difficult (Delattre *et al.*, 2010:589; De Paepe *et al.*, 2002:1136-1137).

2.1.7.4 Obesity

Pathophysiologic changes due to obesity such as an increased volume of adipose tissue influence the volume of distribution of a drug (McKinnon & Davis, 2004:280; Velissaris *et al.*, 2014:228). Other pharmacokinetic characteristics of antimicrobials that may be altered include protein binding, renal elimination and hepatic metabolism. Dosing adjustments of some medications are needed in obese patients to reach therapeutic levels, especially in the presence of critical illness (Velissaris *et al.*, 2014:227).

2.1.7.5 Burns

After a thermal injury a patient undergoes physiological changes. During the first 48 hours an increase in capillary permeability and hypovolemia is present (Tiwari, 2012). These changes may lead to an expanded volume of distribution for many drugs (Blanchet *et al.*, 2008:636-637; McKinnon & Davis, 2004:280). After this acute phase a hyperdynamic phase follows, characterised by the release of vasoactive mediators, increased cardiac output (which increases the glomerular filtration rate), plasma protein loss and fluid shifts (Bittner *et al.*, 2015:448; McKinnon & Davis, 2004:280). The alteration in pharmacokinetics and resulting pharmacodynamics can be variable, making antimicrobial therapy difficult (Blanchet *et al.*, 2008:652; McKinnon & Davis, 2004:280).

2.2 Antimicrobial agents

The discovery of penicillin in 1928 by Alexander Fleming saved the lives of millions of people and changed the direction of approaches to treating infectious diseases (Ligon, 2004:58-61). One of the most significant advances in modern medical history is the discovery of antimicrobial agents. Antimicrobials have the potential to save lives of patients that are critically ill suffering from a bacterial infection (Davies & Davies, 2010:417). More than twenty novel classes of antimicrobials were produced between 1930 and 1962 (Coates *et al.*, 2011:184; Powers, 2004:24). Since 1970 only three new classes of antimicrobials have been marketed (Butler & Buss, 2006:919).

Most antimicrobials used to treat bacterial infections might be categorised according to their mechanism of action (Sefton, 2002:557; Soares *et al.*, 2012:296). The ultimate antimicrobial agent should reveal maximal toxicity to the pathogen by stopping bacterial growth or destroying the pathogen while causing minimal damage to the host tissues (Bakheet & Doig, 2010; Sefton, 2002:557).

The discussion of antimicrobials in the mini-dissertation will primarily focus on the general characterisation and classification of antimicrobial agents, such as the mechanism of action, spectrum of activity, adverse effects, and common indications.

The classification of beta-lactam antimicrobials is depicted in Table 2-2 (adapted from Calderwood, 2016a) and all other antibacterial classes in Table 2-3 (Gallagher & MacDougall, 2013:93-144).

Table 2-2: Classification of beta-lactam antimicrobials

Classification of beta-lactam antimicrobials	Antimicrobial agents
Beta-lactamase sensitive penicillins: natural penicillins	<i>Phenoxymethylpenicillin (penicillin VK)</i>
	<i>Benzylpenicillin (penicillin G)</i>
Beta-lactamase sensitive penicillins with extended spectrum: aminopenicillins	<i>Amoxicillin</i>
	<i>Ampicillin</i>
Beta-lactamase inhibitor combinations	<i>Amoxicillin/clavulanate</i> <i>Piperacillin/tazobactam</i>
Beta-lactamase resistant penicillin: antistaphylococcal penicillins	<i>Cloxacillin</i>
	<i>Flucloxacillin</i>
Other beta-lactam antibacterials: cephalosporins and related substances	<i>First generation:</i> <i>Cefazolin</i> <i>Cephalexin</i> <i>Cefadroxil</i>
	<i>Second generation:</i> <i>Cefaclor</i> <i>Cefoxitin</i> <i>Cefuroxime</i> <i>Cefprozil</i> <i>Loracarbef</i>
	<i>Third generation:</i> <i>Cefixime</i> <i>Cefotaxime</i> <i>Ceftazidime</i> <i>Ceftriaxone</i> <i>Cefpodoxime</i>
	<i>Fourth generation:</i> <i>Cefepime</i> <i>Cefpirome</i>
	<i>Fifth generation:</i> <i>Ceftaroline</i>
Carbapenems	<i>Imipenem/cilastatin</i>
	<i>Meropenem</i>
	<i>Ertapenem</i>
	<i>Doripenem</i>
Monobactams	<i>Aztreonam</i>

Table 2-3: Classification of other antibacterial agents

<i>Classification of other antibacterials</i>	<i>Antimicrobial agents</i>
<i>Glycopeptides</i>	<i>Teicoplanin</i> <i>Vancomycin</i>
<i>Fluoroquinolones</i>	<i>Ciprofloxacin</i> <i>Gatifloxacin</i> <i>Gemifloxacin</i> <i>Levofloxacin</i> <i>Lomefloxacin</i> <i>Moxifloxacin</i> <i>Norfloxacin</i> <i>Ofloxacin</i>
<i>Aminoglycosides</i>	<i>Gentamycin</i> <i>Tobramycin</i> <i>Amikacin</i> <i>Streptomycin</i>
<i>Tetracyclines</i>	<i>Doxycycline</i> <i>Minocycline</i>
<i>Glycylcyclines</i>	<i>Tigecycline</i>
<i>Macrolides</i>	<i>Azithromycin</i> <i>Clarithromycin</i> <i>Erythromycin</i>
<i>Ketolides</i>	<i>Telithromycin</i>
<i>Oxazolidinones</i>	<i>Linezolid</i>
<i>Nitro-imidazoles</i>	<i>Metronidazole</i>
<i>Nitrofurans & fosfomycin</i>	<i>Nitrofurantoin</i> <i>Fosfomycin</i>
<i>Cyclic lipopeptides</i>	<i>Daptomycin</i>
<i>Folate antagonists</i>	<i>Trimethoprim/sulfamethoxazole</i> <i>Dapsone</i>
<i>Lincosamides</i>	<i>Clindamycin</i>
<i>Polymyxins</i>	<i>Colistin</i>

2.2.1 Beta-lactam antimicrobials

The most commonly prescribed drugs are the beta-lactam antimicrobials. The beta-lactam ring is the structural feature which the group shares (Calderwood, 2016a). This class of antimicrobials includes the penicillins, cephalosporins and carbapenems. Monobactams are structurally similar and have little or no cross-allergenicity with other beta-lactams. Characteristics that all beta-lactams share (Gallagher & MacDougall, 2013:49-50), include the following:

- **Hypersensitivity reactions.** These reactions can be caused by any beta-lactam, and range from mild rashes to the drugs to acute interstitial nephritis to anaphylaxis. Although there is some cross-sensitivity, there is no way to predict how often it will occur.
- **Seizures.** High doses of any beta-lactam can cause seizures. Doses should therefore be adjusted based on patients' renal function to avoid accumulation to toxic levels.
- **The mechanism of action.** All beta-lactams have the same mechanism of action; beta-lactams inhibit transpeptidases which is the penicillin-binding proteins in the bacterial cell wall.
- **Lack of activity against atypical organisms** such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*.
- **Lack of activity against methicillin-resistant *Staphylococcus aureus* (MRSA) infections**, except ceftaroline, which is a fifth generation cephalosporin.

The beta-lactam category is broad and is divided into functional groups (Calderwood, 2016a). Grouping of these agents is discussed according to spectrum of activity in subsequent paragraphs.

2.2.1.1 Beta-lactamase sensitive penicillins: natural penicillins

Agents of this group include phenoxymethylpenicillin (penicillin VK) and benzylpenicillin (penicillin G). These are natural penicillins that must be dosed frequently or given by continuous infusion due to a very short half-life. Depot formulations (e.g. procaine, benzathine) are long-acting and are available for intramuscular administration. The oral form of benzylpenicillin is phenoxymethylpenicillin (Gallagher & MacDougall, 2013:54).

- **Mechanism of action**

Beta-lactam agents inhibit peptidoglycan cross-linking in the cell wall which leads to autolysis and cell death. Inhibition of the synthesis of the cell wall results in a bactericidal therapeutic effect against susceptible bacteria (Gallagher & MacDougall, 2013:53; Mosby's Drug Reference for Health Professions, 2014:1260-1262; UpToDate, 2016a; UpToDate, 2016b).

- **Spectrum of activity**

Phenoxymethylpenicillin is usually susceptible against *Streptococcus* (Group A, B, C, G), *Streptococcus pneumoniae*, *Streptococcus anginosus*, *Actinomyces israelii*, *Pasteurella multocida*, *Clostridium diphtheriae*, and *Peptostreptococci* (Antimicrobial Therapy, Inc., 2016).

Benzylpenicillin is usually susceptible against *Treponema pallidum*, *Streptococcus* (Group A, B, C, G), *Streptococcus pneumoniae*, *Streptococcus anginosus*, *Enterococcus faecalis*, *Pasteurella multocida*, *Actinomyces israelii*, *Propionibacterium acnes*, *Leptospira* spp.,

Clostridium diphtheria, *Clostridium perfringens*, *Neisseria meningitidis*, and *Peptostreptococci* (Antimicrobial Therapy, Inc., 2016).

- **Adverse effects**

Frequently experienced adverse effects include mild hypersensitivity reactions (chills, fever and rash), diarrhoea, nausea and vomiting. Rare adverse effects are bleeding, allergic reactions and interstitial nephritis. Serious reactions that can be experienced are severe hypersensitivity reactions, antimicrobial-associated colitis and superinfections from high dosages or prolonged therapy (Lennon Limited, 1996; Mosby's Drug Reference for Health Professions, 2014:1261-1262; Sandoz, 2012).

- **Common indications**

Phenoxymethylpenicillin is indicated for the treatment of *Streptococcal* pharyngitis, periodontal infections and for prophylaxis of recurrent rheumatic fever (Lennon Limited, 1996; Medscape, 2016a; Mosby's Drug Reference for Health Professions, 2014:1261-1262).

Benzylopenicillin is indicated for the treatment of syphilis and particularly neurosyphilis (Antimicrobial Therapy, Inc., 2016; Gallagher & MacDougall, 2013:55; Medscape, 2016b; Sandoz, 2012). Other indications include *meningococcal* meningitis, *Streptococcal* infections (such as pneumonia and endocarditis) and *Streptococcal* Group B infections (Antimicrobial Therapy, Inc., 2016; Medscape, 2016b; Mosby's Drug Reference for Health Professions, 2014:1260; Sandoz, 2012).

2.2.1.2 Beta-lactamase sensitive penicillins with extended spectrum: aminopenicillins

Antimicrobials included in this group are amoxicillin and ampicillin.

- **Mechanism of action**

These agents cause autolysis and cell death due to the inhibition of cross-linking of peptidoglycan in the cell wall. Inhibition of bacterial cell wall synthesis results in a bactericidal therapeutic effect in susceptible micro-organisms (Gallagher & MacDougall, 2013:59; GlaxoSmithKline, 2006a; Mosby's Drug Reference for Health Professions, 2014:91, 97; Pfizer Incorporated, 2007; UpToDate, 2016c).

- **Spectrum of activity**

Aminopenicillins have predictable activity against streptococci, most enterococci, *Listeria clostridia* and some other anaerobic bacteria. Amoxicillin is clinically effective against

Actinomyces israelii, *Borrelia burgdorferi*, *Enterococcus faecalis*, *Neisseria meningitidis*, *Pasteurella multocida* and *Peptostreptococci* (Antimicrobial Therapy, Inc., 2016).

Ampicillin is clinically effective against *Actinomyces israelii*, *Borrelia burgdorferi*, *Enterococcus faecalis*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Pasteurella multocida*, and *Peptostreptococci* (Antimicrobial Therapy, Inc., 2016).

- **Adverse effects**

Oral aminopenicillins cause a high incidence of gastro-intestinal disturbances. Other frequent adverse effects experienced include oral and vaginal candidiasis. Effects occasionally experienced include generalised rash, urticaria and phlebitis or thrombophlebitis with intravenous administration. Serious reactions include antimicrobial-associated colitis, other superinfections and severe hypersensitivity reactions (anaphylaxis and acute interstitial nephritis) (Medscape, 2016c; Medscape, 2016e; Mosby's Drug Reference for Health Professions, 2014:91, 98).

- **Common indications**

Amoxicillin is frequently prescribed for the treatment of ear, nose and throat infections, including *Streptococcal* pharyngitis (i.e. so-called "strep throat"), and otitis media (Antimicrobial Therapy, Inc., 2016; Gallagher & MacDougall, 2013:60; GlaxoSmithKline, 2006a). Other indications for amoxicillin include genito-urinary tract infections, skin and skin structure infections, tonsillitis, lower respiratory tract infections and eradication of *Helicobacter pylori* infection (GlaxoSmithKline, 2006a; Medscape, 2016c; Mosby's Drug Reference for Health Professions, 2014:91).

Ampicillin is indicated for endocarditis prophylaxis, uncomplicated gonococcal infections and respiratory tract infections (Medscape, 2016e; Mosby's Drug Reference for Health Professions, 2014:91).

Aminopenicillins are not active against staphylococci because they almost always produce penicillinases (Gallagher & MacDougall, 2013:59). For any beta-lactam agent to achieve bactericidal activity against enterococci it has to be combined with an aminoglycoside (or other cell wall agent such as vancomycin) (Arias *et al.*, 2010:556). Amoxicillin is a better choice for oral therapy and ampicillin for intravenous therapy (Gallagher & MacDougall, 2013:60).

2.2.1.3 Beta-lactamase inhibitor combinations

Included in this group are amoxicillin/clavulanate and piperacillin/tazobactam.

- **Mechanism of action**

Amoxicillin and piperacillin inhibit bacterial cell wall synthesis (Mosby's Drug Reference for Health Professions, 2014:93, 1314). The beta-lactamase inhibitors (clavulanate and tazobactam) mimic the structure of beta-lactams and bind irreversibly to the beta-lactamase to prevent the enzyme from destroying any beta-lactam antimicrobials that are co-administered, freeing up the beta-lactam to destroy the organism (Gallagher & MacDougall, 2013:65).

- **Spectrum of activity**

Combination products are only active against the bacteria that the beta-lactam in the combination has intrinsic activity against. The beta-lactamase inhibitor does not enhance the activity - it only frees up the beta-lactam to kill the organism (Gallagher & MacDougall, 2013:65). Amoxicillin/clavulanate is usually effective against *Streptococcus* (Group A, B, C, G), *Streptococcus pneumoniae*, *Streptococcus anginosus*, *Enterococcus faecalis*, methicillin-susceptible *Staphylococcus aureus* (MSSA), *Staphylococcus saprophyticus*, *Moraxella catarrhalis*, *Haemophilus influenzae*, *Escherichia coli*, *Klebsiella* sp., *Salmonella* sp., *Shigella* spp., *Proteus mirabilis*, *Proteus vulgaris*, *Pasteurella multocida*, *Actinomyces israelii*, *Bacteroides fragilis*, *Prevotella melaninogenica*, *Clostridium perfringens*, *Fusobacterium necrophorum* and *Peptostreptococci* (Antimicrobial Therapy, Inc., 2016).

Piperacillin/tazobactam is usually effective against *Streptococcus* (Group A, B, C, G), *Streptococcus pneumoniae*, *Streptococcus anginosus*, *Enterococcus faecalis*, MSSA, *Neisseria meningitidis*, *Moraxella catarrhalis*, *Haemophilus influenzae*, *Escherichia coli*, *Klebsiella* sp., *Enterobacter cloacae*, *Enterobacter aerogenes*, *Serratia marcescens*, *Salmonella* sp., *Shigella* spp., *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Providencia reggeri*, *Morganella morganii*, *Citrobacter koseri*, *Citrobacter freundii*, *Actinomyces israelii*, *Aeromonas hydrophila*, *Pseudomonas aeruginosa*, *Bacteroides fragilis*, *Prevotella melaninogenica*, *Clostridium diphtheria*, *Clostridium perfringens*, *Fusobacterium necrophorum*, and *Peptostreptococci* (Antimicrobial Therapy, Inc., 2016).

- **Adverse effects**

Frequently experienced adverse effects include gastro-intestinal disturbances, rash, headache and oral or vaginal candidiasis. Serious reactions include antimicrobial-associated colitis, superinfections (due to altered bacterial balance) and severe hypersensitivity reactions

(anaphylaxis and interstitial nephritis) and hepatotoxicity (Mosby's Drug Reference for Health Professions, 2014:94, 1315). Piperacillin/tazobactam may cause seizures, other neurologic reactions and rare bleeding disorders (Medscape, 2016f; Mosby's Drug Reference for Health Professions, 2014:94, 1315).

- **Common indications**

This group is used for empiric therapy of nosocomial infections and for mixed infections since they have activity against aerobes and anaerobes (Gallagher & MacDougall, 2013:67).

Amoxicillin/clavulanate can be used to treat infections with suspected beta-lactamase producing organisms (Antimicrobial Therapy, Inc., 2016; Gallagher & MacDougall, 2013:67-68). Indications of amoxicillin/clavulanate include treatment of respiratory tract infections, sinusitis and otitis media (GlaxoSmithKline, 2006b; Medscape, 2016d; Mosby's Drug Reference for Health Professions, 2014:93). Other indications for amoxicillin/clavulanate are animal/human bite wounds, erysipelas, pyelonephritis, skin abscess, and diabetic foot (Medscape, 2016d).

Piperacillin/tazobactam can be used as empiric therapy for the treatment of nosocomial pneumonia (Medscape, 2016f). Other indications include severe infections, community-acquired pneumonia, intra-abdominal infections, and skin and soft tissue infections (Litha Pharma, 2012; Medscape, 2016f).

2.2.1.4 Beta-lactamase resistant penicillin: antistaphylococcal penicillins

Cloxacillin and flucloxacillin are antimicrobial agents of this group.

- **Mechanism of action**

All beta-lactams cause autolysis and cell death due to the inhibition of peptidoglycan cross-linking in the cell wall. These agents inhibit the bacterial cell-wall synthesis in susceptible microorganisms, which results in a bactericidal therapeutic effect (Gallagher & MacDougall, 2013:57; UpToDate, 2016g).

- **Spectrum of activity**

These agents are clinically effective against *Streptococcus* (Group A, B, C, G), *Streptococcus pneumoniae*, *Streptococcus anginosus*, MSSA, *Staphylococcus lugdunensis*, *Staphylococcus coagulase-negative* species, and *Staphylococcus saprophyticus* (Antimicrobial Therapy, Inc., 2016).

Cloxacillin and flucloxacillin are therapeutically interchangeable. Therefore, if *Staphylococcus aureus* is effective against cloxacillin, it will be effective against flucloxacillin (Gallagher & MacDougall, 2013:57).

- **Adverse effects**

Adverse effects that could be experienced include hypotension, confusion, fever, lethargy, seizures, abdominal pain, diarrhoea, rash, hepatitis, pseudomembranous colitis, thrombophlebitis, bronchospasm, angioedema, neutropenia, thrombocytopenia, haemolytic anaemia, haematuria, and interstitial nephritis (Antimicrobial Therapy, Inc., 2016; UpToDate, 2016g). Phlebitis could also be a problem with these penicillins (Gallagher & MacDougall, 2013:57).

- **Common indications**

Antistaphylococcal penicillins must be dosed frequently due to their short half-life (Gallagher & MacDougall, 2013:57). Cloxacillin and flucloxacillin are indicated for MSSA infections, such as endocarditis, osteomyelitis, and skin and soft-tissue infections (Antimicrobial Therapy, Inc., 2016; Gallagher & MacDougall, 2013:58; GlaxoSmithKline, 2005; Pharmicare Limited, 1999). Other indications of cloxacillin include septic arthritis (off-label) (UpToDate, 2016g), MSSA pneumonia, nosocomial pneumonia and septicemia (Pharmacare Limited, 1999; UpToDate, 2016g). The antistaphylococcal penicillins may be an alternative for patients without beta-lactam allergies infected with MSSA (Gallagher & MacDougall, 2013:57-58).

2.2.1.5 Other beta-lactam antibacterials: cephalosporins and related substances

Cephalosporins are grouped into generations that correlate with their general types of antimicrobial activity (refer to Figure 2-6, adapted from Gallagher & MacDougall, 2013:70).

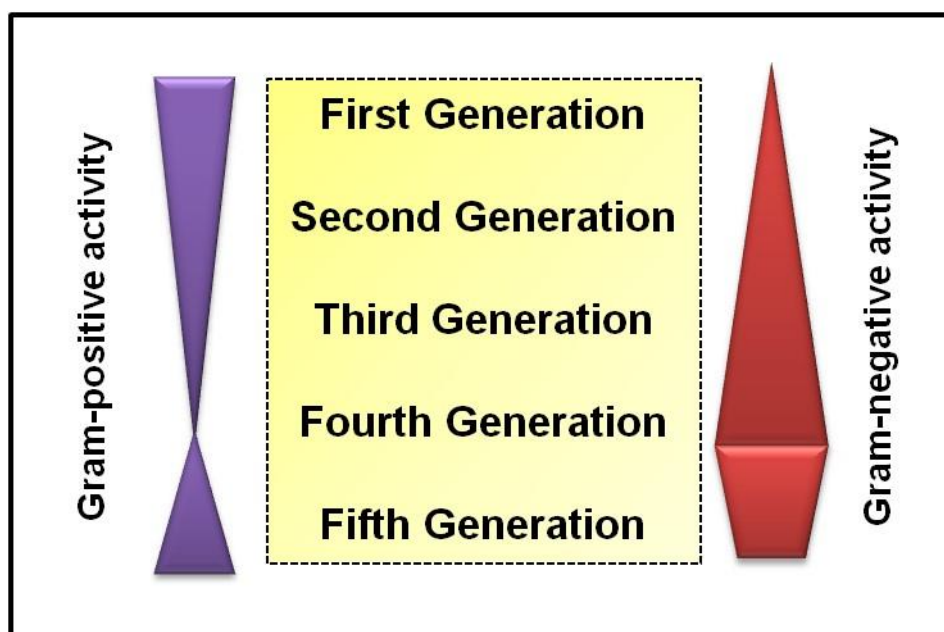


Figure 2-6: Activity of cephalosporin by generation

The risks and benefits should be considered when using any cephalosporin in a patient with penicillin allergy due to some cross-allergenicity with penicillins. The patient's validity of allergies should be assessed. Nausea is a less important side-effect than hives and any signs of anaphylaxis. Generally cephalosporins are more resistant to beta-lactamases than penicillins (Gallagher & MacDougall, 2013:70). The spectra of activity of cephalosporins are indicated in Table 2-4 (adapted from Antimicrobial Therapy, Inc., 2016).

Table 2-4: Spectrum of activity for cephalosporin antimicrobial agents

COMPARISON OF ANTIBACTERIAL SPECTRA															
Generation cephalosporins		1st			2nd				3rd					4th	5th
Organisms		Cefazolin	Cephalexin	Cefadroxil	Cefaclor/ Loracarbef	Cefoxitin	Cefuroxime	Cefprozil	Cefixime	Cefotaxime	Ceftazidime	Ceftriaxone	Cefpodoxime	Cefepime	Ceftaroline
GRAM-POSITIVE	<i>Streptococcus</i> Group A, B, C, G	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	<i>Streptococcus pneumoniae</i>	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	<i>Viridans streptococci</i>	+	+	+	+	+	+	0	+	+	±	+	+	+	+
	<i>Enterococcus faecalis</i>	0	0	0	0	0	0	0	0	0	0	0	0	0	+
	<i>Staphylococcus aureus</i> (MSSA)	+	+	+	+	+	+	+	0	+	±	+	+	+	+
	<i>Staphylococcus aureus</i> (MRSA)	0	0	0	0	0	0	0	0	0	0	0	0	0	+
	<i>Staphylococcus aureus</i> (CA-MRSA)	0	0	0	0	0	0	0	0	0	0	0	0	0	+
	<i>Staphylococcus epidermidis</i>	±	±	±	±	±	±	±	0	±	±	±	±	±	+
	<i>Corynebacterium jeikeium</i>	0	0	0	0	0	0	0	0	0	0	0			
	<i>Listeria monocytogenes</i>	0	0	0	0	0	0	0	0	0	0	0	0	0	
GRAM-NEGATIVE	<i>Neisseria gonorrhoeae</i>	+	0	0	±	±	±	±	+	±	±	±	+	±	±
	<i>Neisseria meningitidis</i>	0	0	0	±	±	+	±	±	+	±	+		+	+
	<i>Moraxella catarrhalis</i>	±	0	0	±	+	+	+	+	+	+	+	+	+	+
	<i>Haemophilus influenzae</i>	+	0		+	+	+	+	+	+	+	+	+	+	+

COMPARISON OF ANTIBACTERIAL SPECTRA															
Generation cephalosporins		1st			2nd				3rd					4th	5th
Organisms		Cefazolin	Cephalexin	Cefadroxil	Cefaclor/ Loracarbef	Cefoxitin	Cefuroxime	Cefprozil	Cefixime	Cefotaxime	Ceftazidime	Ceftriaxone	Cefpodoxime	Cefepime	Ceftaroline
GRAM-NEGATIVE	<i>Escherichia coli</i>	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	<i>Klebsiella</i> sp.	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	<i>Escherichia coli</i> / <i>Klebsiella</i> sp. ESBL+	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	<i>Escherichia coli</i> / <i>Klebsiella</i> sp. KPC+	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	<i>Enterobacter</i> sp., AmpC neg	0	0	0	0	0	±	0	0	+	+	+	0	+	+
	<i>Enterobacter</i> sp., AmpC pos	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	<i>Serratia</i> spp.	0	0	0	0	0	0	0	±	+	+	+	0	+	+

+ = susceptible; ± = variably susceptible/resistant; 0 = usually resistant; blank no data; CA-MRSA = community-acquired methicillin-resistant *Staphylococcus aureus*; ESBL= Extended-spectrum beta-lactamases; KPC = *Klebsiella pneumoniae* carbapenemase

COMPARISON OF ANTIBACTERIAL SPECTRA															
Generation cephalosporins		1 st			2 nd				3 rd					4 th	5 th
Organisms		Cefazolin	Cephalexin	Cefadroxil	Cefaclor/ Loracarbef	Cefoxitin	Cefuroxime	Cefprozil	Cefixime	Cefotaxime	Ceftazidime	Ceftriaxone	Cefpodoxime	Cefepime	Ceftaroline
GRAM-NEGATIVE	<i>Salmonella</i> sp.	0	0	0					+	+	+	+	+	+	+
	<i>Shigella</i> spp.	0	0	0					+	+	+	+	+	+	
	<i>Proteus mirabilis</i>	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	<i>Proteus vulgaris</i>	0	0	0	0	+	+	0	+	+	+	+	±	+	+
	<i>Providencia</i> sp.	0	0	0	0	+	0	0	+	+	+	+		+	+
	<i>Morganella</i> spp.	0	0	0	0	+	±	0	0	+	+	+	0	+	+
	<i>Citrobacter freundii</i>	0	0	0	0	0	0	0	0	+	0	+	0	+	
	<i>Citrobacter diversus</i>	0	0	0	0	±	±	0		+	+	+		+	+
	<i>Citrobacter</i> sp.	0	0		±	±	±	0	+	+	+	+	+	+	+
	<i>Aeromonas hydrophila</i>	0	0			±	+	0	+	+	+	+		+	+
	<i>Acinetobacter</i> sp.	0	0	0	0	0	0	0	0	0	±	0		±	
	<i>Pseudomonas aeruginosa</i>	0	0	0	0	0	0	0	0	0	+	0	0	+	0
	<i>Burkholderia cepacia</i>	0	0	0	0	0	0	0	0	±	+	±		±	0
	<i>Stenotrophomonas maltophilia</i>	0	0	0	0	0	0	0	0	0	±	0		0	0
	<i>Yersina enterocolitica</i>	0				±	±		+	+	±	+		+	
	<i>Legionella</i> spp.	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	<i>Pasteurella multocida</i>		0				+		+	+		+	+	+	
	<i>Haemophilus ducreyi</i>					+			+	+	+	+			

COMPARISON OF ANTIBACTERIAL SPECTRA															
Generation cephalosporins		1 st			2 nd				3 rd				4 th	5 th	
Organisms		Cefazolin	Cephalexin	Cefadroxil	Cefaclor/ Loracarbef	Cefoxitin	Cefuroxime	Cefprozil	Cefixime	Cefotaxime	Ceftazidime	Ceftriaxone	Cefpodoxime	Cefepime	Ceftaroline
ANAEROBES	Actinomyces											+			
	Bacteroides fragilis	0	0		0	+	0	0	0	0	0	0		0	0
	Prevotella melaninogenica				+	+	+	+	+	+	+	±		0	
	Clostridium difficile					0				0				0	
	Clostridium (not difficile)					+	+	+	0	+	+	+			
	Fusobacterium necrophorum					+									
	Peptostreptococi		+		+	+	+	+	+	+	+	+		+	

+ = susceptible; ± = variably susceptible/resistant; 0 = usually resistant; blank no data

2.2.1.5.1 First-generation cephalosporins

First-generation agents are cefazolin, cephalixin and cefadroxil. These agents are good alternatives to antistaphylococcal penicillins and cause less phlebitis. Because they do not cross the blood-brain barrier completely, they should not be used for treating central nervous system infections (Gallagher & MacDougall, 2013:72).

- **Mechanism of action**

These agents cause autolysis and cell death due to the inhibition of peptidoglycan cross-linking in the cell wall. Due to the inhibition of cell-wall synthesis these first-generation cephalosporins have a bactericidal effect in susceptible micro-organisms (Gallagher & MacDougall, 2013:71; Mosby's Drug Reference for Health Professions, 2014:271-273).

- **Adverse effects**

Frequent adverse effects experienced are discomfort with intramuscular administration, oral and vaginal candidiasis, mild diarrhoea, and mild abdominal cramping. Serious reactions include antibiotic-associated colitis and superinfections, nephrotoxicity and severe hypersensitivity reactions marked by severe pruritus, angioedema, bronchospasm, and anaphylaxis (Mosby's Drug Reference for Health Professions, 2014:272-273).

- **Common indications**

The most common indication of first-generation cephalosporins is surgical prophylaxis. The duration of therapy for surgical prophylaxis should be limited to 24 hours (Gallagher & MacDougall, 2013:71-72).

Cefazolin is indicated for treatment of cholecystitis (biliary tract infections), uncomplicated urinary tract infections and endocarditis, and peri-operative prophylaxis (B. Braun Medical Incorporated, 2000; Medscape, 2016g; UpToDate, 2016i).

Cephalexin is indicated for the treatment of respiratory tract infections, otitis media, skin and soft tissue infections, genito-urinary tract infections, and dental infections caused by susceptible micro-organisms (Ranbaxy Limited, 2005).

Cefadroxil is indicated for the treatment of pharyngitis, skin and skin structure infections, tonsillitis, urinary tract infections (Bristol-Myers Squibb Limited, 1993; Mosby's Drug Reference for Health Professions, 2014:270; UpToDate, 2016k), and lower respiratory tract infections (Bristol-Myers Squibb Limited, 1993).

2.2.1.5.2 Second-generation cephalosporins and loracarbef

Second-generation agents include cefaclor, cefoxitin, cefuroxime, cefprozil and loracarbef.

- **Mechanism of action**

These agents cause autolysis and cell death by inhibiting cross-linking of peptidoglycan in the cell wall and therefore cause a bactericidal therapeutic effect in susceptible micro-organisms (Gallagher & MacDougall, 2013:73; Mosby's Drug Reference for Health Professions, 2014:300).

- **Adverse effects**

Frequent side-effects experienced due to second generation cephalosporins include discomfort with intramuscular administration, oral and vaginal candidiasis, mild diarrhoea, and mild abdominal cramping. Nephrotoxicity, antibiotic-associated colitis, superinfections and hypersensitivity reactions may also occur (Mosby's Drug Reference for Health Professions, 2014:301). Cefoxitin is a cephamycin due to its activity against anaerobes in the gastrointestinal tract. Therefore, cefoxitin can be used for surgical prophylaxis in abdominal surgery. Loracarbef is actually a carbapenem, but have similar effects than the second generation cephalosporins. Second-generation cephalosporins do not cross the blood-brain barrier enough to treat central nervous system infections (Gallagher & MacDougall, 2013:75).

- **Common indications**

Cefaclor is used for the treatment of acute bacterial exacerbations of chronic bronchitis, lower respiratory tract infections, otitis media, pharyngitis and tonsillitis, uncomplicated skin and skin structure infections, and urinary tract infections (Hexal Pharma Limited, 2000a; Mosby's Drug Reference for Health Professions, 2014:268; UpToDate, 2016l).

Cefoxitin is indicated for the treatment of gynaecological infections and perioperative prophylaxis (B. Braun Medical Incorporated, 2013; Mosby's Drug Reference for Health Professions, 2014:285; UpToDate, 2016m). This agent is also indicated for the treatment of moderate to severe infections caused by susceptible organisms, such as bone and joint infections, intra-abdominal infections, lower respiratory tract infections, septicaemia, skin and skin structure infections, and urinary tract infections (B. Braun Medical Incorporated, 2013, UpToDate, 2016m).

Cefuroxime is indicated for treatment of acute bacterial maxillary sinusitis (tablets and suspension only), early detection of Lyme disease (tablets only), pharyngitis/tonsillitis (tablets and oral suspension only), and peri-operative surgical prophylaxis (injection only) (Mosby's Drug Reference for Health Professions, 2014:300; UpToDate, 2016n). Other indications include urinary tract infection, skin and skin-structure infections, septicaemia, meningitis, gonorrhoea,

bone and joint infections (B. Braun Medical Incorporated, 2007a), and lower respiratory tract infections (B. Braun Medical Incorporated, 2007; UpToDate, 2016n).

Cefprozil is used for the treatment of pharyngitis/tonsillitis, otitis media, secondary bacterial infection of acute bronchitis, acute bacterial exacerbation of chronic bronchitis, uncomplicated skin and skin structure infections (Bristol-Myers Squibb Limited, 2005a; Mosby's Drug Reference for Health Professions, 2014:289; UpToDate, 2016o), and uncomplicated urinary tract infections (Bristol-Myers Squibb Limited, 2005a).

When these agents are used for surgical prophylaxis and an infection does develop, an alternative agent should be used, such as a beta-lactamase inhibitor combination or another gram-negative agent together with metronidazole (Gallagher & MacDougall, 2013:75).

2.2.1.5.3 Third-generation cephalosporins

Agents of this generation of cephalosporins are cefixime, cefotaxime, ceftazidime, ceftriaxone, and cefpodoxime.

- **Mechanism of action**

Third-generation cephalosporins inhibit cross-linking of peptidoglycan in the cell wall that leads to autolysis and cell death. The therapeutic effects of the third-generation cephalosporins are bactericidal in susceptible micro-organisms (Gallagher & MacDougall, 2013:77; Mosby's Drug Reference for Health Professions, 2014:297).

- **Adverse effects**

Third-generation cephalosporins are associated with *Clostridium difficile*-associated diarrhoea (Gallagher & MacDougall, 2013:78). Frequent adverse effects include oral and vaginal candidiasis, mild diarrhoea and mild abdominal cramping. Adverse effects occasionally and rarely experienced include nausea, serum sickness-like reactions and allergic reactions. Serious adverse effects of this group include antibiotic-associated colitis, superinfections and nephrotoxicity. Cefotaxime can cause granulocytopenia with prolonged therapy (more than ten days) whereas ceftazidime and ceftriaxone can increase the internationally normalised ratio (INR) (Mosby's Drug Reference for Health Professions, 2014:280, 282, 287, 293, 299).

- **Common indications**

Ceftazidime are unlike the other third-generation agents due to its antipseudomonal activity and lack of activity against gram-positive organisms. Cefotaxime, ceftazidime and ceftriaxone cross the blood-brain barrier and are useful for treating central nervous system infections. Ceftriaxone

have dual modes of elimination via both renal and biliary excretion (Gallagher & MacDougall, 2013:78-79).

Cefixime can be used for the treatment of urinary tract infections caused by susceptible micro-organisms, gonococcal infections and *Streptococcus pyogenes* infections (Medscape, 2016h; Merck Limited, 1992; UpToDate, 2016p).

Cefotaxime can be used for the treatment of bacteraemia/septicaemia, genito-urinary infections, gynaecologic infections, and surgical prophylaxis (B. Braun Medical Incorporated, 2007b; Medscape, 2016i; Mosby's Drug Reference for Health Professions, 2014:281; UpToDate, 2016q). Other indications include central nervous system infections, bone and/or joint infections, intra-abdominal infections, and skin and skin-structure infections caused by susceptible micro-organisms (B. Braun Medical Incorporated, 2007b).

Ceftazidime is indicated for the treatment of bacterial septicaemia, intra-abdominal infections, lower respiratory tract infections, skin and skin-structure infections, and urinary tract infections (Generix International SA Limited, 2005; Mosby's Drug Reference for Health Professions, 2014:292; UpToDate, 2016r). Other indications include bone and joint infections, central nervous system infections, empiric therapy in immunocompromised patients and gynaecologic infections (Mosby's Drug Reference for Health Professions, 2014:292; UpToDate, 2016r).

Ceftriaxone can be used for surgical prophylaxis and treatment of bacterial infections such as acute bacterial otitis media, uncomplicated gonorrhoea (Mosby's Drug Reference for Health Professions, 2014:297-298; UpToDate, 2016s), meningitis, and skin and skin-structure infections (B. Braun Medical Incorporated, 2009; Mosby's Drug Reference for Health Professions, 2014:297-298; UpToDate, 2016s). Other indications include the treatment of intra-abdominal infections, pelvic inflammatory disease (B. Braun Medical Incorporated, 2009; Medscape, 2016k; UpToDate, 2016s), lower respiratory tract infections, urinary tract infections, bacterial septicaemia and for surgical prophylaxis (B. Braun Medical Incorporated, 2009).

Cefpodoxime is indicated for the treatment of acute otitis media, pharyngitis or tonsillitis, chronic bronchitis, pneumonia and acute maxillary sinusitis (Mosby's Drug Reference for Health Professions, 2014:287; Ranbaxy Limited, 2003; UpToDate, 2016t).

2.2.1.5.4 Fourth-generation cephalosporins

Fourth-generation cephalosporins agents are cefepime and cefpirome.

- **Mechanism of action**

These agents cause cross-linking of peptidoglycan in the cell wall which leads to autolysis and cell death (Gallagher & MacDougall, 2013:81). The therapeutic effect is bactericidal in susceptible micro-organisms (Mosby's Drug Reference for Health Professions, 2014:277).

- **Adverse effects**

Frequent effects experienced include oral and vaginal candidiasis, mild diarrhoea, and mild abdominal cramping. Occasional and rare effects include nausea, serum sickness-like reactions and allergic reactions. Serious reactions that can be caused by fourth-generation cephalosporins include antibiotic-associated colitis, superinfections, nephrotoxicity and hypersensitivity reactions (Mosby's Drug Reference for Health Professions, 2014:280).

- **Common indications**

Cefepime is the broadest-spectrum cephalosporin and can be used as empiric therapy when treating febrile neutropenia and nosocomial infections, but not advised for community-acquired infections. Therapy should be de-escalated when treating empirically with cefepime (Gallagher & MacDougall, 2013:81-82).

Cefepime is indicated for the treatment of febrile neutropenia, intra-abdominal infections, moderate to severe pneumonia, skin and skin-structure infections and urinary tract infections (B. Braun Medical Incorporated, 2006; Medscape, 2016m; Mosby's Drug Reference for Health Professions, 2014:277; UpToDate, 2016u).

Cefpirome is indicated for treating lower respiratory tract infections, complicated upper and lower urinary tract infections, bacteraemia, septicaemia and neutropenic fever caused by susceptible organisms (UpToDate, 2016v).

2.2.1.5.5 Fifth-generation cephalosporins

Ceftaroline is the only agent of this group. The gram-negative activity of ceftaroline is less compared to fourth-generation cephalosporins, especially against *Pseudomonas aeruginosa* (Gallagher & MacDougall, 2013:85).

- **Mechanism of action**

Ceftaroline inhibits cross-linking of peptidoglycan in the cell wall which causes autolysis and cell death. This fifth-generation cephalosporin also binds to penicillin-binding protein 2a leading to the anti-MRSA activity of this agent (Gallagher & MacDougall, 2013:83-84). The therapeutic effect is bactericidal in susceptible micro-organisms (Mosby's Drug Reference for Health Professions, 2014:290).

- **Adverse effects**

Occasionally experienced effects include diarrhoea, nausea, rash, phlebitis, constipation, vomiting, insomnia, hypokalaemia, pruritus, and headache. Serious reactions include antibiotic-associated colitis, nephrotoxicity and hypersensitivity reactions (Mosby's Drug Reference for Health Professions, 2014:291).

- **Common indications**

Ceftaroline is indicated for community acquired pneumonia and skin and skin-structure infections (Medscape, 2016xa; UpToDate, 2016w). This agent is uniquely active against resistant gram-positive pathogens, including methicillin-resistant and vancomycin-resistant *Staphylococcus aureus* and vancomycin-insensitive *Staphylococcus aureus* (Mosby's Drug Reference for Health Professions, 2014:290).

2.2.1.6 Carbapenems

Imipenem/cilastatin, meropenem, ertapenem, and doripenem are carbapenems.

- **Mechanism of action**

Imipenem penetrates the cell membrane of the bacteria and binds to penicillin-binding protein thereby inhibiting cell-wall synthesis. Cilastatin prevents renal metabolism of imipenem by inhibiting the enzyme dehydropeptidase (Mosby's Drug Reference for Health Professions, 2014:824-825). Meropenem, ertapenem and doripenem cause cell death in most susceptible organisms by binding to the penicillin-binding protein and inhibiting synthesis of bacterial cell walls (Gallagher & MacDougall, 2013:87; Mosby's Drug Reference for Health Professions, 2014:1012).

- **Spectrum of activity**

Imipenem/cilastatin is usually effective against *Streptococcus* (Group A, B, C, G), *Streptococcus pneumoniae*, *Viridans streptococcus*, MSSA, *Staphylococcus* coagulase-negative species, *Neisseria meningitidis*, *Moraxella catarrhalis*, *Haemophilus influenzae*, *Escherichia coli* (including ESBL+), *Klebsiella* sp., (including ESBL+), *Enterobacter cloacae*, *Enterobacter*

aerogenes, *Serratia marcescens*, *Salmonella* sp., *Shigella* spp., *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Providencia reggeri*, *Morganella morganii*, *Citrobacter koseri*, *Citrobacter freundii*, *Aeromonas hydrophila*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Yersinia enterocolitica*, *Pasteurella multocida*, *Actinomyces israelii*, *Bacteroides fragilis*, *Prevotella melaninogenica*, *Clostridium perfringens*, *Fusobacterium necrophorum* and *Peptostreptococci* (Antimicrobial Therapy, Inc., 2016; UpToDate, 2016x).

Meropenem is usually effective against *Streptococcus* (Group A, B, C, G), *Streptococcus pneumoniae*, *Viridans streptococcus*, *Streptococcus anginosus*, MSSA, *Staphylococcus* coagulase-negative species, *Listeria monocytogenes*, *Neisseria meningitidis*, *Neisseria gonorrhoeae*, *Moraxella catarrhalis*, *Haemophilus influenzae*, *Escherichia coli* (including ESBL+), *Klebsiella* sp. (including ESBL+), *Enterobacter cloacae*, *Enterobacter aerogenes*, *Serratia marcescens*, *Salmonella* sp., *Shigella* spp., *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Providencia reggeri*, *Morganella morganii*, *Citrobacter koseri*, *Citrobacter freundii*, *Acinetobacter baumannii*, *Aeromonas hydrophila*, *Actinomyces israelii*, *Pseudomonas aeruginosa*, *Burkholderia cepacia*, *Bacteroides fragilis*, *Prevotella melaninogenica*, *Clostridium perfringens*, *Fusobacterium necrophorum* and *Peptostreptococci* (Antimicrobial Therapy, Inc., 2016).

Ertapenem is usually effective against *Streptococcus* (Group A, B, C, G), *Streptococcus pneumoniae*, *Viridans streptococcus*, *Streptococcus anginosus*, MSSA, *Staphylococcus* coagulase-negative species, *Neisseria meningitidis*, *Neisseria gonorrhoeae*, *Moraxella catarrhalis*, *Haemophilus influenzae*, *Escherichia coli* (including ESBL+), *Klebsiella* sp., (including ESBL+), *Enterobacter cloacae*, *Enterobacter aerogenes*, *Serratia marcescens*, *Salmonella* sp., *Shigella* spp., *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Providencia reggeri*, *Morganella morganii*, *Citrobacter koseri*, *Citrobacter freundii*, *Aeromonas hydrophila*, *Pasteurella multocida*, *Actinomyces israelii*, *Bacteroides fragilis*, *Prevotella melaninogenica*, *Clostridium perfringens*, *Fusobacterium necrophorum* and *Peptostreptococci* (Antimicrobial Therapy, Inc., 2016).

Doripenem is usually effective against *Streptococcus* (Group A, B, C, G), *Streptococcus pneumoniae*, *Viridans streptococcus*, *Streptococcus anginosus*, MSSA, *Staphylococcus* coagulase-negative species, *Neisseria meningitidis*, *Neisseria gonorrhoeae*, *Moraxella catarrhalis*, *Haemophilus influenzae*, *Escherichia coli* (including ESBL+), *Klebsiella* sp., (including ESBL+), *Enterobacter cloacae*, *Enterobacter aerogenes*, *Serratia marcescens*, *Salmonella* sp., *Shigella* spp., *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Providencia reggeri*, *Morganella morganii*, *Citrobacter koseri*, *Citrobacter freundii*, *Acinetobacter baumannii*, *Actinomyces israelii*, *Aeromonas hydrophila*, *Pseudomonas aeruginosa*, *Yersinia*

enterocolitica, *Pasteurella multocida*, *Bacteroides fragilis*, *Prevotella melaninogenica*, *Clostridium perfringens*, *Fusobacterium necrophorum* and *Peptostreptococci* (Antimicrobial Therapy, Inc., 2016).

- **Adverse effects**

This group may elicit an allergic reaction in patients with penicillin allergy (Gallagher & MacDougall, 2013:89). Occasional effects experienced include diarrhoea, nausea, vomiting, rash and pruritus. Serious reactions include antibiotic-associated colitis, superinfections, anaphylactic reactions and seizures (Mosby's Drug Reference for Health Professions, 2014:521, 589, 824-825, 1013). Imipenem/cilastatin has a higher risk to induce seizures. Risk can be reduced by calculating appropriated doses for patients with renal impairment and avoiding the use of imipenem/cilastatin in patients with meningitis, because the drug crosses the blood-brain barrier more freely when the meninges are inflamed (Gallagher & MacDougall, 2013:88).

- **Common indications**

With the exception of ertapenem, all carbapenems are broad spectrum agents and are good choices for many nosocomial infections (Gallagher & MacDougall, 2013:89). Imipenem/cilastatin is indicated for the treatment of lower respiratory and urinary tract infections, intra-abdominal infections, gynaecological infections, bone and joint infections and skin and skin-structure infections. The drug is also indicated for endocarditis and bacterial septicaemia (Merck & Co Incorporated, 2016; Mosby's Drug Reference for Health Professions, 2014:825; UpToDate, 2016x).

Meropenem is indicated for bacterial meningitis, complicated skin and skin-structure infections, and intra-abdominal infections in susceptible organisms (AstraZeneca Pharmaceuticals, 2014; Mosby's Drug Reference for Health Professions, 2014:1012; UpToDate, 2016y). Off-label indications include the treatment of febrile neutropenia and community-acquired pneumonia (Medscape, 2016p).

Ertapenem is indicated for the treatment of moderate to severe infections caused by susceptible organisms including acute pelvic infections, community-acquired pneumonia, intra-abdominal infections, complicated skin and skin-structure infections, complicated urinary tract infections, and prophylaxis of surgical-site infections in colorectal surgery (Merck & Co. Incorporated, 2013; Mosby's Drug Reference for Health Professions, 2014:587; UpToDate, 2016z).

Doripenem is indicated for the treatment of complicated intra-abdominal infections and complicated urinary tract infections, including pyelonephritis caused by susceptible organisms

(Mosby's Drug Reference for Health Professions, 2014:520; Shionogi & Co. Limited, 2009; UpToDate, 2016aa). Doripenem is not approved for the treatment of any pneumonia (Antimicrobial Therapy, Inc., 2016).

2.2.1.7 Monobactams

Aztreonam is the only agent in this class.

- **Mechanism of action**

Aztreonam is a monobactam antimicrobial agent that inhibits the bacterial cell wall synthesis and has a bactericidal therapeutic effect in susceptible micro-organisms (Mosby's Drug Reference for Health Professions, 2014:156).

- **Spectrum of activity**

Spectrum of activity include *Moraxella catarrhalis*, *Haemophilus influenzae*, *Escherichia coli*, *Klebsiella* sp., *Enterobacter cloacae*, *Enterobacter aerogenes*, *Salmonella* sp., *Serratia marcescens*, *Shigella* spp., *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Providencia reggeri*, *Morganella morganii*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Aeromonas hydrophila*, *Pseudomonas aeruginosa*, *Yersinia enterocolitica* and *Pasteurella multocida* (Antimicrobial Therapy, Inc., 2016; Medscape, 2016q).

- **Adverse effects**

Occasional effects experienced include nausea, vomiting, diarrhoea and rash. Serious reactions include antibiotic-associated colitis and hypersensitivity reactions. Aztreonam should be used with caution in patients with hepatic and renal impairment (Mosby's Drug Reference for Health Professions, 2014:157). Aztreonam seems to be safe to administer to patients allergic to beta-lactams, except in patients allergic to ceftazidime specifically. Ceftazidime and aztreonam also share the same spectrum of activity (Gallagher & MacDougall, 2013:91).

- **Common indications**

Aztreonam is indicated for the treatment of pyelonephritis, cystitis and gonorrhoea caused by susceptible organisms (Bristol-Myers Squibb Limited, 2001a). Other indications include the treatment of lower respiratory tract infections, septicaemia, skin and skin-structure infections, and intra-abdominal infections (UpToDate, 2016ba).

2.2.2 Glycopeptides

Antimicrobial agents of the glycopeptide group include teicoplanin and vancomycin.

- **Mechanism of action**

Vancomycin is a tricyclic glycopeptide antimicrobial that binds to the bacterial cell wall, alter cell membrane permeability and inhibit RNA synthesis which results in a bactericidal therapeutic effect in susceptible micro-organisms (Mosby's Drug Reference for Health Professions, 2014:1691). Teicoplanin inhibit peptidoglycan synthesis (Yim *et al.*, 2014:31).

- **Spectrum of activity**

Teicoplanin is susceptible against *Streptococcus* (Group A, B, C, G), *Streptococcus pneumoniae*, *Enterococcus faecalis*, *Staphylococcus aureus* (MSSA, community-acquired MRSA (CA-MRSA) and hospital-acquired MRSA (HA-MRSA)), *Staphylococcus* coagulase-negative species, *Streptococcus anginosus*, *Viridans streptococci*, *Corynebacterium jeikeium*, *Clostridium difficile*, *Clostridium perfringens* and *Peptostreptococci* (Antimicrobial Therapy, Inc., 2016).

Vancomycin is usually susceptible against *Streptococcus* (Group A, B, C, G), *Streptococcus pneumoniae*, *Streptococcus anginosus*, *Enterococcus faecalis*, *Viridans streptococci*, *Staphylococcus aureus* (MSSA, CA-MRSA and HA-MRSA), *Staphylococcus* coagulase-negative species, *Corynebacterium jeikeium*, *Listeria monocytogenes*, *Arcanobacterium haemolyticum*, *Clostridium difficile*, *Clostridium perfringens* and *Peptostreptococci* (Antimicrobial Therapy, Inc., 2016).

- **Adverse effects**

Teicoplanin can cause hypersensitivity reactions such as fever and skin reactions, a decrease in platelet count, anaemia, and neutropenia (Antimicrobial Therapy, Inc., 2016). Frequently experienced effects due to vancomycin usage are azotaemia, mild increase in serum creatinine and changes in potassium levels. Rarely experienced effects include phlebitis, thrombophlebitis, dizziness, vertigo, tinnitus, chills, rash, fever and necrosis with extravasation. Serious reactions include nephrotoxicity, ototoxicity and red man syndrome due to too-rapid infusion, thrombocytopenia, neutropenia, and hypersensitivity reactions. Vancomycin should be used with caution in patients with pre-existing hearing impairment or renal dysfunction since ototoxicity and nephrotoxicity may occur (Mosby's Drug Reference for Health Professions, 2014:1692). Vancomycin requires pharmacokinetic monitoring where trough concentrations are used to monitor the elimination of the drug and the toxicity and peak concentrations for

calculating patient-specific pharmacokinetic parameters, but do not predict efficacy or safety (Gallagher & MacDougall, 2013:95).

- **Common indications**

Teicoplanin is indicated for the treatment of infections caused by gram-positive bacteria and peritonitis associated with continuous ambulatory peritoneal dialysis (Roussel Laboratories Limited, 1994; UpToDate, 2016da), endocarditis, septicaemia, osteomyelitis, respiratory infections, skin and soft tissue infections, and urinary tract infections (Roussel Laboratories Limited, 1994). Other indications include the treatment of *Clostridium difficile*-associated diarrhoea and surgical prophylaxis (UpToDate, 2016da).

Vancomycin is indicated for the treatment of pseudomembranous colitis caused by *Clostridium difficile*, staphylococcal enterocolitis and endocarditis (Medscape, 2016r; Mosby's Drug Reference for Health Professions, 2014:1691). Off-label treatment indications of vancomycin include community-acquired pneumonia, Group B *Streptococcus*, prosthetic joint infections, skin and soft tissue necrotising infections, surgical site infections, and surgical prophylaxis (UpToDate, 2016ca). Absorption of oral vancomycin is very poor and is only indicated for the treatment of *Clostridium difficile* (Gallagher & MacDougall, 2013:95).

2.2.3 Fluoroquinolones

Fluoroquinolone antimicrobials include ciprofloxacin, gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin and ofloxacin.

- **Mechanism of action**

Ciprofloxacin, levofloxacin, norfloxacin, gemifloxacin, and ofloxacin interferes with bacterial cell replication by inhibiting the enzyme DNA gyrase in susceptible bacteria which results in a bactericidal therapeutic effect (Mosby's Drug Reference for Health Professions, 2014:343, 741, 924, 1172, 1180). Moxifloxacin (Mosby's Drug Reference for Health Professions, 2014:1100), gatifloxacin (Mosby's Drug Reference for Health Professions, 2014:737) and lomefloxacin (Beberok *et al.*, 2013:689, 698) interferes with bacterial DNA replication by inhibiting topoisomerase II and IV in susceptible organisms which results in a bactericidal effect.

- **Spectrum of activity**

Ciprofloxacin is the fluoroquinolone with the greatest activity against aerobic gram-negative bacilli. Susceptibility include (but not limited to) *Francisella tularensis*, *Haemophilus ducreyi*, *Brucella* spp., *Acinetobacter baumannii*, MSSA, *Staphylococcus* coagulase-negative species, *Moraxella catarrhalis*, *Haemophilus influenzae*, *Escherichia coli* (including ESBL+), *Klebsiella* sp. (including ESBL+), *Enterobacter cloacae*, *Enterobacter aerogenes*, *Serratia marcescens*,

Salmonella sp., *Shigella* spp., *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Providencia reggeri*, *Morganella morganii*, *Citrobacter koseri*, *Citrobacter freundii*, *Aeromonas hydrophila*, *Pseudomonas aeruginosa*, *Yersina enterocolitica*, *Legionella* spp., *Leptospira* spp., *Pasteurella multocida*, *Chlamydophila psittaci*, *Vibrio cholerae* and *Mycoplasma pneumoniae* (Antimicrobial Therapy, Inc., 2016).

Gatifloxacin is active against MSSA, *Staphylococcus* coagulase-negative species, *Streptococcus pneumoniae*, *Viridans streptococci*, *Moraxella catarrhalis*, *Haemophilus influenzae*, *Escherichia coli*, *Klebsiella* sp., *Enterobacter cloacae*, *Enterobacter aerogenes*, *Enterococcus faecalis*, *Serratia marcescens*, *Salmonella* sp., *Shigella* spp., *Proteus mirabilis*, *Proteus vulgaris*, *Citrobacter koseri*, *Citrobacter freundii*, *Aeromonas hydrophila*, *Yersina enterocolitica*, *Legionella* spp., *Pasteurella multocida*, *Chlamydophila* sp. and *Mycoplasma pneumoniae* (Antimicrobial Therapy, Inc., 2016).

Gemifloxacin is active against *Streptococcus pneumoniae*, *Viridans streptococcus*, *Enterococcus faecalis*, MSSA, *Staphylococcus* coagulase-negative species, *Listeria monocytogenes*, *Neisseria gonorrhoeae*, *Moraxella catarrhalis*, *Haemophilus influenzae*, *Escherichia coli*, *Klebsiella* sp., *Enterobacter cloacae*, *Enterobacter aerogenes*, *Serratia marcescens*, *Salmonella* sp., *Shigella* spp., *Proteus mirabilis*, *Proteus vulgaris*, *Citrobacter koseri*, *Citrobacter freundii*, *Aeromonas hydrophila*, *Legionella* spp., *Pasteurella multocida*, *Chlamydia trachomatis*, *Chlamydophila psittaci* and *Mycoplasma pneumoniae* (Antimicrobial Therapy, Inc., 2016).

Levofloxacin is a broad spectrum fluoroquinolone and effective against *Chlamydia trachomatis*, *Kingella kingae*, *Acinetobacter baumannii*, *Streptococcus pneumoniae*, *Viridans streptococcus*, *Enterococcus faecalis*, MSSA, *Staphylococcus* coagulase-negative species, *Listeria monocytogenes*, *Moraxella catarrhalis*, *Haemophilus influenzae*, *Escherichia coli* (including ESBL+), *Klebsiella* sp. (including ESBL+), *Enterobacter cloacae*, *Enterobacter aerogenes*, *Serratia marcescens*, *Salmonella* sp., *Shigella* spp., *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Providencia reggeri*, *Morganella morganii*, *Citrobacter koseri*, *Citrobacter freundii*, *Aeromonas hydrophila*, *Yersina enterocolitica*, *Legionella* spp., *Leptospira* spp., *Pseudomonas aeruginosa*, *Pasteurella multocida*, *Chlamydophila psittaci*, *Mycoplasma pneumoniae* and *Peptostreptococci* (Antimicrobial Therapy, Inc., 2016).

Lomefloxacin has activity against gram-negative bacilli which includes *Pseudomonas* spp., *Klebsiella* spp., *Escherichia coli*, and *Haemophilus influenzae* (Naber, 2002:18). The drug also has activity against the fungus *Candida albicans* (El-Halim et al., 2011:17).

Moxifloxacin is active against *Streptococcus pneumoniae*, *Viridans streptococci*, *Enterococcus faecalis*, MSSA, *Staphylococcus* coagulase-negative species, *Moraxella catarrhalis*, *Haemophilus influenzae*, *Escherichia coli* (including ESBL+), *Klebsiella* sp. (including ESBL+), *Enterobacter cloacae*, *Enterobacter aerogenes*, *Serratia marcescens*, *Salmonella* sp., *Shigella* spp., *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Providencia reggeri*, *Morganella morganii*, *Citrobacter koseri*, *Citrobacter freundii*, *Yersina enterocolitica*, *Legionella* spp., *Listeria monocytogenes*, *Leptospira* spp., *Mycoplasma genitalium*, *Pasteurella multocida*, *Chlamydophila psittaci*, *Chlamydia trachomatis*, *Mycoplasma pneumoniae*, *Acinetobacter baumannii*, *Prevotella melaninogenica* and *Peptostreptococci* (Antimicrobial Therapy, Inc., 2016).

Norfloxacin is effective against (but not limited to) *Campylobacter jejuni*, *Citrobacter koseri*, *Citrobacter freundii*, *Enterobacter cloacae*, *Enterobacter aerogenes*, *Enterococcus faecalis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Legionella pneumophila*, *Proteus mirabilis*, *Providencia stuartii*, *Providencia reggeri*, *Pseudomonas aeruginosa*, *Salmonella* sp., *Serratia marcescens*, *Shigella* spp., MSSA and *Staphylococcus saprophyticus* (Medscape, 2016za).

Ofloxacin is effective against MSSA, *Staphylococcus* coagulase-negative species, *Moraxella catarrhalis*, *Haemophilus influenzae*, *Escherichia coli* (including ESBL+), *Klebsiella* sp. (including ESBL+), *Enterobacter cloacae*, *Enterobacter aerogenes*, *Kingella kingae*, *Serratia marcescens*, *Salmonella* sp., *Shigella* spp., *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Providencia reggeri*, *Morganella morganii*, *Citrobacter koseri*, *Citrobacter freundii*, *Yersina enterocolitica*, *Legionella* spp., *Leptospira* spp., *Mycoplasma genitalium*, *Pasteurella multocida*, *Chlamydophila psittaci*, *Chlamydia trachomatis*, *Mycoplasma pneumoniae*, *Acinetobacter baumannii* and *Aeromonas hydrophila* (Antimicrobial Therapy, Inc., 2016).

- **Adverse effects**

Fluoroquinolones may exacerbate myasthenia gravis, cause QT-interval prolongation, central nervous system adverse effects, tendon rupture and irreversible peripheral neuropathy (Mosby's Drug Reference for Health Professions, 2014:345).

Frequently experienced effects caused by the use of ciprofloxacin include nausea, diarrhoea, dyspepsia, vomiting, constipation, crystalluria, flatulence, and confusion. Serious reactions caused by ciprofloxacin include superinfections, nephropathy, irreversible peripheral neuropathy, cardiopulmonary arrest, chest pain, cerebral thrombosis and tendon inflammation or rupture (Mosby's Drug Reference for Health Professions, 2014:344-345).

Occasionally experienced effects due to gatifloxacin ophthalmic usage include conjunctival irritation, increased tearing and corneal inflammation. Serious reactions that could be caused by

this drug include conjunctival haemorrhage and the risk of developing superinfections (Mosby's Drug Reference for Health Professions, 2014:737).

Occasionally experienced effects due to gemifloxacin usage include diarrhoea, rash and nausea. Serious reactions include antibiotic-associated colitis, hypersensitivity reactions, tendon ruptures and peripheral neuropathy, convulsions, QT-interval prolongation and risk of pro-arrhythmia, pseudotumor cerebri, exacerbation of myasthenia and irreversible peripheral neuropathy (Mosby's Drug Reference for Health Professions, 2014:742).

Occasionally experienced effects of levofloxacin usage include diarrhoea, nausea, abdominal pain, headache, dizziness, drowsiness, and light-headedness. Serious reactions associated with levofloxacin usage include antibiotic-associated colitis, superinfections, tendon rupture, peripheral neuropathy, seizures, QT- interval prolongation, exacerbations of myasthenia gravis, benign intracranial hypertension and hypersensitivity reactions including photosensitivity (Mosby's Drug Reference for Health Professions, 2014:926-927).

The most common effects caused by lomefloxacin usage are headache, nausea, diarrhoea, abdominal pain, dizziness and phototoxicity (Pharmacare Limited, 2001).

Frequent side effects caused by moxifloxacin usage include nausea and diarrhoea. Dizziness, headache, abdominal pain, and vomiting are occasionally experienced due to usage. Serious reactions include pseudomembranous colitis, superinfections, tendinopathy and tendon rupture, QT-interval prolongation, seizures, serious hypersensitivity reactions, benign intracranial hypertension, exacerbation of myasthenia and peripheral neuropathy (Mosby's Drug Reference for Health Professions, 2014:1101).

Norfloxacin usage can cause burning skin, photophobia and a bitter taste in the mouth. Other frequent effects are headache, nausea and dizziness. Serious reactions include superinfections, anaphylaxis, Stevens-Johnson syndrome, peripheral neuropathy, hypoglycaemia, tendonitis and tendon rupture, and hypersensitivity reactions (Mosby's Drug Reference for Health Professions, 2014:1173).

Frequently experienced effects due to ofloxacin usage include nausea, headache and insomnia. Serious reactions include antibiotic-associated colitis, superinfections, hypersensitivity reactions, arthropathy, tendonitis or tendon rupture, and peripheral neuropathy (Mosby's Drug Reference for Health Professions, 2014:1181).

- **Common indications**

Both ciprofloxacin and levofloxacin have activity against *Pseudomonas*. The bioavailability of all fluoroquinolones is 80 to 100%. Therefore, the intravenous dose is the same as the oral dose, except for ciprofloxacin where the oral dose is 1.25 times the intravenous dose. Chelating agents such as calcium, magnesium, iron, anti-acids, milk or vitamins significantly decrease the bioavailability of fluoroquinolones when administered together (Gallagher & MacDougall, 2013:99). Administration should therefore be separated by at least two hours (Bushra *et al.*, 2011:82; Gallagher & MacDougall, 2013:99).

Ciprofloxacin is indicated for the treatment of the following infections caused by susceptible organisms: urinary tract infections, skin and skin-structure infections, bone and joint infections, infectious diarrhoea, gonorrhoea (Bayer Limited, 2003a; Mosby's Drug Reference for Health Professions, 2014:343; UpToDate, 2016ea), prostatitis, and acute sinusitis (Mosby's Drug Reference for Health Professions, 2014:343; UpToDate, 2016ea). Other indications include the treatment of acute uncomplicated cystitis in females, lower respiratory tract infections (Bayer Limited, 2003a; UpToDate, 2016ea), complicated intra-abdominal infections (in combination with metronidazole), typhoid fever caused by *Salmonella typhi*, nosocomial pneumonia, and empirical therapy in febrile neutropenic patients (in combination with piperacillin) (UpToDate, 2016ea).

Gatifloxacin is indicated for the treatment of bacterial conjunctivitis (Medscape, 2016ab; Mosby's Drug Reference for Health Professions, 2014:737). Other treatment indications include community acquired pneumonia, acute bacterial exacerbation of chronic bronchitis, acute sinusitis, uncomplicated skin and skin structure infections, urinary tract infections, pyelonephritis and uncomplicated gonorrhoea (Bristol-Myers Squibb Limited, 2005b).

Gemifloxacin is indicated for the treatment of acute bacterial exacerbations of chronic bronchitis, community-acquired pneumonia (Medscape, 2016u; Mosby's Drug Reference for Health Professions, 2014:741; Pharmacare Limited, 2014; UpToDate, 2016ha) and for the treatment of urinary tract infections caused by susceptible micro-organisms (Pharmacare Limited, 2014).

Levofloxacin is indicated for the treatment of community-acquired pneumonia, including multi-drug resistant strains of *Staphylococcus pneumoniae*, nosocomial pneumonia, chronic bronchitis, urinary tract infections, acute pyelonephritis, skin or skin-structure infections (Pharmacare Limited, 2008; UpToDate, 2016fa), acute bacterial rhinosinusitis, chronic bacterial prostatitis and prophylaxis, and treatment of plague due to *Yersinia pestis* (UpToDate, 2016fa).

Lomefloxacin is indicated for the treatment of urinary tract infections caused by susceptible organisms and acute exacerbation of chronic bronchitis (Pharmacare Limited, 2001; Rossiter, 2010:298).

Moxifloxacin is indicated for the treatment of the following infections caused by susceptible bacteria: mild to moderate community-acquired pneumonia, acute bacterial sinusitis, acute exacerbation of chronic bronchitis, skin and skin-structure infections (Bayer Limited, 2003b; Medscape, 2016t; UpToDate, 2016ga), intra-abdominal infections and prophylaxis, and treatment of plague (Medscape, 2016t; UpToDate, 2016ga).

Norfloxacin is indicated for the treatment of upper and lower urinary tract infections caused by susceptible micro-organisms (Cipla-Medpro Limited, 2001).

Ofloxacin is indicated for the treatment of cystitis, pyelonephritis, lower respiratory tract infections, gonorrhoea, tuberculosis, urethritis, and cervicitis due to *Chlamydia trachomatis* (Rossiter, 2010:300).

2.2.4 Aminoglycosides

Gentamycin, tobramycin, amikacin, and streptomycin are agents of this class of antimicrobials.

- **Mechanism of action**

Aminoglycosides irreversibly bind to the protein of bacterial ribosomes, interfering with the protein synthesis of susceptible micro-organisms (Mosby's Drug Reference for Health Professions, 2014:72, 742, 1533, 1625) thereby exerting a bactericidal therapeutic effect (Maurin & Raoult, 2001:2977).

- **Spectrum of activity**

This class of antimicrobial agents has good activity against problematic pathogens such as *Pseudomonas* and *Acinetobacter* (Gallagher & MacDougall, 2013:101). Gentamycin, tobramycin and amikacin are effective against MSSA, *Moraxella catarrhalis*, *Haemophilus influenzae*, *Escherichia coli* (including ESBL+), *Klebsiella* sp. (including ESBL+), *Enterobacter cloacae*, *Enterobacter aerogenes*, *Aeromonas hydrophila*, *Campylobacter jejuni*, *Campylobacter coli*, *Citrobacter koseri*, *Citrobacter freundii*, *Shigella* spp., *Serratia marcescens*, *Proteus vulgaris*, *Proteus mirabilis*, *Morganella morganii*, *Pseudomonas aeruginosa*, *Salmonella* sp., and *Yersina enterocolitica*. Amikacin is effective against *Mycobacterium avium* and *Nocardia* sp. Gentamycin has activity against *Bartonella* spp. and *Francisella tularensis* (Antimicrobial Therapy, Inc., 2016).

Aminoglycosides are synergistic with cell wall-active antibiotics against the following organisms: *Enterococcus faecalis*, *Listeria monocytogenes* and *Brucella* spp. Streptomycin has activity against *Mycobacterium tuberculosis*, *Viridans streptococci* and enterococcal isolates (Antimicrobial Therapy, Inc., 2016; UpToDate, 2016la).

- **Adverse effects**

Aminoglycoside agents have a narrow therapeutic index and improper dosing can lead to toxicity. Serum levels of the drug can help guide appropriate dosing and reduce the risk of toxicity, but they must be drawn correctly to have a meaningful interpretation. Doses should be based on a patient's ideal or adjusted body weight, rather than their total body weight to avoid overdosing since most toxicities caused by aminoglycosides are dose-related (Gallagher & MacDougall, 2013:101-103).

Occasional effects experienced from gentamycin usage include thrombophlebitis, phlebitis and hypersensitivity reactions. Serious reactions that may occur include nephrotoxicity, irreversible ototoxicity, neurotoxicity, superinfections, and paraesthesia of the conjunctiva or mydriasis with ophthalmic application of gentamycin. Tobramycin can occasionally cause phlebitis and thrombophlebitis with intravenous administration of the agent. Serious reactions include nephrotoxicity, irreversible ototoxicity, neurotoxicity, superinfections, and anaphylaxis. Frequent side-effects caused by intravenous administration of amikacin include phlebitis and thrombophlebitis. Effects occasionally and rarely experienced include hypersensitivity reactions and neuromuscular blockade. Serious reactions may include nephrotoxicity, ototoxicity and neuromuscular blockade. Streptomycin can cause hypotension, drowsiness, headache, rash, paraesthesia, drug fever, nausea, vomiting, anaemia, arthralgia, weakness and tremor. Serious reactions include nephrotoxicity, irreversible ototoxicity and neurotoxicity (Mosby's Drug Reference for Health Professions, 2014:74, 745, 1534, 1626-1627).

- **Common indications**

Aminoglycosides have a synergetic effect with beta-lactam agents and glycopeptides (Gallagher & MacDougall, 2013:101). Gentamycin is indicated for the treatment of susceptible bacterial infections such as bone infections, respiratory tract infections, skin and soft tissue infections, urinary tract infections, and septicaemia (Bodene Limited, 2006; Mosby's Drug Reference for Health Professions, 2014:743; UpToDate, 2016ia). The drug is also indicated for infective endocarditis (Medscape, 2016ya; UpToDate, 2016ia).

Tobramycin is indicated for the treatment of bacterial infections caused by susceptible gram-negative bacilli and used in combination therapy for the treatment of infections caused by gram-positive bacteria (Medscape, 2016v; UpToDate, 2016ja). Infections include skin and skin-

structure, bone and joint-, respiratory tract-, intra-abdominal, complicated urinary tract infections, septicaemia (Hospira Incorporated, 2011; Mosby's Drug Reference for Health Professions, 2014:1626), and bronchopulmonary infections in patients with cystic fibrosis (Mosby's Drug Reference for Health Professions, 2014:1626).

Amikacin is used for the treatment of serious infections caused by gram-negative organisms such as *Pseudomonas*, *Escherichia coli*, *Proteus*, *Providencia*, *Klebsiella*, *Enterobacter*, *Serratia* and *Acinetobacter*. These include infections such as bone infections, respiratory tract infections, endocarditis, and septicaemia (UpToDate, 2016ka). Other indications include the treatment of urinary tract infection (Bristol-Myers Squibb Limited, 2001b; Medscape, 2016w; Mosby's Drug Reference for Health Professions, 2014:73) and hospital-acquired pneumonia (Medscape, 2016w).

Streptomycin is indicated for the treatment of tuberculosis in combination with other antituberculosis agents and is used when the primary agents are contra-indicated due to intolerance or toxicity (Mosby's Drug Reference for Health Professions, 2014:1533; UpToDate, 2016la; X-Gen Pharmaceuticals Incorporated, 2011). Other indications include treatment of tularaemia (rabbit fever), plague, streptococcal endocarditis, enterococcal endocarditis and brucellosis (Medscape, 2016x; X-Gen Pharmaceuticals Incorporated, 2011).

2.2.5 Tetracyclines and glycyclines

Agents of the tetracycline class include doxycycline and minocycline, whereas tigecycline is of the glycycline class.

- **Mechanism of action**

Tetracyclines and glycyclines bind to the bacterial ribosome that causes inhibition of bacterial protein synthesis (Gallagher & MacDougall, 2013:105). The therapeutic effect is bacteriostatic in susceptible micro-organisms (Mosby's Drug Reference for Health Professions, 2014:527, 1076, 1608).

- **Spectrum of activity**

Doxycycline is effective against *Staphylococcus aureus* (CA-MRSA, HA-MRSA and MSSA), *Moraxella catarrhalis*, *Haemophilus influenzae*, *Aeromonas hydrophila*, *Escherichia coli*, *Francisella tularensis*, *Brucella* spp., *Mycoplasma pneumoniae*, *Rickettsia* sp., *Arcanobacterium haemolyticum*, *Borrelia burgdorferi*, *Bartonella* spp., *Chlamydia trachomatis*, *Chlamydophila psittaci*, *Leptospira* spp., *Prevotella melaninogenica*, *Pasteurella multocida*, *Staphylococcus* coagulase-negative species, *Treponema pallidum*, *Vibrio cholerae*, *Yersinia enterocolitica*,

Yersinia pestis, *Clostridium perfringens*, and *Peptostreptococci* (Antimicrobial Therapy, Inc., 2016).

Minocycline is effective against *Staphylococcus* coagulase-negative species, *Staphylococcus aureus* (MSSA, CA-MRSA and HA-MRSA), *Moraxella catarrhalis*, *Haemophilus influenzae*, *Aeromonas hydrophila*, *Brucella* spp., *Borrelia burgdorferi*, *Bartonella* spp., *Chlamydia trachomatis*, *Chlamydophila psittaci*, *Mycoplasma pneumoniae*, *Rickettsia* sp., *Actinomyces israelii*, *Prevotella melaninogenica*, *Clostridium perfringens*, *Legionella* spp., *Leptospira* spp., *Francisella tularensis*, *Yersinia pestis* and *Peptostreptococci* (Antimicrobial Therapy, Inc., 2016).

Tigecycline is usually effective against *Acinetobacter baumannii*, *Streptococcus* (Group A, B, C, G), *Streptococcus pneumoniae*, *Enterococcus faecalis*, *Enterococcus faecium*, *Staphylococcus aureus* (MSSA, CA-MRSA and HA-MRSA), *Staphylococcus* coagulase-negative species, *Streptococcus anginosus*, *Viridans streptococci*, *Corynebacterium jeikeium*, *Haemophilus influenzae*, *Aeromonas hydrophila*, *Escherichia coli* (including ESBL+ and KPC+), *Klebsiella* sp. (including ESBL+ and KPC+), *Enterobacter cloacae*, *Enterobacter aerogenes*, *Salmonella* sp., *Shigella* spp., *Serratia marcescens*, *Citrobacter koseri*, *Citrobacter freundii*, *Proteus vulgaris*, *Proteus mirabilis*, *Stenotrophomonas maltophilia*, *Pasteurella multocida*, *Chlamydophila psittaci*, *Legionella* spp., *Mycoplasma pneumoniae*, *Bacteroides fragilis*, *Prevotella melaninogenica*, *Clostridium perfringens*, *Fusobacterium necrophorum* and *Peptostreptococci* (Antimicrobial Therapy, Inc., 2016).

- **Adverse effects**

The dosage of doxycycline does not need to be adjusted in renal or hepatic dysfunction (Gallagher & MacDougall, 2013:107). Frequent effects caused by doxycycline include anorexia, severe photosensitivity, nausea, vomiting and dysphagia. Serious reactions include benign intracranial hypertension, hepatotoxicity, fatty degeneration of liver, pancreatitis and discoloration of teeth, serious hypersensitivity reactions (anaphylaxis, Stevens-Johnson syndrome, DRESS syndrome, and superinfections (Mosby's Drug Reference for Health Professions, 2014:529).

Frequently caused effects due to minocycline usage include dizziness, light-headedness, diarrhoea, vomiting, nausea, severe photosensitivity, abdominal cramping, drowsiness and vertigo. Serious reactions include anaphylaxis, benign intracranial pressure, pseudomembranous colitis, tinnitus, interstitial nephritis, azotaemia, metabolic acidosis, acute renal failure, discoloration of teeth, oesophageal ulceration from improper administration, and superinfections such as fungal infections (Mosby's Drug Reference for Health Professions, 2014:1077).

Frequent effects caused by tigecycline usage include vomiting, nausea, diarrhoea, abdominal pain, headache and an increased alanine transaminase (ALT). Serious reactions include hypersensitivity reactions, tinnitus and hearing loss, benign increased intracranial pressure, interstitial nephritis, azotaemia, discoloration of teeth, metabolic acidosis, acute renal failure, pancreatitis, hepatitis with jaundice, eosinophilia, pseudomembranous colitis and superinfections (especially fungal) (Mosby's Drug Reference for Health Professions, 2014:1609).

- **Common indications**

The bioavailability of doxycycline and minocycline is approximately 100%. The oral bioavailability is significantly decreased when administered with calcium, iron, multivitamins or antacids because tetracyclines chelate cations (Gallagher & MacDougall, 2013:106-107). Doxycycline is indicated for the treatment of bacterial infections caused by susceptible micro-organisms. These are infections such as respiratory tract infections, urinary tract infections, brucellosis, rickettsia, severe acne, psittacosis, gonococcal infections, syphilis (when penicillin is contra-indicated), and trachoma (Medscape, 2016y; Mosby's Drug Reference for Health Professions, 2014:528; Quatromed Limited, 2000; UpToDate, 2016ma). Other indications include the treatment of rosacea, intestinal amebiasis, the prevention of rheumatic fever and malaria prophylaxis (Medscape, 2016y; Mosby's Drug Reference for Health Professions, 2014:528; UpToDate, 2016ma).

Minocycline is indicated for the treatment of acne vulgaris, gonococcal infections and syphilis (when penicillin is contra-indicated) (Hexal Pharma Limited, 2000b; Medscape, 2016z; Mosby's Drug Reference for Health Professions, 2014:528; UpToDate, 2016na). Other indications include upper and lower respiratory tract infections, trachoma and inclusion conjunctivitis, cholera, rickettsia infections, brucellosis, tularaemia and Lyme disease (Hexal Pharma Limited, 2000b).

Tigecycline is indicated for the treatment of the following infections caused by susceptible organisms; community-acquired pneumonia, intra-abdominal infections, and skin and skin-structure infections (Medscape, 2016aa; Mosby's Drug Reference for Health Professions, 2014:1608; UpToDate, 2016oa; Wyeth Pharmaceuticals Incorporated, 2013). Tigecycline distributes highly into many tissues due to its large volume of distribution. The drug achieves low urinary concentration and is not therefore recommended for urinary tract infections. It is not an excellent choice for treating primary bloodstream infections due to the fact that the drug reaches low bloodstream concentrations because of its extensive distribution. Tigecycline have a mortality disadvantage compared to other antimicrobial agents (Gallagher & MacDougall, 2013:107).

2.2.6 Macrolides and ketolides

Agents of this class include the macrolides azithromycin, clarithromycin, erythromycin and telithromycin (which is a ketolide).

- **Mechanism of action**

Macrolides and ketolides prevent/inhibit protein synthesis of the bacterial cell wall by binding to the bacterial ribosome. The therapeutic effect of the macrolides in susceptible micro-organisms is bacteriostatic but azithromycin and clarithromycin may have a bactericidal effect when high enough dosages are used. Telithromycin has a bactericidal therapeutic effect in susceptible micro-organisms (Gallagher & MacDougall, 2013:109; Mosby's Drug Reference for Health Professions, 2014:153, 348, 590; 1568).

- **Spectrum of activity**

Azithromycin is effective against *Arcanobacterium haemolyticum*, *Bordetella pertussis*, *Bartonella* spp., *Moraxella catarrhalis*, *Haemophilus influenzae*, *Legionella* spp., *Haemophilus ducreyi*, *Chlamydophila psittaci*, *Neisseria gonorrhoeae*, *Pasteurella multocida*, *Salmonella* sp., *Treponema pallidum*, *Vibrio cholerae*, *Leptospira* spp., *Chlamydia trachomatis*, *Camphylobacter jejuni*, *Mycoplasma pneumoniae*, *Mycobacterium avium*, *Actinomyces israelii*, and *Clostridium perfringens* (Antimicrobial Therapy, Inc., 2016).

Clarithromycin is effective against *Leptospira* spp., *Moraxella catarrhalis*, *Haemophilus influenzae*, *Legionella* spp., *Chlamydophila psittaci*, *Chlamydia trachomatis*, *Arcanobacterium haemolyticum*, *Actinomyces israelii*, *Bordetella pertussis*, *Borrelia burgdorferi*, *Corynebacterium diphtheria*, *Campylobacter jejuni*, *Bartonella* spp., and *Clostridium perfringens* (Antimicrobial Therapy, Inc., 2016).

Erythromycin is effective against *Moraxella catarrhalis*, *Legionella* spp., *Haemophilus ducreyi*, *Chlamydophila psittaci*, *Mycoplasma pneumoniae* and *Actinomyces israelii* (Antimicrobial Therapy, Inc., 2016; UpToDate, 2016pa).

Telithromycin is usually effective against *Streptococcus* (Group A, B, C, G), *Streptococcus pneumoniae*, MSSA, *Moraxella catarrhalis*, *Haemophilus influenzae*, *Chlamydophila psittaci* and *Mycoplasma pneumoniae* (Antimicrobial Therapy, Inc., 2016; UpToDate, 2016qa).

- **Adverse effects**

This group includes potent inhibitors of drug-metabolising Cytochrome P450 enzymes and could have interactions with other drugs when co-administered (Gallagher & MacDougall, 2013:110). Occasionally caused effects due to clarithromycin usage include diarrhoea, nausea,

abdominal pain and altered (metallic) taste. Serious reactions include antibiotic-associated colitis, superinfections, hepatotoxicity, QT-interval prolongation, thrombocytopenia, DRESS syndrome, and Henoch-Schonlein purpura (Mosby's Drug Reference for Health Professions, 2014:349).

Occasionally caused effects from azithromycin usage include nausea, diarrhoea, abdominal pain and vomiting. Serious reactions include antibiotic-associated colitis, superinfections, acute interstitial nephritis, cholestatic jaundice, hepatotoxicity, hepatic necrosis, QT-interval prolongation and serious arrhythmias (Mosby's Drug Reference for Health Professions, 2014:155).

Common effects caused by the intravenous preparation of erythromycin are abdominal cramping or discomfort and thrombophlebitis. Oral preparations can cause diarrhoea, urticarial, vomiting, rash, and nausea. Serious reactions include antibiotic-associated colitis, superinfections, reversible hearing loss if high dosages are used in patients with renal or hepatic impairment, anaphylaxis, hepatotoxicity, ventricular arrhythmias, and QT-interval prolongation (Mosby's Drug Reference for Health Professions, 2014:592).

Occasionally caused effects from telithromycin usage include headache, nausea, dizziness, and diarrhoea. Serious reactions include hepatic dysfunction, severe hypersensitivity reactions, QT-interval prolongation, arrhythmias, and myasthenia gravis with life-threatening and fatal respiratory depression, antibiotic-associated colitis, superinfections, and vagal symptoms with loss of consciousness (Mosby's Drug Reference for Health Professions, 2014:1569).

- **Common indications**

Azithromycin is indicated for the treatment of community-acquired pneumonia, acute pelvic inflammatory disease and uncomplicated gonococcal infections (Medscape, 2016ba; Pfizer Incorporated, 2000; UpToDate, 2016sa). Other indications include the treatment of acute bacterial exacerbations of chronic obstructive pulmonary disease, acute otitis media, genital ulcer disease, acute bacterial sinusitis, pharyngitis, tonsillitis, uncomplicated skin and skin-structure infections, cat scratch disease and *Mycobacterium avium*-complex infection (Medscape, 2016ba; UpToDate, 2016sa). A three to five-day course of azithromycin is usually adequate for most infections due to the prolonged half-life of the drug (Gallagher & MacDougall, 2013:111).

Clarithromycin is indicated for the treatment of acute exacerbation of chronic bronchitis, acute maxillary sinusitis, mycobacterial infections, pharyngitis, tonsillitis, pneumonia, skin and skin-structure infection, and peptic ulcer disease due to *Helicobacter pylori*, in combination with

amoxicillin, H₂-receptor antagonist or proton pump inhibitor (Medscape, 2016ca; Mosby's Drug Reference for Health Professions, 2014:348; Ranbaxy Limited, 2007; UpToDate, 2016ra).

Erythromycin is indicated for the treatment of susceptible bacterial infections of the respiratory tract, pharyngitis, skin and soft tissue (Mosby's Drug Reference for Health Professions, 2014:590; Pharmacare Limited, 2004), and urinary tract infections (Pharmacare Limited, 2004). Off-label indications include *Campylobacter* gastro-enteritis treatment and gastroparesis management (Mosby's Drug Reference for Health Professions, 2014:590; UpToDate, 2016pa). Erythromycin is more used nowadays as a gastro-intestinal prokinetic due to its adverse effects, drug interactions and frequent dosing (Gallagher & MacDougall, 2013:109). Erythromycin stimulates gastro-intestinal motility effects by acting as a motilin receptor agonist in the gut and gallbladder, stimulating enteric nerves and smooth muscle and triggering a phase of migrating myoelectric complex (Hawkyard & Koerner, 2007:349-350). The drug can therefore be used to increase contractile force and accelerate intraluminal transit (Hawkyard & Koerner, 2007:348).

Telithromycin is indicated for the treatment of community-acquired pneumonia (Medscape, 2016da; Mosby's Drug Reference for Health Professions, 2014:1568; Sanofi-Aventis, 2007; UpToDate, 2016qa).

2.2.7 Oxazolidinones

Linezolid is the only agent of the oxazolidinones class.

- **Mechanism of action**

Linezolid is an oxazolidinone that binds on the 23S subunit of ribosomal RNA, thereby preventing formation of a complex that is essential for bacterial translation. The therapeutic effect is bacteriostatic against enterococci and staphylococci and bactericidal against streptococci (Mosby's Drug Reference for Health Professions, 2014:944).

- **Spectrum of activity**

Linezolid has activity against (but not limited to) *Streptococcus* (Group A, B, C, G), *Streptococcus pneumoniae*, vancomycin-resistant *Enterococcus faecium*, vancomycin-resistant *Enterococcus faecalis*, *Staphylococcus aureus* (MSSA, CA-MRSA and HA-MRSA), *Staphylococcus* coagulase-negative species, *Viridans streptococci*, *Streptococcus anginosus*, *Corynebacterium jeikeium*, *Listeria monocytogenes*, *Clostridium perfringens*, *Arcanobacterium haemolyticum*, *Actinomyces israelii*, and *Peptostreptococci* (Antimicrobial Therapy, Inc., 2016).

- **Adverse effects**

Normally linezolid is well tolerated, but can cause bone-marrow suppression and most commonly thrombocytopenia after two or more weeks of therapy. Linezolid is a monoamine oxidase inhibitor and can cause serotonin syndrome when administered with serotonergic agents such as serotonin reuptake inhibitors. A dosage of linezolid does not need to be adjusted in renal or hepatic dysfunction (Gallagher & MacDougall, 2013:114-115). Effects from linezolid usage that occurs occasionally include diarrhoea, nausea and headaches. Serious effects include thrombocytopenia, myelosuppression, antibiotic-associated colitis, superinfections, serotonin syndrome or hypertension with serotonergic or pressor agents, optic neuropathy with prolonged therapy, lactic acidosis, symptomatic hypoglycaemia in diabetic patients, and peripheral neuropathy (Mosby's Drug Reference for Health Professions, 2014:945).

- **Common indications**

Linezolid has broad spectrum gram-negative activity and excellent oral bioavailability (Gallagher & MacDougall, 2013:113). Linezolid is indicated for the treatment of vancomycin-resistant infections, pneumonia, and skin and skin-structure infections caused by susceptible bacteria (Medscape, 2016ea; Mosby's Drug Reference for Health Professions, 2014:944; Pfizer Incorporated, 2008; UpToDate, 2016ta).

2.2.8 Nitro-imidazoles

Metronidazole is the sole class agent.

- **Mechanism of action**

Metronidazole is a nitro-imidazole derivative that inhibits nucleic acid synthesis by disrupting bacterial and protozoal DNA. The therapeutic effect is bactericidal, antiprotozoal, amoebicidal, and trichomonacidal with good anaerobic coverage (Mosby's Drug Reference for Health Professions, 2014:1057).

- **Spectrum of activity**

Metronidazole is only active against anaerobic organisms such as *Bacteroides fragilis*, *Clostridium difficile*, *Clostridium perfringens*, *Fusobacterium necrophorum* and *Prevotella melaninogenica* (Antimicrobial Therapy, Inc., 2016).

- **Adverse effects**

Systemic effects frequently caused due to metronidazole usage include anorexia, dry mouth nausea, and a metallic taste. Serious reactions due to metronidazole usage include peripheral neuropathy, seizures and furry tongue, glossitis, cystitis, dysuria, pancreatitis, and flattening of T-waves on ECG readings due to oral therapy (Mosby's Drug Reference for Health Professions, 2014:1059). Metronidazole can cause disulfiram-like reactions when consumed with alcohol, due to its inhibition of aldehyde dehydrogenase. Metronidazole potentiates the anticoagulant properties of warfarin by the inhibiting warfarin metabolism. Warfarin dosage should be reduced when used in combination. The bioavailability of metronidazole is almost 100%. Metronidazole also disturbs the normal (primarily anaerobic) gastro-intestinal flora (Gallagher & MacDougall, 2013:117-119).

- **Common indications**

Metronidazole is indicated for the treatment of anaerobic bacterial infections, sexually transmitted diseases, bacterial vaginosis, colorectal surgical infections, trichomoniasis, amebiasis and gardnerella infections. Off-label indications include giardiasis, *Helicobacter pylori* eradication, non-gonococcal urethritis and pelvic inflammatory disease (Medscape, 2016fa). Anaerobic bacterial infections include bacterial septicaemia, bone and joint infections, central nervous system infections, endocarditis, gynaecologic infections, intra-abdominal infections, lower respiratory tract infections, and skin and skin-structure infections (Mosby's Drug Reference for Health Professions, 2014:1057; Pharmacare Limited, 2000a; UpToDate, 2016ua).

2.2.9 Nitrofurans and fosfomycin

Agents include nitrofurantoin and fosfomycin.

- **Mechanism of action**

Nitrofurantoin inhibits bacterial DNA, RNA and protein synthesis and cell-wall synthesis by altering or inactivating ribosomal proteins. The therapeutic effect in susceptible micro-organisms is bacteriostatic and bactericidal at high concentrations (Mosby's Drug Reference for Health Professions, 2014:1159). Fosfomycin prevents formation of bacterial cell walls by inhibiting the synthesis of peptidoglycan. The therapeutic effect is bactericidal in susceptible micro-organisms (Mosby's Drug Reference for Health Professions, 2014:717).

- **Spectrum of activity**

Nitrofurantoin has activity against vancomycin-resistant *Enterococcus faecalis*, vancomycin-resistant *Enterococcus faecium*, *Klebsiella pneumoniae*, *Escherichia coli* and *Staphylococcus saprophyticus* (Antimicrobial Therapy, Inc., 2016).

Fosfomycin has activity against vancomycin-resistant *Enterococcus faecalis*, vancomycin-resistant *Enterococcus faecium*, *Staphylococcus aureus* (MSSA, CA-MRSA and HA-MRSA), *Escherichia coli* (including ESBL+ and KPC+), *Klebsiella* sp. (including ESBL+ and KPC+), *Enterobacter cloacae*, *Enterobacter aerogenes*, *Staphylococcus* coagulase-negative species, *Staphylococcus lugdunensis*, *Serratia marcescens*, *Citrobacter koseri* and *Citrobacter freundii* (Antimicrobial Therapy, Inc., 2016).

- **Adverse effects**

Frequently caused effects of nitrofurantoin include anorexia, dark urine, vomiting and nausea. Serious reactions include haemolytic anaemia, hepatotoxicity, peripheral neuropathy, Stevens-Johnson syndrome, anaphylaxis, interstitial pneumonitis, pulmonary fibrosis, superinfections, and pseudomembranous colitis (Mosby's Drug Reference for Health Professions, 2014:1160). Occasionally caused effects due to fosfomycin usage include diarrhoea, nausea, rhinitis, dizziness, back pain and headache. Serious reactions include hypersensitivity such as angioedema or hepatic reaction and superinfections with prolonged usage (Mosby's Drug Reference for Health Professions, 2014:718).

- **Common indications**

Nitrofurantoin and fosfomycin require high concentrations for antimicrobial activity. These concentrations are only reached where the agents concentrate in the urine. Patients with renal dysfunction with a creatinine of less than 50 ml/min should not use these agents since they may have insufficient accumulation of the drug in the urine for activity (Gallagher & MacDougall, 2013:111-123). Nitrofurantoin is indicated for the treatment of urinary tract infections caused by susceptible micro-organisms (Medscape, 2016ga; Mosby's Drug Reference for Health Professions, 2014:1159; SmithKline Beecham Pharmaceuticals Limited, 1991).

Fosfomycin is indicated for the treatment of urinary tract infections (acute cystitis) and prostatitis caused by susceptible micro-organisms (Medscape, 2016ha; Mosby's Drug Reference for Health Professions, 2014:717).

2.2.10 Cyclic lipopeptides

Daptomycin stands alone in the cyclic lipopeptide class.

- **Mechanism of action**

Daptomycin has a unique mechanism of action and target when compared with other antimicrobials. The drug binds to the cell membrane of gram-positive bacteria, weakens it and allows the leaking of essential ions out of the organisms (Gallagher & MacDougall, 2013:129). The agent causes rapid depolarisation of the membrane potential by binding to the bacterial

membranes. The loss of membrane potential leads to the inhibition of synthesis of protein, DNA and RNA. The therapeutic effect is bactericidal in susceptible micro-organisms (Mosby's Drug Reference for Health Professions, 2014:422).

- **Spectrum of activity**

Daptomycin has activity against *Arcanobacterium haemolyticum*, *Streptococcus* (Group A, B, C, G), vancomycin-resistant *Enterococcus faecalis*, vancomycin-resistant *Enterococcus faecium*, *Viridans streptococci*, *Streptococcus anginosus*, *Staphylococcus saprophyticus*, *Staphylococcus lugdunensis*, *Staphylococcus aureus* (MSSA, CA-MRSA and HA-MRSA), *Staphylococcus coagulase-negative species*, *Peptostreptococci*, *Propionibacterium acnes* and *Corynebacterium jeikeium* (Antimicrobial Therapy, Inc., 2016; Medscape, 2016ia).

- **Adverse effects**

Frequently caused adverse effects due to daptomycin usage include anaemia, constipation, nausea, peripheral injection site reactions, diarrhoea, vomiting, peripheral oedema, chest pain, insomnia, hypertension, and hypotension. Serious reactions include skeletal muscle myopathy, hypersensitivity reactions, eosinophilic pneumonia, antibiotic-associated colitis, superinfections, and renal failure (Mosby's Drug Reference for Health Professions, 2014:423).

- **Common indications**

Daptomycin is indicated for the treatment of skin infections caused by susceptible micro-organisms, *Staphylococcus aureus* bacteraemia (including right-sided endocarditis), and complicated skin and skin-structure gram-positive bacterial infections (Cubist Pharmaceuticals Incorporated, 2015; Medscape, 2016ii; Mosby's Drug Reference for Health Professions, 2014:422; UpToDate, 2016xa). Daptomycin has activity against resistant gram-positive organisms. Daptomycin should not be used for the treatment of pneumonia, because human pulmonary surfactant binds to daptomycin rendering it inactive. Concentrations of creatinine kinase and renal function should be monitored during daptomycin therapy (Gallagher & MacDougall, 2013:130).

2.2.11 Folate antagonists

Agents of the folate antagonist class include trimethoprim/sulfamethoxazole and dapsone.

- **Mechanism of action**

Trimethoprim/sulfamethoxazole is a combination of a sulphonamide and folate antagonist that has a bactericidal therapeutic effect in susceptible micro-organisms. The agent acts by blocking essential nucleic acid synthesis (Mosby's Drug Reference for Health Professions, 2014:375).

Dapsone prevents normal utilisation of bacterial para-aminobenzoic acid for synthesis of folic acid and inhibits bacterial growth (Mosby's Drug Reference for Health Professions, 2014:420).

- **Spectrum of activity**

Trimethoprim/sulfamethoxazole has activity against *Staphylococcus aureus* (MSSA, CA-MRSA and HA-MRSA), *Bordetella pertussis*, *Brucella* spp., *Enterobacter cloacae*, *Enterobacter aerogenes*, *Kingella kingae*, *Haemophilus influenzae*, *Pasteurella multocida*, *Listeria monocytogenes*, *Moraxella catarrhalis*, *Aeromonas hydrophila*, *Burkholderia cepacia*, *Stenotrophomonas maltophilia*, *Staphylococcus lugdunensis*, *Staphylococcus saprophyticus*, *Klebsiella granulomatis*, *Nocardia asteroides*, *Nocardia brasiliensis*, *Yersina enterocolitica*, *Francisella tularensis*, *Serratia marcescens*, *Staphylococcus* coagulase-negative species, *Yersina enterocolitica*, *Yersina pestis* and *Legionella* spp. (Antimicrobial Therapy, Inc., 2016).

Dapsone has activity against *Pneumocystis jiroveci*, *Toxoplasma gondii* and *Mycobacterium leprae* (Antimicrobial Therapy, Inc., 2016).

- **Adverse effects**

Trimethoprim/sulfamethoxazole has a significant drug interaction with warfarin and INR should be monitored when administered together. For IV administration trimethoprim/sulfamethoxazole needs to be diluted with large volumes of dilutant. Careful consideration should take place in patients who are fluid-restricted such as those with heart failure. Cross-reactions to other sulphonamide containing drugs may be experienced in patients allergic to trimethoprim/sulfamethoxazole (Gallagher & MacDougall, 2013:135-136).

Frequent adverse effects caused by trimethoprim/sulfamethoxazole usage include urticaria, anorexia, nausea, vomiting, and rash that generally occur 7 to 14 days after therapy begins. Serious reactions include fever, rash, sore throat, purpura, Stevens-Johnson syndrome, toxic epidermal necrolysis, agranulocytosis, aplastic anaemia, fulminant hepatic necrosis and other blood dyscrasias (adverse haematological effects), myelosuppression, decreased platelet count, thrombotic and idiopathic thrombocytopenic purpura, QT-interval prolongation, ventricular tachycardia and *torsade de pointes* (Mosby's Drug Reference for Health Professions, 2014:377).

Frequently caused effects from dapsone usage include methemoglobinemia, rash and haemolytic anaemia. Serious reactions include drug-induced hepatitis, peripheral neuropathy, Stevens-Johnson syndrome, agranulocytosis, aplastic anaemia and blood dyscrasias (Mosby's Drug Reference for Health Professions, 2014:421).

- **Common indications**

Dosing of trimethoprim/sulfamethoxazole is based on the trimethoprim component. Trimethoprim/sulfamethoxazole has good oral bioavailability (Gallagher & MacDougall, 2013:135). Trimethoprim/sulfamethoxazole is indicated for the treatment of chronic bronchitis, bacterial meningitis, *Pneumocystis* pneumonia, shigellosis, traveller's diarrhoea, and urinary tract infections caused by susceptible micro-organisms (Antimicrobial Therapy, Inc., 2016; Medscape, 2016ja). Other indications include nocardiosis, prostatic infections (Antimicrobial Therapy, Inc., 2016; Rossiter, 2010:297) and skin infections (Impilo Drugs Limited, 2003) caused by susceptible organisms.

Dapsone is indicated for the treatment of dermatitis herpetiformis and leprosy (Mosby's Drug Reference for Health Professions, 2014:420; Medscape, 2016ka; Pharmacare Limited, 2000b). Other off-label indications include severe aphthous ulcers, bullous systemic lupus erythematosus, pemphigus vulgaris, *Pneumocystis* pneumonia (PCP) and *Toxoplasma gondii* encephalitis in HIV-infected patients (UpToDate, 2016za).

2.2.12 Lincosamides

Clindamycin is the only agent of the lincosamide class registered in South Africa.

- **Mechanism of action**

Clindamycin binds to the bacterial ribosomal receptor sites thereby inhibiting protein synthesis of the bacterial cell wall. The agent has a bacteriostatic therapeutic effect in susceptible micro-organisms. Serious reactions include antibiotic-associated colitis, superinfections, blood dyscrasias (leukopenia, thrombocytopenia) and nephrotoxicity (oliguria, proteinuria, azotaemia) (Mosby's Drug Reference for Health Professions, 2014:35).

- **Spectrum of activity**

Clindamycin has activity against *Streptococcus* (Group A, B, C, G), *Streptococcus pneumoniae*, *Staphylococcus aureus* (MSSA and CA-MRSA), *Staphylococcus lugdunensis*, *Staphylococcus saprophyticus*, *Staphylococcus* coagulase-negative species, *Streptococcus anginosus*, *Actinomyces israelii*, *Arcanobacterium haemolyticum*, *Capnocytophaga* sp., *Corynebacterium diphtheriae* and *Prevotella melaninogenica*. Variably susceptibility/resistance exists against *Bacteroides fragilis*, *Fusobacterium necrophorum*, *Peptostreptococci* and *Clostridium perfringens* (Antimicrobial Therapy, Inc., 2016).

- **Adverse effects**

Frequently experienced effects include abdominal pain, diarrhoea, vomiting and nausea (Mosby's Drug Reference for Health Professions, 2014:375).

- **Common indications**

The oral bioavailability of clindamycin is nearly 100%, but the oral dosages are lower than the intravenous doses due to gastro-intestinal intolerance (Gallagher & MacDougall, 2013:139). Clindamycin is indicated for the treatment of bone and joint infections, skin and soft tissue infections, lower respiratory tract infections (Hexal Pharma Limited, 2005; Mosby's Drug Reference for Health Professions, 2014:354; UpToDate, 2016ab), gynaecological infections, intra-abdominal infections, septicaemia (Mosby's Drug Reference for Health Professions, 2014:354; UpToDate, 2016ab), and toxic shock syndrome caused by susceptible micro-organisms (Medscape, 2016a).

2.2.13 Polymyxins

Colistin is an agent of the polymyxin class.

- **Mechanism of action**

Colistin targets the lipopolysaccharide component of the outer membrane. Polymyxins have a high affinity for the lipopolysaccharide due to its strong positive charge and a hydrophobic acyl chain. The drug causes disruption of the membrane by interacting electrostatically with these molecules and competitively displaces divalent cations from them. This causes an increase of permeability of the cell envelope, leakage of cell contents and cell death (Yahav *et al.*, 2012:18).

- **Spectrum of activity**

Colistin has activity against multi-drug resistant gram-negative organisms such as *Escherichia coli* (including ESBL+ and KPC+), *Klebsiella* sp. (including ESBL+ and KPC+), *Enterobacter cloacae*, *Enterobacter aerogenes*, *Acinetobacter baumannii*, *Aeromonas hydrophila*, *Citrobacter koseri*, *Citrobacter freundii*, and *Pseudomonas aeruginosa*. Variably susceptibility/resistance exists against the organism *Stenotrophomonas maltophilia* (Antimicrobial Therapy, Inc., 2016).

- **Adverse effects**

Colistin can cause neurotoxicity, dizziness, peripheral paraesthesia, slurred speech, pruritus, skin rash, urticarial, gastric distress, decreased urinary output, acute renal failure and weakness of the lower extremity, apnoea, and respiratory distress (UpToDate, 2016bb). Renal function should be monitored in patients receiving colistin (Gallagher & MacDougall, 2013:144).

- **Common indications**

Colistin is indicated for the treatment of chronic or acute infections due to sensitive strains of some gram-negative bacilli which are unresponsive to other antimicrobial agents (Medscape, 2016ma; UpToDate, 2016bb) such as lower respiratory tract and urinary tract infections (Tay Pharmaceuticals Limited, 2011). Inhalation treatment with colistin is indicated for *Pseudomonas aeruginosa* lung infections in patients with cystic fibrosis (Tay Pharmaceuticals Limited, 2011).

Colistin is not recommended to be used alone, but rather as part of combination therapy (Antimicrobial Therapy, Inc., 2016; Gallagher & MacDougall, 2013:143). Combination therapy is recommended to achieve a maximum therapeutic effect. Colistin enhances the activity of the companion drug by reducing the membrane permeability of the organism and thereby allows the companion drug to overcome resistance mechanisms (Antimicrobial Therapy, Inc., 2016). Rifampicin (Gallagher & MacDougall, 2013:143) and carbapenems (Antimicrobial Therapy, Inc., 2016) can be used in combination with colistin.

2.3 Antifungal drugs and antimycobacterial drugs

Antifungals and antimycobacterial classes are summarised in Table 2-5 (Gallagher & MacDougall, 2013:170-199) and Table 2-6 respectively (Rossiter, 2010:316).

Table 2-5: Classification of antifungals

Classification of antifungals	Antimicrobial agents
<i>Polyenes</i>	<i>Amphotericin B</i> <i>Amphotericin B (lipid formulations)</i>
<i>Azoles</i>	<i>Ketoconazole</i> <i>Fluconazole</i> <i>Itraconazole</i> <i>Voriconazole</i>
<i>Echinocandins</i>	<i>Caspofungin</i> <i>Micafungin</i> <i>Anidulafungin</i>

Table 2-6: Classification of antimycobacterials

Classification of antimycobacterials	Antimycobacterial agents
First line agents	<i>Rifampicin</i>
	<i>Isoniazid</i>
	<i>Ethambutol</i>
	<i>Pyrazinamide</i>
	<i>Streptomycin</i>

2.3.1 Antifungal drugs

2.3.1.1 Polyenes

Two forms of polyenes are available, namely amphotericin B and lipid formulations of amphotericin B.

- **Mechanism of action**

Polyenes act by binding to the sterols in the membrane of the fungal cell, leading to leakage of cell content and cell death (Gallagher & MacDougall, 2013:171).

- **Spectrum of activity**

Amphotericin B has activity against *Aspergillus* species (except *Aspergillus terreus*), *Candida albicans*, *Candida dubliniensis*, *Candida krusei*, *Candida tropicalis*, *Candida parapsilosis*, *Cryptococcus neoformans*, *Coccidioidomyces immitis/posadasii*, *Histoplasma capsulatum*, and *Blastomyces dermatitidis* (Antimicrobial Therapy, Inc., 2016; Medscape, 2016na). Amphotericin B is also active against mucorales and *Sporothrix schenckii* (Antimicrobial Therapy, Inc., 2016).

- **Adverse effects**

Significant adverse effects include hypotension, chills, headache, hypokalaemia, hypomagnesemia, gastro-intestinal effects, anaemia, renal insufficiency and tachypnea (UpToDate, 2016cb). Fevers, chills and rigours can be infusion-related. Nephrotoxicity is caused by direct effects on distal tubule and indirect effects through vasoconstriction of the afferent arteriole. Magnesium and potassium wasting are results due to the nephrotoxicity. Lipid formulations have less nephrotoxicity (Gallagher & MacDougall, 2013:172). Administration of normal saline before and after infusion of amphotericin can provide protection to the kidneys in order to minimise nephrotoxicity (Gallagher & MacDougall, 2013:174).

- **Common indications**

Amphotericin B is indicated for the treatment of life-threatening fungal infections (Bristol-Myers Squibb Limited, 2005c). Indications include cryptococcal meningitis in HIV-infected patients, empiric fungal therapy in febrile neutropenic patients, visceral leishmaniasis, fungal infections due to *Aspergillus* sp., *Candida* sp. and/or *Cryptococcus* sp. (Rossiter, 2010:306-307; UpToDate, 2016cb; UpToDate, 2016db). Care should be taken when dosing, since the two formulations are not equivalent in potency (Gallagher & MacDougall, 2013:173).

2.3.1.2 Azoles

Ketoconazole, fluconazole, itraconazole and voriconazole are agents of the azole class.

2.3.1.2.1 Ketoconazole

- **Mechanism of action**

Ketoconazole is a fungistatic antifungal agent that inhibits the vital component of fungal cell formation, namely the synthesis of ergosterol. The agent damages the fungal cell membrane (Mosby's Drug Reference for Health Professions, 2014:881).

- **Spectrum of activity**

The antimicrobial spectrum includes dermatophytes, *Candida albicans*, *Candida dubliniensis*, *Candida parapsilosis*, *Candida tropicalis*, *Candida guilliermondii*, *Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces dermatitidis* and *Paracoccidioides brasiliensis* (Antimicrobial Therapy, Inc., 2016).

- **Adverse effects**

Occasionally causes adverse effects due to ketoconazole usage – these include nausea and vomiting. Serious reactions include hematologic toxicity by thrombocytopenia, haemolytic anaemia, adrenal insufficiency, hepatotoxicity, anaphylaxis or angioedema, and QT-interval prolongation (Mosby's Drug Reference for Health Professions, 2014:882). Azoles inhibit cytochrome P450 and drug interactions should be monitored (Gallagher & MacDougall, 2013:179).

- **Common indications**

Ketoconazole is indicated for the treatment of systemic fungal infections caused by susceptible micro-organisms including blastomycosis, histoplasmosis, paracoccidioidomycosis, coccidioidomycosis, and chromomycosis in patients who have failed or are intolerant to other antifungal therapies (Janssen Pharmaceuticals Incorporated, 2013; Medscape, 2016oa;

Mosby's Drug Reference for Health Professions, 2014:881; UpToDate, 2016eb). Other indications include dermatologic conditions such as *tinea corporis*, *tinea capitis*, *tinea manus*, *tinea cruris*, *tinea pedis* and seborrheic dermatitis (Mosby's Drug Reference for Health Professions, 2014:881).

2.3.1.2.2 Fluconazole

- Mechanism of action

Fluconazole is a fungistatic antifungal that interferes with the enzyme necessary for ergosterol formation, namely cytochrome P450. The agent directly damages the fungal membrane and alters its function (Mosby's Drug Reference for Health Professions, 2014:676-677).

- Spectrum of activity

Fluconazole has an antimicrobial spectrum against *Candida albicans*, *Candida dubliniensis*, *Candida parapsilosis*, *Candida tropicalis*, *Candida guilliermondii*, *Cryptococcus neoformans* and *Coccidioides immitis*. *Candida krusei* and *Candida glabrata* are resistant to fluconazole (Antimicrobial Therapy, Inc., 2016).

- Adverse effects

Fluconazole use occasionally causes hypersensitivity reactions, dizziness, dyspepsia, drowsiness, headache, diarrhoea, constipation, nausea and vomiting, abdominal pain and taste perversion. Serious reactions include exfoliative skin disorders, serious hepatic effects, *torsade de pointes*, seizures, QT- interval prolongation, blood dyscrasias, and anaphylaxis (Mosby's Drug Reference for Health Professions, 2014:679). Azoles inhibit cytochrome P450; users should therefore be monitored for drug interactions (Gallagher & MacDougall, 2013:179).

- Common indications

Fluconazole is indicated for the treatment of oropharyngeal candidiasis, oesophageal candidiasis, urinary tract candidiasis, cryptococcal meningitis, and prophylaxis of candidiasis in patients undergoing bone marrow transplants, vaginal candidiasis, and systemic candida infections (Medscape, 2016pa; Mosby's Drug Reference for Health Professions, 2014:677; Pfizer Incorporated, 2011; UpToDate 2016fb). The treatment of onychomycosis is another indication (Mosby's Drug Reference for Health Professions, 2014:677). Fluconazole has a high bioavailability; switching to an oral formulation as soon as an oral preparation can be tolerated by the patient is therefore advisable (Gallagher & MacDougall, 2013:183).

2.3.1.2.3 Itraconazole

- Mechanism of action

Itraconazole is a fungistatic antifungal that inhibits a vital component of fungal cell formation, namely the synthesis of ergosterol. The agent damages the cell membrane causing alteration of its function (Mosby's Drug Reference for Health Professions, 2014:874).

- Spectrum of activity

Itraconazole has activity against *Candida albicans*, *Candida dubliniensis*, *Candida tropicalis*, *Candida parapsilosis*, *Candida guilliermondii*, *Blastomyces dermatitidis* and *Histoplasma capsulatum*. The agent also has *in vitro* activity against *Aspergillus* (Antimicrobial Therapy, Inc., 2016).

- Adverse effects

Frequently and occasionally caused effects due to itraconazole usage include nausea, rash, diarrhoea, vomiting, headache, peripheral oedema, fatigue, fever, and hypertension. Serious reactions include hepatitis and worsening of heart failure (Mosby's Drug Reference for Health Professions, 2014:876). Capsules should always be taken with a full meal. Agents that decrease gastric acidity can lower the absorption of itraconazole. Since azoles inhibit cytochrome P450 liver enzymes patients should be monitored for possible drug-drug interactions (Gallagher & MacDougall, 2013:186-187).

- Common indications

Itraconazole is indicated for the treatment of blastomycosis, aspergillosis, histoplasmosis (Jansen Pharmaceutica Limited, 2004; Medscape, 2016qa; Mosby's Drug Reference for Health Professions, 2014:875; UpToDate, 2016gb) and oropharyngeal/oesophageal candidiasis (Medscape, 2016qa; Mosby's Drug Reference for Health Professions, 2014:875; UpToDate, 2016gb). Itraconazole capsules are used for the treatment of onychomycosis (Gallagher & MacDougall, 2013:186; Jansen Pharmaceutica Limited, 2004; Mosby's Drug Reference for Health Professions, 2014:875). The drug is also indicated for vulvovaginal candidiasis and dermatomycosis which do not respond to conventional therapy (Jansen Pharmaceutica Limited, 2004).

2.3.1.2.4 Voriconazole

- Mechanism of action

Voriconazole is a triazole derivative that damages the fungal cell wall by inhibiting ergosterol synthesis that is a vital component of fungal cell formation (Mosby's Drug Reference for Health Professions, 2014:1719).

- Spectrum of activity

Voriconazole has antimicrobial activity against *Candida albicans*, *Candida dubliniensis*, *Candida tropicalis*, *Candida parapsilosis*, *Candida guilliermondii*, *Cryptococcus neoformans*, *Aspergillus fumigates*, *Aspergillus flavus*, *Aspergillus terreus*, *Scedosporium apiospermum* and *Dematiaceous* moulds (Antimicrobial Therapy, Inc., 2016). Activity also exists against *Candida glabrata* and *Candida krusei* (Antimicrobial Therapy, Inc., 2016; Medscape, 2016ra).

- Adverse effects

Frequently caused effects due to voriconazole use include abnormal vision, nausea, rash, fever and vomiting. Serious reactions include hepatotoxicity, optic neuritis, papilledema, QT-interval prolongation or arrhythmias, anaphylactoid-like reactions during drug infusion, fluorosis and periostitis with long-term therapy, acute renal failure with intravenous therapy and photosensitivity reactions (Mosby's Drug Reference for Health Professions, 2014:1721). Patients should be monitored for drug-drug interactions since voriconazole is an inhibitor and substrate of the cytochrome P450 liver enzyme system. Voriconazole is difficult to dose correctly due to high variable interpatient pharmacokinetics and nonlinear elimination. The intravenous formulation contains a cyclodextrin vehicle which can accumulate in patients with renal insufficiency and may be nephrotoxic (Gallagher & MacDougall, 2013:190-191).

- Common indications

Voriconazole is indicated for the treatment of invasive aspergillosis, oesophageal candidiasis, candidemia in non-neutropenic patients, disseminated or deep tissue *Candida* infections and serious fungal infection caused by *Scedosporium apiospermum* and *Fusarium* spp. (Medscape, 2016ra; Mosby's Drug Reference for Health Professions, 2014:1721 Mosby's Drug Reference for Health Professions, 2014:1719; Pfizer Incorporated, 2015; UpToDate, 2016hb). Oral voriconazole has high bioavailability which allows switching to oral preparations as soon as oral preparations can be tolerated by the patient (Gallagher & MacDougall, 2013:189).

2.3.1.3 Echinocandins

Agents of the echinocandins class include caspofungin, micafungin and anidulafungin. The differences between the echinocandins are minor and mostly pharmacokinetic in nature (Gallagher & MacDougall, 2013:197).

- **Mechanism of action**

Caspofungin, micafungin and anidulafungin inhibits glycan synthesis thereby damaging the membrane of the fungal cell. The therapeutic effect of this class is fungicidal (Mosby's Drug Reference for Health Professions, 2014:107, 265, 1061).

- **Spectrum of activity**

Caspofungin, micafungin and anidulafungin has antimicrobial activity against *Candida albicans*, *Candida dubliniensis*, *Candida glabrata*, *Candida tropicalis*, *Candida krusei* and *Aspergillus* sp. (Antimicrobial Therapy, Inc., 2016).

- **Adverse effects**

Caspofungin can cause abdominal discomfort, mild cramps, faintness, griping and nausea. Serious reactions that caspofungin can cause include chronic constipation and loss of normal bowel function with long-term usage. Chronic use or overdose can lead to electrolyte disturbances such as hypokalaemia, hypocalcaemia, metabolic acidosis or alkalosis, malabsorption, persistent diarrhoea, and weight loss. Vomiting and muscle weakness may result because of electrolyte disturbances (Mosby's Drug Reference for Health Professions, 2014:267).

Frequently caused effects due to micafungin usage include diarrhoea, vomiting, nausea, pyrexia, thrombocytopenia, hypokalaemia, mucosal inflammation, and constipation. Serious reactions include hypersensitivity reactions or anaphylaxis. Isolated cases of acute intravascular haemolysis, hepatic dysfunction and acute renal failure have been reported (Mosby's Drug Reference for Health Professions, 2014:1062).

Occasionally caused effects of anidulafungin use include abnormal liver function and diarrhoea, whereas serious reactions include histamine-mediated symptoms such as flushing, rash, dyspnoea, pruritus, urticaria and hypotension (Mosby's Drug Reference for Health Professions, 2014:108).

- **Common indications**

Caspofungin is indicated for the treatment of invasive candidiasis and aspergillosis, oesophageal candidiasis and empiric fungal therapy in patients with febrile neutropenia (Medscape, 2016sa; Merck & Co Incorporated, 2005; Mosby's Drug Reference for Health Professions, 2014:265; UpToDate, 2016ib).

Micafungin is indicated for treating oesophageal candidiasis and prophylaxis of *Candida* infections (Astellas Pharma Incorporated, 2007; Medscape, 2016ta; Mosby's Drug Reference for Health Professions, 2014:1061; UpToDate, 2016jb). Other indications include the treatment of candidemia, invasive candidiasis, candida peritonitis and abscesses (Medscape, 2016ta; Mosby's Drug Reference for Health Professions, 2014:1061; UpToDate, 2016jb).

Anidulafungin is indicated for the treatment of *Candida* infections and candidemia including those of oesophageal, peritoneal and intra-abdominal locus (Medscape, 2016ua; Pfizer Incorporated, 2012; UpToDate, 2016kb).

2.3.2 Antimycobacterials

Antimycobacterials agents include rifampicin and isoniazid (other includes ethambutol, pyrazinamide and streptomycin).

2.3.2.1 Rifampicin

- **Mechanism of action**

Rifampicin interferes with the synthesis of bacterial RNA by binding to DNA-dependent RNA polymerase, preventing its attachment to DNA and blocking transcription of RNA. The therapeutic effect is bactericidal in susceptible micro-organisms (Mosby's Drug Reference for Health Professions, 2014:1431).

- **Spectrum of activity**

Rifampicin is clinically active against *Staphylococcus aureus* (MSSA, CA-MRSA and HA-MRSA), *Neisseria meningitidis*, *Legionella* spp., *Haemophilus influenzae* and *Mycobacterium* species (Antimicrobial Therapy, Inc., 2016).

- **Adverse effects**

Expected effects caused by rifampicin include red-orange or red-brown discoloration of urine, faeces, saliva, sputum, sweat, skin or tears. Serious reactions that could be caused include hepatotoxicity, hepatitis, Steven-Johnson syndrome, antibiotic-associated colitis and blood dyscrasias. Soft contact lenses may be permanently stained due to rifampicin usage (Mosby's

Drug Reference for Health Professions, 2014:1432-1433). Rifampicin is a strong enzyme-inducer and can enhance metabolism of certain drugs and metabolism of endogenous substrates (Medscape, 2016va).

- **Common indications**

Rifampicin is indicated for the treatment of active tuberculosis in combination with other antimycobacterial agents and the elimination of *Neisseria meningitidis* in asymptomatic carriers (Medscape, 2016va; Sanofi-Aventis, 2013). Other indications include *Staphylococcus aureus* infections (in combination with other antimicrobial agents) and prophylaxis of *Haemophilus influenzae* infection (Antimicrobial Therapy, Inc., 2016; Mosby's Drug Reference for Health Professions, 2014:1432).

2.3.2.2 Isoniazid

- **Mechanism of action**

Isoniazid is an isonicotinic acid derivative that inhibits synthesis of mycolic acid and causes bacterial cell wall disruption and loss of acid-fast properties in susceptible mycobacteria. The drug is only active during bacterial cell division and has a bactericidal therapeutic effect in susceptible mycobacteria (Mosby's Drug Reference for Health Professions, 2014:866).

- **Spectrum of activity**

Isoniazid has activity against *Mycobacterium tuberculosis*, *Mycobacterium bovis* and *Mycobacterium kansasii* (Antimicrobial Therapy, Inc., 2016).

- **Adverse effects**

Frequently and occasionally caused adverse effects from isoniazid usage include nausea, vomiting, diarrhoea, abdominal pain, flushing, rash, elevated blood pressure, palpitations, and sinus tachycardia. Serious reactions include neurotoxicity and optic neuritis (Mosby's Drug Reference for Health Professions, 2014:867). Isoniazid treatment may cause severe and sometimes fatal hepatitis (Medscape, 2016wa).

- **Common indications**

Isoniazid is indicated for the treatment of active and latent tuberculosis infections in combination with one or more antimycobacterial agent (Medscape, 2016wa; Rossiter, 2010:317; UpToDate, 2016mb).

2.4 Pitfalls and considerations in antimicrobial prescribing

According to Burke and Cunha (2011:13-15), there are a few pitfalls in antimicrobial prescribing, namely:

- To treat non-infectious or antibiotic-unresponsive infectious diseases with antimicrobials. This includes medical disorders that mimic infection, fever due to drugs, viral infections and fungal infections.
- The overuse of combination therapy.
- Microbiological factors, such as treating colonisations (not infection).
- Treating persistent fever with antimicrobials. It is important to reassess the antimicrobial regimen rather than adding an additional antimicrobial, for patients with persistent fever on an antimicrobial regimen that appears to be failing.

2.4.1 Contra-indications and drug-interactions

A contra-indication is defined as a factor or a reason that prohibits the administration of a drug (Mosby's Dictionary of Medicine, Nursing & Health Professions, 2006:454). Interactions between drugs (drug-drug interactions) can be defined as pharmacological or clinical responses to the administration of two or more drugs that are different from the response when administered individually (Rodrigues *et al.*, 2015:367). The activity of the one drug is influenced by the other substance and the effects of the drug are increased or decreased or they produce a new effect that neither of the two drugs produces on their own (Bushra *et al.*, 2011:77).

Interactions between antimicrobial drugs can be classified according to their combined effect being equal, greater or less than that expected based on their individual effects. It can also be classified as additive, synergistic or antagonistic. Synergistic drug-drug interactions cause the combined effect to be greater than the expected additive sum. A strong kind of antagonism occurs when the combined inhibitory effect of two drugs is weaker than the expected additive sum and also weaker than the effect of the drugs alone (Bollenbach *et al.*, 2009:707).

Drug-drug interactions can be rated according to the severity of the interaction. The Lexicomp® classification system for drug interactions (Armahizer *et al.*, 2012:2) is displayed in Table 2-7.

Table 2-7: Drug-drug interaction scale rating

Rating	Designation	Explanation	
X	<i>Contra-indicated</i>	<i>Avoid combination</i>	<i>Drugs are contraindicated for simultaneous use</i>
D	<i>Major</i>	<i>Therapy modification to be considered</i>	<i>Interaction may be life threatening. Medical intervention may be required to minimise or prevent serious adverse events</i>
C	<i>Moderate</i>	<i>Monitor therapy</i>	<i>Interaction may influence the patient's condition. Alteration in therapy might be needed</i>
B	<i>Minor</i>	<i>No action needed</i>	<i>Interaction has limited clinical effects. May include an increase in frequency or severity of side effects, but a major alteration in therapy are not required</i>
A	<i>Unknown</i>	<i>No known interaction</i>	<i>Unknown</i>

Interactions may also occur between drugs and food (food-drug interactions), as well as between drugs and herbs (drug-herbal) interactions. Food may increase or reduce the effect of the drug. Food-drug interactions that are clinically relevant are caused by food-induced changes to the bioavailability of the drug which in result are related to the clinical effect of most drugs (Bushra *et al.*, 2011:77). Drug-disease interactions are due to the worsening of pre-existing diseases, conditions or syndromes by medication. These are more common in older adults due to their multiple chronic diseases and the use of multiple medications (Lindblad *et al.*, 2006:1134).

2.4.2 Duration of therapy

Even with the assistance of prescribing guidelines deciding on initiating treatment, choosing the appropriate empiric therapy is not a straightforward decision. Starting empiric treatment does not always mean the patient must complete a fixed treatment course. In practice, empiric therapy is continued too often without review even after diagnostic tests indicate an alternative diagnosis for which no antimicrobial therapy is needed or a sufficient narrower spectrum agent exists (Gilbert, 2015:122).

Duration of therapy needs to be adjusted for each patient specific according to their needs. Extended therapy may be required in patients with immune impairment, chronic bacterial infections, fungal infections or when treating certain bacterial intracellular pathogens. No benefits are provided by prolonged therapy; prolonged therapy increases the risk of adverse effects, drug interactions and superinfections (Burke & Cunha, 2011:13, 11).

A common misconception about antimicrobial therapy is that resistance will emerge if an antimicrobial course is not completed (Gilbert, 2015:122). The longer opportunistic bacteria are subjected to the exposure of antimicrobials, the greater the risk of selecting antibiotic resistance. In the hospital setting biomarkers can guide the prescriber when to stop antimicrobial treatment (Llewelyn *et al.*, 2017:2). The recommended duration of therapy for most infections is five to fourteen days depending on the clinical syndrome, the causative organism, whether source control is possible and patient's response to therapy (Gilbert, 2015:122). The current Infectious Diseases Society of America (IDSA) guidelines' recommendations for duration of treatment based on expert opinion and retrospective case studies recommend five to seven days for infections caused by coagulase-negative staphylococci. For gram-negative organisms and enterococci seven to fourteen days are recommended and two to six weeks for *Staphylococcus aureus* (Mermel *et al.*, 2009:24-30).

For many syndromes associated with bacteraemia there is no difference in outcomes when shorter courses of therapy are used. Longer courses of antimicrobial therapy are indicated when the site of infection is relatively inaccessible and often these infections need surgical removal of the source or drainage of puss to be cured (Gilbert, 2015:122).

Inappropriate treatment can be described as excessive treatment (duration of therapy) in addition to inadequate treatment (insufficient dosage or drugs that do not match the pathogen) (Davey & Marwick, 2008:S15; Mettler *et al.*, 2007). Inappropriate empiric therapy for infections in critically ill hospitalised patients are associated with poor outcomes, including increased morbidity and mortality as well as increased length of stay (Leekha *et al.*, 2011:157; Marquet *et al.*, 2015:1). Antimicrobial treatment failure is often associated with empiric therapy, although it may develop with definitive therapy (García, 2009:S14). Insufficient antimicrobial coverage is usually the reason for empirical antimicrobial treatment failure (Currie *et al.*, 2014; García, 2009:S14). Treatment decisions are often based on achieving a balance between the risk of a narrow-spectrum agent and unwanted effects of broad-spectrum agents (i.e. adverse effects, development of resistance and cost). Antimicrobial treatment failure can occur due to non-infectious and predisposing factors even if the appropriate antimicrobial is used (García, 2009:S14).

2.5 Resistance

Over the recent years the effectiveness of antimicrobials in treating common infections has decreased due to the arrival of untreatable strains (Laxminarayan *et al.*, 2013:1057). Resistance against antimicrobials can be defined as resistance of micro-organisms to antimicrobials to which they were originally sensitive (Jindal *et al.*, 2015:178). Continued high rates of

hospitalisation, high rates of antimicrobial use in hospitals, community and agriculture contributed to the growing resistance and forcing the use of more expensive and broad spectrum antimicrobials (Laxminarayan *et al.*, 2013:1057). Increased mobility of patients or carriers of the resistant organisms are contributing to the global spread of antimicrobial resistance (Jindal *et al.*, 2015:178; Tenover, 2006:S4). Even the most resistant bacteria can be inhibited or destroyed by a high enough concentration of an antimicrobial, but not all patients can tolerate very high bacteriostatic concentrations with a bactericidal effect, which would be required in such cases (Coculescu, 2009:114).

Resistant strains of bacteria had been detected even before penicillin was discovered (Laxminarayan *et al.*, 2013:1057). As soon as antibacterial drugs were used, bacteria responded by producing various forms of resistance (Tenover, 2006:S3). One of the great advantages of antimicrobial development was the reduced mortality and morbidity when used against infectious diseases. Unfortunately the emergence of resistance to antimicrobials threatens to undermine these benefits (Song, 2003:S1). The level and complexity of resistance mechanisms produced by bacterial pathogens enlarge with the increase of antimicrobial use (Tenover, 2006:S3). Antimicrobial resistance leads to treatment failure, prolonged duration of hospitalisation, increased cost and mortality (Gyssens, 2011:11).

Resistance develops as a result of the formations of mutations in microbes (Laxminarayan *et al.*, 2013:1057). Some strains of organisms have become resistant to all commonly available antimicrobials (Ventola, 2015:277).

Resistance of bacteria to antimicrobials can be natural (intrinsic, innate) or acquired by mutating the endogenous genes or by the incorporation of exogenous genes of resistance (Bakry *et al.*, 2014:154; Coculescu, 2009:115).

Intrinsic resistance develops when bacterial strains are inherently resistant to certain compounds and resistance cannot be transferred horizontally (Bakry *et al.*, 2014:154). Some species of bacteria are naturally resistant to certain classes of antimicrobials. All strains of these bacteria are equally resistant to the specific antibacterial class (Tenover, 2006:S4).

Acquired resistance is of great concern due to the fact that it occurs when bacteria that had initially been susceptible to an antibacterial agent become resistant to it either by incorporating new genetic material or as a result of mutations (Fernández & Hancock, 2012:661; Tenover, 2006:S4). Table 2-8 (adapted from Tenover, 2006:S3-S4) describes the mechanisms by which bacteria may become resistant.

Table 2-8: Mechanisms of bacterial resistance

Mechanism of antimicrobial resistance of bacteria	Examples
<i>Acquire genes encoding enzymes, such as beta-lactamases that destroy the antimicrobial before it might have an effect</i>	<i>Erythromycin ribosomal methylase in staphylococci</i>
<i>Acquire efflux pumps that force out the antimicrobial from the cell before it can reach its target site and have an effect</i>	<i>Efflux of fluoroquinolones in Staphylococcus aureus</i>
<i>Acquire several genes for a metabolic pathway which eventually produces altered bacterial cell walls that do not contain the binding site of the antimicrobial agent</i>	<i>The change in penicillin-binding protein 2b in pneumococci, which results in resistance</i>
<i>Acquire mutations that limit the access of antimicrobial agents to intracellular target sites through down-regulation of porin genes</i>	<i>Outer membrane protein F (OmpF porin) in Escherichia coli</i>

Acquired resistance develops through mutation and/or horizontal gene events (Bakry *et al.*, 2014:154). The term ‘horizontal gene transfer’ refers to resistance of bacteria that develops through the acquisition of new genetic material from other resistant organisms (Ternent *et al.*, 2015:2).

Horizontal evolution may occur between strains of the same species or between different bacterial species or genera. Genetic exchange mechanisms include conjugation, transduction and transformation (Alanis, 2005:700). During conjugation mobile genetic elements are being transferred from a donor to a recipient cell. Transduction is when the resistant genes are transferred from one bacterium to another via bacteriophage (Bakry *et al.*, 2014:154-155). Transformation is the process where bacteria acquire and incorporate DNA segments from other bacteria that have released their DNA complement into the environment after cell lysis. Resistance genes can be moved into previously susceptible strains. The genes are then incorporated into the chromosome of the recipient by recombination or transposition and may cause changes in the gene sequence (Aleksun & Levy, 2007:1038; Bakry *et al.*, 2014:154-156). Thus transformation can move resistance genes into previously susceptible strains (Tenover, 2006:S5).

Many bacteria have become resistant to multiple classes of antimicrobials through genetic exchange mechanisms. What is concerning is that these multi-drug resistant bacteria tend to occur most often in healthcare institutions. Antimicrobial use selects strains of bacteria carrying resistance-conferring mutations which destroy the susceptible strains but allow the newly-resistant strains to grow and survive (Tenover, 2006:S5). Vertical evolution is the term used for acquired resistance that develops due to chromosomal mutation and selection (Ternent *et al.*, 2015:2).

A gram-negative bacterium transfers plasmid-containing resistance genes to an adjacent bacterium during conjugation which joins the two organisms (Grohmann *et al.*, 2003:278; Tenover, 2006:S5). Gram-positive bacteria normally initiate conjugation by production of sex pheromones by the mating pair, which allows the exchange of DNA (Grohmann *et al.*, 2003:278; Tenover, 2006:S5).

Several pathways of genetic exchange among gram-positive and gram-negative organisms exist (Džidić *et al.*, 2008:17; Tenover, 2001:S110). Genetic exchange pathways among bacterial genera are illustrated in Figure 2-7 (adapted from Tenover, 2001:S110). Gram-negative organisms are on the left side of the dotted line and gram-positive on the right side. The black arrows indicate genetic exchanges that cross from gram-positive to gram-negative organisms (Tenover, 2001:S109).

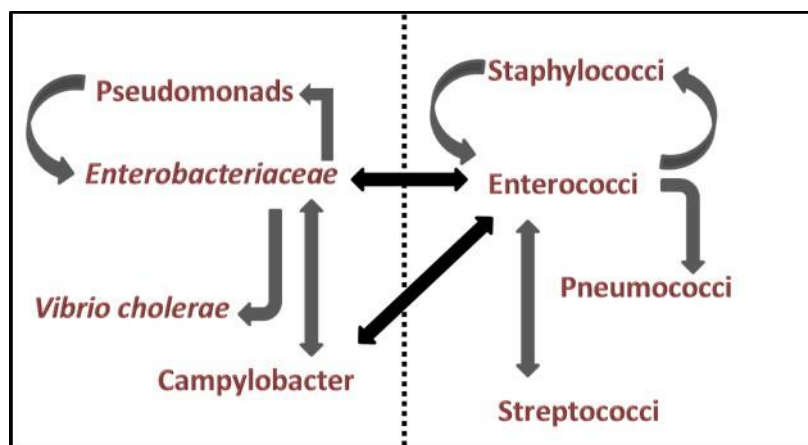


Figure 2-7: Genetic exchange of antimicrobial agent resistance among organisms

Concerned pathogens among gram-positive organisms include resistant *Staphylococcus aureus* and *Enterococcus* species (Ventola, 2015:280). Staphylococcal resistance is a serious concern due to the fact that *Staphylococcus aureus* is a leading cause of hospital- and community acquired infections (Llarrull *et al.*, 2009:4051). Methicillin-resistant *Staphylococcus aureus* is not only resistant to methicillin (which was developed against penicillinase-producing *Staphylococcus aureus*), but to other antimicrobials such as aminoglycosides, macrolides, tetracycline, trimethoprim/sulfamethoxazole, cephalosporins, carbapenems, beta-lactam/beta-lactamase combinations, and lincosamides (Lim & Webb, 2005:890). These MRSA strains are resistant to disinfectants as well. In 2002 MRSA resistant strains were detected against vancomycin, which was developed for the treatment of MRSA infections specifically (Nikaido, 2009:119-120).

Gram-negative resistant pathogens of concern among nosocomial infections are ESBLs. The most common ESBL producing strains are found in *Klebsiella pneumoniae*, *Klebsiella oxytoca* and *Escherichia coli*. Other pathogens which produce ESBL strains includes *Pseudomonas aeruginosa*, *Enterobacter*, *Citrobacter*, *Proteus mirabilis*, *Morganella morganii*, *Serratia marsescens*, *Burkholderia cepacia* and *Capnocytophaga ochracea* (Tsering *et al.*, 2009). These strains contain a membrane barrier that has low permeability and a collection of efficient multi-drug efflux pumps which make them resistant to almost all antimicrobial agents (Nikaido, 2009:119-120).

The emergence of multi-drug resistant (MDR) and pan-drug resistant gram-negative pathogens that are of concern include Enterobacteriaceae (mostly *Klebsiella pneumoniae*), *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. These organisms are mostly responsible for causing the most serious gram-negative infections in healthcare settings (Ventola, 2015:281). Resistant bacteria are becoming not only a problem within healthcare institutions, but in communities as well (Laupland & Church, 2014:650). In the community clinically important bacteria such MRSA and ESBL-producing *Escherichia coli* are more frequently observed (Laupland & Church, 2014:650; Ventola, 2015:281). Community associated MRSA strains are less resistant to antimicrobials, but are more likely to produce toxins, such as Panton Valentine leukocidin (Otto, 2013:327; Tenover, 2006:S4). Panton Valentine leukocidin is a porin-like toxin and associated with dermonecrosis and necrotising pneumonia (Watkins *et al.*, 2012:1179-1182). Organisms associated with increased resistance and mortality in healthcare institutions includes staphylococci, enterococci, *Klebsiella pneumoniae*, *Pseudomonas* spp., *Escherichia coli*, *Enterobacter* spp. and coagulase-negative staphylococci (Lode, 2005:781; Tenover, 2006:S3).

Antimicrobial therapy is indispensable when procedures are performed such as heart surgery, diabetes-related chronic infections, post-organ transplantation and for aggressive immune-modulating therapy for auto-immune diseases such as rheumatoid arthritis and other malignancies (Jindal *et al.*, 2015:179). Antimicrobial resistance might force the return to the pre-antimicrobial era of the 1930s and 1940s (Carlet *et al.*, 2012:1). Two challenges are faced, the first being micro-organisms are becoming extremely resistant to existing antimicrobials and secondly the antimicrobial pipeline has become very dry, in particular for gram-negative bacteria (Jindal *et al.*, 2015:179).

2.6 Special patient groups

Patient characteristics that influence antimicrobial therapy consist of severity of illness, patient age, comorbid conditions, status of immune system, site of infection, history of drug allergy or intolerance, mental status or vital sign abnormalities and laboratory abnormalities (Cassiere, 1998; Ezeanolue *et al.*, 2006:68).

Thorough consideration of an elderly adult's need for antimicrobial therapy should be made due to the increased risk of an adverse drug event, a harmful drug interaction, risk of polypharmacy, and due to the role of older adults acting as a reservoir for resistant pathogens. Antimicrobial therapy in older patients is influenced by more than just physiological changes. Elderly adults are predisposed to suboptimal therapeutic efficacy due to comorbidities and immuno-senescence, the dysregulated immune function associated with aging (Faulkner *et al.*, 2005:997). Pharmacokinetic parameters of antimicrobials are affected by physiological changes that occur with aging (Müller, 2010:206).

When treating critically ill patients in the ICU the choice of antimicrobial for empirical treatment of bacterial infections is based predominantly on the identity and susceptibility pattern of bacteria isolated commonly in that unit. The timing of the first dose in the critically ill septic patient is essential (McKenzie, 2011:ii25). Intravenous antimicrobials should be administered within the first hour after recognition of severe sepsis and septic shock according to the Surviving Sepsis Campaign as stated in the 2008 International guidelines for Management of Severe Sepsis and Septic Shock (Dellinger *et al.*, 2008:22).

In support of the Surviving Sepsis Campaign, Kumar *et al.* (2006:1594-1595) demonstrated that delayed effective antimicrobial therapy by even one hour following onset of septic shock-related hypotension can increase the mortality rate significantly. The study further demonstrated that the most important factor affecting the outcome after the onset of hypotension is the timing of the initial dose of the antimicrobial agent. Altered PK parameters among ICU patients include decreased renal function; hyperdynamic state and the use of vaso-active drugs have direct implications for the antimicrobial serum concentrations (Macedo *et al.*, 2013:24). Other physiologically mediated changes to PK include hypoproteinaemia and organ failure (i.e. gastrointestinal, renal, hepatic and cardiovascular) (Roberts *et al.*, 2012:187).

2.7 Antimicrobial combinations

Combination antimicrobial therapy is widely recognised as a useful strategy for increasing the chances to effectively cover the offending organism(s) upon initiation of empiric therapy and to decrease the selection of resistance (Buyck *et al.*, 2014:258). Synergistic antimicrobial activity is another potential benefit of combination antimicrobial therapy (Belley *et al.*, 2008:3820).

Concepts for combination therapy that are important include that the mechanisms of action of the two drugs must not interfere with each other and result in an antagonistic interaction and that the target cells be assumed to be in a phenotypically susceptible state. Three important categories of combination therapy are those that inhibit targets in different pathways; those that inhibit distinct nodes in the same pathway; and those that inhibit the very same target in different ways (Fischbach, 2011:519). The synergistic effect of the combination determines the potential benefit of adding a second antimicrobial agent (Tamma *et al.*, 2012:452).

Effective *in vitro* antimicrobial combinations are usually evaluated by using the checkerboard method or by time-kill experiments using static antimicrobial concentrations (Hickman *et al.*, 2014:O268). Synergy represents an enhanced antibacterial effect after 24 hours compared with the effects of the individual antimicrobials. Mechanisms of synergy are not often completely understood, but possible explanations do exist for some antimicrobials (Tängdén, 2014:151).

2.8 Antibigrams

A cumulative antibiogram is the result of antimicrobial susceptibility testing of specific micro-organisms to a spectrum of antimicrobial drugs of a micro-organism obtained from results of clinical isolates which are tested against a panel of antimicrobial agents (Horvat, 2010:S6; Joshi, 2010:277). The selection of appropriate empiric therapy is the primary use of a cumulative antibiogram (Hindler & Stelling, 2007:868; Horvat, 2010:S6). Compiling an antibiogram is a complex process that requires laboratory and information (IT) resources, and is work intensive (Hill *et al.*, 2015:1264).

2.8.1 Use and necessity of antibigrams

Primary goals of compiling an antibiogram are to guide therapy, to be an educational tool for prescribers and to monitor resistant trends (Hindler & Stelling, 2007:867; Lautenbach & Nachamkin, 2006:409). Antimicrobial resistance is a progressive process associated with antimicrobial use (Critchley & Karlowsky, 2004:502). According to the IDSA (2011:S400) resistance enables microbes to escape from being destroyed by antimicrobial drugs. Resistance

against antimicrobials arises and increases in incremental steps making infectious diseases more difficult to treat (Critchley & Karlowsky, 2004:502; IDSA, 2011:S400).

The development and usage of surveillance systems resulted from the desire to monitor and predict antimicrobial resistance (Critchley & Karlowsky, 2004:502). Goals identified for surveillance systems include:

- Identifying, understanding and predicting or monitoring resistance trends (Critchley & Karlowsky, 2004:503; Masterton, 2008:S22).
- Detecting appearance of new resistant mechanisms (Critchley & Karlowsky, 2004:503).
- Developing, implementing and monitoring of the impact of new empirical antimicrobial prescribing, infection control, and public health guidelines trends (Critchley & Karlowsky, 2004:503; Joshi, 2010:277).
- Identification of outbreaks of resistant organisms (Critchley & Karlowsky, 2004:503; Tseng, *et al.*, 2012).
- Assisting in the finding of a bioterrorist event (Critchley & Karlowsky, 2004:503; Das & Kataria, 2010:255).
- Identifying potential cellular targets for new antimicrobial agents (Critchley & Karlowsky, 2004:503; Rossolini & Thaller, 2010:1,3).
- Identifying the need for new diagnostic tests (Critchley & Karlowsky, 2004:503; Peeling *et al.*, 2010:S2-S4).
- Educating healthcare providers, patients and the general public (Critchley & Karlowsky, 2004:503).
- Providing data for new drug applications (Critchley & Karlowsky, 2004:502-503).

Antibiograms are needed to assess local susceptibility rates and to guide in selecting empiric antimicrobial therapy. It is indispensable for the monitoring of resistance trends over time within an institution and to compare susceptibility rates across institutions (Joshi, 2010:277).

2.8.2 Guidelines and decoding of antibiograms

The CLSI has published the first guidelines (M39-A) for the preparation of cumulative antibiograms in 2002 (NCCLS, 2002:1) and revised them in 2009 and 2014 (Moehring *et al.*, 2015:2977). The M39-A document provides recommendations for the collection, analysis and presentation of cumulative antimicrobial susceptibility test data with the goal of guiding clinicians in the selection of antimicrobials for empiric treatment and to promote the reporting of reliable and consistent antibiogram data (Joshi, 2010:278; NCCLS, 2002:1; Zapantis *et al.*, 2005:2629). The CLSI recommends the following for susceptibility data presentation (NCCLS, 2002:5-8):

- Final verified susceptibility results should be reported on an antibiogram.
- The percentage susceptibility should be calculated and the isolates with intermediate susceptibility should not be included.
- For *Streptococcus pneumoniae*, the percentage susceptibility and the percentage of isolates with intermediate susceptibility for penicillin should be calculated and listed as well as the percentage susceptibility for cefotaxime or ceftriaxone using both the meningitis and non-meningitis breakpoints.
- For *Viridians streptococci*, calculate and list both the percentage susceptibility and percentage of isolates with intermediate susceptibility for penicillin.
- For *Staphylococcus aureus*, the percentage susceptibility for all isolates should be calculated and listed, as well as for the subset of MRSA.
- Quantitative test measurements (inhibition zone diameters for the disk diffusion and MIC values for dilution testing) and qualitative test interpretations (whether an isolate is classified as susceptible, resistant or intermediate) should be recorded in separate fields. Test measurements are important in evaluating the quality of susceptibility test results and in understanding the epidemiology of antimicrobial-resistant bacteria subpopulations.

The CLSI recommends the following for antibiogram methodology (NCCLS, 2002:6-9):

- “Per cent susceptibility” should be used for each organism-antimicrobial agent combination.
- Isolates from the same patient should be excluded from antibiograms for a one-year time period.
- Antibiograms should be compiled annually, and if there are a large number of isolates, it may be done six monthly or more frequently.
- Results for antimicrobial agents that are tested routinely should be included.
- Each antimicrobial reported must be appropriate for the organism isolated. Reporting of susceptibilities for an organism with intrinsic resistance to the antimicrobial should be avoided.
- Only the first isolate from a patient should be included irrespective of the specimen.
- Diagnostic isolates should be included, not colonisations.
- Isolates for surveillance cultures should not be included (e.g. nasal surveillance for MRSA).

The CLSI recommends the following for morphologic grouping and number of isolates (NCCLS, 2002:10-12):

- Recommends that organisms should be separated by morphology.
- The inclusion of the total number of isolates collected for each organism is recommended, along with the inclusion of data only for those with 30 or more isolates. If less than 30 isolates of a species are encountered during one-year period, it is acceptable to include the isolates, but to state the number in a footnote.

- Interpretation of organisms with less than 30 isolates should be interpreted with caution.
- If fewer than 30 isolates species can be combined (e.g. *Citrobacter* spp.) or multiple years of data can be combined.
- Small numbers of isolates (<10) should not be included in the report.

The CLSI recommends the following for antimicrobial description (NCCLS, 2002:11):

- The use of complete antimicrobial names is vaguely recommended by the M39-A document.

The CLSI recommends the following for data (NCCLS, 2002:11):

- A dash is recommended to be used in each antibiogram data box when a drug is either not tested at the institution or when it is known to be clinically ineffective.

For the final antibiogram at least five most frequently isolated organisms for gram-positive and gram-negative organisms should be used. The percentage susceptibility to antimicrobials for gram-positive and gram-negative isolates should be illustrated separately. The antibiogram should be presented in a tabular form (Joshi, 2010:279). See Table 2-9 for the layout and presentation of an antibiogram (adapted from Boehme *et al.*, 2010:65).

Table 2-9: Example of the presentation of an antibiogram

<i>All bacterial isolates in Hospital A from 01 January to 31 December 2015</i>	<i>Number of isolates</i>	<i>Ampicillin</i>	<i>Cefazolin</i>	<i>Ceftazidime</i>	<i>Ceftriaxone</i>	<i>Ciprofloxacin</i>	<i>Erythromycin</i>	<i>Gentamycin</i>	<i>Imipenem</i>	<i>Levofloxacin</i>	<i>Piperacillin/tazobactam</i>	<i>Trimethoprim/sulfamethoxazole</i>	<i>Vancomycin</i>
Gram-negative													
<i>Escherichia coli</i>	80	70	70	90	73	70	-	74	90	-	75	74	-
<i>Enterobacter cloacae</i>	45	-	-	88	80	63	-	86	93	-	81	81	-
<i>Klebsiella pneumoniae</i>	50	-	66	83	84	58	-	83	80	-	77	73	-
<i>Proteus mirabilis</i>	65	80	73	91	81	63	-	74	79	-	87	65	-
<i>Pseudomonas aeruginosa</i>	70	-	-	95	79	77	-	73	83	-	74	-	-
Gram-positive													
<i>Staphylococcus aureus</i>	100	-	-	-	-		55	89	-	63	-	69	0
Methicillin/oxacillin-resistant <i>Staphylococcus aureus</i>	50	-	-	-	-		3	77	-	-	-	71	88
<i>Enterococcus faecalis</i>	55	75	-	-	-		57	-	-	-	-	-	96
<i>Enterococcus faecium</i>	40	-	-	-	-		56	-	-	-	-	-	83
<i>Streptococcus pneumoniae</i>	80	-	-	-	8		60	-	-	41	-	-	77

2.8.3 Hospital cumulative antibiograms

In healthcare facilities the monitoring of antimicrobial resistance trends is commonly performed using an annual summary of susceptibility rates, known as a cumulative antibiogram report (Hindler & Stelling, 2007:867). Institution-specific cumulative antibiogram reports guide the choice of empirical antibacterial therapy in hospitalised patients for the management of infections in patients for whom microbiological test data to target treatment are not available yet (Hindler & Stelling, 2007:868). These hospital cumulative antibiograms report the mean susceptibility rates of bacterial isolates collected from other patients previously hospitalised at the same institution. Guidelines for the preparation of a cumulative antibiogram recommends to only include the first isolate per episode of a patient's infection in order to reduce the overestimation of antimicrobial resistance (Kuster *et al.*, 2008:1452).

Important factors according to Hindler and Stelling (2007:873) to remember when using cumulative antibiogram data are:

- Cumulative antibiograms compiled according to the CLSI are to be used as a guide to empiric therapy of initial infections.
- Culturing practices, patient population, specimen collection practices and laboratory antimicrobial susceptibility testing policies can influence the percentage susceptibility for a specific drug-pathogen combination.
- Data will be skewed if some drugs included in the cumulative antibiogram are only tested on selected isolates.
- If repeated isolates are not eliminated from the analysis the percentage susceptibility will in most cases be lower than analysis from which repeated isolates are eliminated.
- The percentage susceptibility may vary depending on the method used to eliminate repeated isolates.
- A practical guideline is the first isolate per patient algorithm which has immediate relevance to guiding empirical therapy decisions.
- Small samples are vulnerable to increases or decreases in the percentage susceptibility.

2.8.4 Limitations of antibiograms

Antibiograms should not be relied upon as the only tool for guiding therapy. Limitations according to Boehme *et al.* (2010:71) and Pakyz (2007:1309-1310) include:

- Usually the MIC values are not included. Trends below the resistance threshold (known as the "MIC creep") are not reflected.

- Patient factors are not taken into account. These factors include history of infections or past antimicrobial use. Age could influence resistance patterns for certain drugs and a patient's underlying medical condition may affect how well an antimicrobial works.
- Normal antibiogram data are the result from single organism-antimicrobial combinations and do not show trends in cross-resistance of an organism to other drugs, nor do they reveal synergistic properties of antimicrobial combinations.
- Antibiograms do not reveal additional information, such as timing of the isolate in relation to the admission of the patient to the hospital (to determine whether it was community or healthcare acquired).
- Combining susceptibility data across the entire hospital can be misleading since hospital-wide susceptibility data may hide trends in specific hospital units. Resistance to antimicrobials is normally more prevalent in ICUs than in other units of the hospital
- *Pseudomonas aeruginosa* isolates from patients with cystic fibrosis are commonly combined with other isolates of *pseudomonas* on the antibiogram
- The susceptibility data of antibiograms represents isolates from various body sites.

2.9 Antimicrobial stewardship

Antimicrobial stewardship can be described as a programme and interventions designed to improve antimicrobial prescribing that supports selection of the dosing, route of administration and duration of antimicrobial therapy to optimise clinical outcomes while minimising unintended consequences of antimicrobial use such as toxicity, selection of pathogenic organisms, and emergence of resistance (Ashley *et al.*, 2014:S112; Griffith *et al.*, 2012:63). The ultimate goals of antimicrobial stewardship programs are to improve patient care and healthcare outcomes. Measurements for antimicrobial stewardship programmes can be divided into four main categories: patient outcomes, unintended consequences, process measures, antimicrobial utilisation and costs (Ashley *et al.*, 2014:S112).

Antimicrobial stewardship programmes are among the best methods to prolong the shelf-life of existing and future antimicrobial agents. Hospital-based programmes dedicated to improve antimicrobial use are helpful in improving the quality of patient care and safety through increased infection cure rates, reducing treatment failures and the improvement of correct prescribing for therapy and prophylaxis (Walia *et al.*, 2015:130). The need for stewardship is created through the rapid decline in new antimicrobials and drug discovery, in addition to the escalating rates of multi-drug resistant organisms (Goff & Rybak, 2012:663).

Antimicrobial stewardship programmes should focus on quality-of-care improvements and disease-based management rather than only on antimicrobial utilisation and cost-savings. Efforts of antimicrobial stewardship should be directed at timely use of the right drug, de-escalation and reduction in treatment duration in facilities (Ashley *et al.*, 2014:S116).

Cumulative susceptibility data are useful to track antimicrobial resistance over time and can be a source of information for hospital infection prevention and antimicrobial stewardship programmes (Moehring *et al.*, 2015:2977).

2.10 Empiric regimens for multi-drug resistant (MDR) organisms

The majority of nosocomial infections are due to MDR organisms. These MDR organisms include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci and gram-negative bacilli such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and Enterobacteriaceae. These organisms are referred to as the “ESKAPE”-organisms (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* species) (Izadpanah & Khalili, 2015:105).

Nosocomial infection sites are classified for surveillance by the National Healthcare Safety Network (NHSN) together with CDCP into 14 major types, with some further categorised into specific infection types, which are specific on the basis of biological and clinical criteria (CDCP, 2017a). The most common types of infections are pneumonia and surgical-site infections followed by gastro-intestinal infections, urinary tract infections and primary bloodstream infections (Magill *et al.*, 2014:1201, 1206).

There are several antimicrobial regimens for treating infections caused by MDR organisms. The majority of the regimens are for empiric treatment and some of them are based on susceptibility patterns (Izadpanah & Khalili, 2015:111).

2.10.1 Multi-drug resistant gram-positive bacteria

2.10.1.1 *Enterococcus* sp.

Normally enterococci are sensitive to beta-lactam antimicrobials and vancomycin. Aminoglycosides are added to the regimen since the combination has a synergistic bactericidal activity against enterococci (Arias *et al.*, 2010:556). Ampicillin resistance among *Enterococcus faecalis* is rare, but the resistance against aminoglycosides is increasing. High levels of resistance to ampicillin and vancomycin are found among *Enterococcus faecium* (Kristich *et al.*, 2014:124). A number of newer agents such as linezolid, daptomycin and tigecycline have been developed by the pharmaceutical industry that have activity against vancomycin-resistant enterococci (VRE), but none of these has been entirely free of resistance (Arias *et al.*, 2010:555; Kristich *et al.*, 2014:124).

The recommended cornerstone therapy for susceptible enterococcal infections remains ampicillin (Hollenbeck & Rice, 2012:428). Vancomycin can be used for patients with penicillin allergy. For *Enterococcus faecalis* native valve endocarditis combination therapy for at least four weeks is recommended, which should consist of a cell wall-active agent (e.g. ampicillin, vancomycin) and an aminoglycoside (e.g. gentamycin) (Fraser, 2016; Nigo *et al.*, 2014:3).

For enterococcal endocarditis infections resistant to vancomycin, ampicillin, penicillin and gentamycin, first line treatment recommendations for *Enterococcus faecium* are to treat with linezolid (600 mg intravenous (IV) or per os (PO) 12 hourly) for a minimum of eight weeks. Alternative treatment options for resistant *Enterococcus faecalis* are to treat with imipenem/cilastatin (500 mg IV every six hours) together with ampicillin (2 gram IV every four hours) for a minimum of eight weeks; or ceftriaxone (2 gram IV every 12 hours) together with ampicillin (2 gram IV every 4 hours) for a minimum of eight weeks (Gilbert *et al.*, 2014:78).

The combination of beta-lactam antimicrobials and daptomycin result in a synergistic activity against vancomycin-resistant *Enterococcus faecium* and *Enterococcus faecalis* (Fraser, 2016; Nigo *et al.*, 2014:10).

2.10.1.2 *Staphylococcus aureus*

Staphylococcal infections (MSSA) can be treated with penicillinase-resistant penicillin such as cloxacillin, flucloxacillin, a cephalosporin or clindamycin (Baorto, 2016; Rayner & Munckhof, 2005:S4-S6). Vancomycin is recommended for staphylococcal strains resistant to penicillinase-resistant penicillins and clindamycin (Baorto, 2016; Rayner & Munckhof, 2005:S7).

Other suggestions include the use of trimethoprim/sulfamethoxazole, rifampicin, doxycycline, linezolid or daptomycin (Liu *et al.*, 2011:e8-e10). Rifampicin is recommended to be used in combination rather than as monotherapy (Baorto, 2016). For empirical therapy against MSSA bacteraemia vancomycin or a beta-lactam agent remains the appropriate choice of therapy (McDanel *et al.*, 2015:361-362; Wong *et al.*, 2016:225,231).

For MRSA bacteraemia, recommendations include vancomycin (15 to 20 mg/kg IV every eight to twelve hours; adjusted to target trough levels of 15 to 20 µg/mL) or daptomycin (6 mg/kg IV 24 hourly) or ceftaroline (600 mg IV eight-hourly) or linezolid (600 mg IV/PO twelve-hourly) (Antimicrobial Therapy, Inc., 2016). Daptomycin in combination with ceftaroline (600 mg IV eight-hourly) are recommended for treatment failures accompanied by severe sepsis (Sakoulas *et al.*, 2014:1331).

For MRSA pneumonia primary regimens include vancomycin (15 to 20 mg/kg IV every eight to twelve hours; adjusted to target trough levels of 15 to 20 µg/mL) or linezolid (600 mg PO/IV 12 hourly). Ceftaroline (600 mg IV eight-hourly) can be used as an alternative (Antimicrobial Therapy, Inc., 2016).

For MRSA native valve endocarditis vancomycin (15 to 20 mg/kg IV every eight to twelve hours; adjusted to target trough levels of 15-20 µg/mL) for 6 weeks is recommended or alternative daptomycin (eight to 12 mg/kg IV 24 hourly) (Antimicrobial Therapy, Inc., 2016).

2.10.1.3 *Streptococcus pneumoniae*

For community-acquired infections in previously healthy adults with no specific risk factors for resistant infections, a macrolide as initial therapy is recommended. The recommended initial therapy for hospitalised patients admitted to a general ward is either a fluoroquinolone such as moxifloxacin or levofloxacin; or a combination of a beta-lactam antimicrobial agent plus a macrolide (File, 2016; Prado, 2016).

For *Streptococcus pneumoniae* resistant to penicillin G ($MIC \geq 8 \mu\text{g/mL}$), first line treatment recommendations (if no meningitis is suspected) include one of the following: ceftriaxone (2 gram IV 24 hourly) or moxifloxacin (400 mg IV every 24 hours) or levofloxacin (750 mg IV every 24 hours) or ceftaroline (600 mg IV every 12 hours) or linezolid (600 mg IV every 12 hours) (Antimicrobial Therapy, Inc., 2016).

For *Streptococcus pneumoniae* resistant to penicillin ($MIC > 2 \mu\text{g/mL}$) recommendations (if meningitis is suspected) include vancomycin (15 to 20 mg/kg IV every 8 to 12 hours; adjusted to target trough levels of 15 to 20 µg/mL) together with ceftriaxone (2 gram IV every 12 hours); or moxifloxacin (400 mg IV every 12 hours) (Antimicrobial Therapy, Inc., 2016).

2.10.2 Multi-drug resistant gram-negative bacilli

2.10.2.1 *Acinetobacter baumannii*

A carbapenem is the drug of choice when treating carbapenem-susceptible MDR *Acinetobacter baumannii* infections (Izadpanah & Khalili, 2015:106).

Agents that can be used for *Acinetobacter baumannii* infections include imipenem/cilastatin (500 mg every six hours up to one gram every six to eight hours), meropenem (500 mg to one gram every eight hours), doripenem (500 mg every eight hours), amikacin (15 mg/kg daily), tobramycin (four to seven mg/kg daily), colistin (one to three million units every eight hours),

tigecycline (100 mg at once then 50 mg every 12 hours) or minocycline (100 mg every 12 hours) (Fishbain & Peleg, 2010:80).

For suspected resistance to all penicillins, cephalosporins, aztreonam, carbapenems, aminoglycosides and fluoroquinolones, first line treatment recommendations include combination therapy with colistin together with imipenem/cilastatin or colistin together with meropenem (Antimicrobial Therapy, Inc., 2016; Fishbain & Peleg, 2010:83; Gilbert *et al.*, 2014:78; Kanafani & Kanji, 2016).

2.10.2.2 Extended spectrum beta-lactamase producing *Escherichia coli*, *Klebsiella pneumoniae* or other *Enterobacteriaceae*

For extended spectrum beta-lactamase (ESBL) producing *Escherichia coli*, *Klebsiella pneumoniae* or other *Enterobacteriaceae* resistant to all cephalosporins, trimethoprim/sulfamethoxazole, fluoroquinolones, and aminoglycosides recommendations include: imipenem/cilastatin (500 mg IV every six hours) or meropenem (one gram IV every eight hours) or doripenem (500 mg IV every eight hours). Doripenem is not recommended for the treatment of pneumonia (Fraser, 2015; Gilbert *et al.*, 2014:78; Madappa, 2016; Qureshi, 2015). Fosfomycin (three gram PO) or nitrofurantoin (100 mg PO 12 hourly) is recommended for urinary tract infections (Antimicrobial Therapy, Inc., 2016).

For carbapenemase producing strains in the critically ill patient combination therapy of colistin and meropenem is recommended (Antimicrobial Therapy, Inc., 2016). The recommended dose of colistin is based on the body weight of the patient and adjusted according to renal function. The recommended adult dosing for critical-ill patients with normal renal function is a loading dose of 12 million units (MU) and a maintenance dose of 3 MU 8 hourly or 4.5 MU 12 hourly (Labuschagne *et al.*, 2016:5).

2.10.2.3 Carbapenemase producing aerobic gram-negative bacilli or *Pseudomonas aeruginosa*

Agents that are recommended for carbapenem-resistant *Enterobacteriaceae* include colistin, tigecycline, fosfomycin, and rifampicin (Kanji & Kanafani, 2011:254; Zavascki *et al.*, 2013).

For *Pseudomonas aeruginosa* one of the following are recommended: piperacillin/tazobactam (4.5 gram every six hours), ceftazidime (two gram every eight hours), cefepime (two gram every eight hours), aztreonam (two gram every eight hours), imipenem/cilastatin (500 mg every six hours up to one gram every eight hours), meropenem (one gram every eight hours), doripenem (500 mg every eight hours), ciprofloxacin (400 mg every eight hours), and levofloxacin (750 mg

IV 24-hourly). Combination therapy of colistin and a carbapenem (imipenem/cilastatin or meropenem) are recommended for critically ill patients with isolates resistant to all beta-lactams, fluoroquinolones and aminoglycosides (Antimicrobial Therapy, Inc., 2016).

2.11 Chapter summary

In this chapter the antimicrobial agents were reviewed. It is evident that antimicrobials should be used sparingly due to increasing resistance of pathogens to agents. Antimicrobials were discussed with the primary focus on the general characterisation and classification of agents, such as mechanism of action, spectrum of activity, adverse effects, and common indications. Mechanisms of resistance and possible empirical treatment suggestions for MDR organisms were investigated. Furthermore, the usage and necessity of antibiograms were discussed and the guidelines for the development of institutional specific antibiograms were outlined.

CHAPTER 3: RESULTS AND DISCUSSION

3.1 Introduction

In this chapter the results obtained from the empirical investigation on retrospective data for the period 1 January 2014 to 31 December 2015 will be discussed. Results are presented in the form of a manuscript (refer to paragraph 3.2). The manuscript entitled: “Prevalence and facility-specific antibiogram of pathogens isolated at a private hospital in the Western Cape, South Africa” were submitted to the journal *“Infection control and hospital epidemiology”*. Annexure E includes the author’s guidelines for this journal or can be viewed online using the following link: <https://www.cambridge.org/core/journals/infection-control-and-hospital-epidemiology/information/instructions-contributors> (accessed 31 Aug. 2017). Proof of submission to the journal is included in Annexure F.

A poster presentation entitled: “Development and presentation of a facility-specific antibiogram for a private hospital in the Western Cape” was presented at the 7th Annual Conference of the South African Society of Clinical Pharmacy (SASOCP) in Johannesburg, South Africa from 8 to 10 June 2017 (refer to paragraph 3.3). The SASOCP Conference is a platform for the promotion of clinical pharmacy in South Africa. The guidelines for the poster presentation are included in Annexure G. Annexure H includes the letter of acceptance for the poster presentation at the SASOCP 7th Annual Conference.

3.2 Manuscript

Prevalence and facility-specific antibiogram of pathogens isolated at a private hospital in the Western Cape, South Africa

Article type:

Original Articles

Authors:

Snyman HM, BPharm

Du Plessis JM, MPharm

Burger JR, PhD (Pharmacy Practice)

Cockeran M, MSc

Institutional affiliation: Medicine Usage in South Africa, Faculty of Health Sciences,

North-West University, Potchefstroom, 2531, South Africa

Corresponding author:

Dr Jesslee M Du Plessis

North-West University

Private Bag X6001

Potchefstroom, 2520

South Africa

jesslee.duplessis@nwu.ac.za

Short title: Prevalence and facility-specific antibiogram

Number of words:

Abstract: 249

Main body: 2799

The data were presented in a poster format at the 7th Annual Conference of the South African Society of Clinical Pharmacy (SASOCP) held in Johannesburg, South Africa, from 8 to 10 June 2017.

Abstract

OBJECTIVE The study aimed to identify the most prevalent pathogens and develop a facility-specific antibiogram of pathogen antimicrobial susceptibilities in order to provide crucial information for appropriate empirical antimicrobial therapy.

DESIGN Descriptive, quantitative, cross-sectional design using retrospective data

SETTING Private hospital in Worcester (173-bed), Inland and Coastal District of the Western Cape, South Africa.

PATIENTS All-inclusive sample of final isolates for patients aged 18 years and older, on data from the databases ICNet[®] Clinical Surveillance Software and PathProvider[®] V.1.4, for the period 1 January 2015 to 31 December 2016.

METHOD Antimicrobial susceptibility for the most prevalent pathogens isolated per hospital unit were identified and presented as a cumulative antibiogram. Appropriate antimicrobial therapy was defined as antimicrobial agents administered as the first dose of which the bacteria isolate was susceptible to at least one of the administered agents.

RESULTS A total of 1424 pathogens (908 gram-negative and 516 gram-positive) were isolated. *Escherichia coli* (34.5%) was the most prevalent organism among gram-negative and methicillin-susceptible *Staphylococcus aureus* (MSSA) (31%) among gram-positive organisms. Gram-positive organisms revealed sensitivity to linezolid, teicoplanin, and vancomycin of 98 to 100%. Among gram-negative isolates *Escherichia coli*, *Klebsiella* species (spp.), *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Enterobacter cloacea* showed 100% susceptibility to carbapenems, while *Pseudomonas aeruginosa* and *Acinetobacter* spp. illustrated susceptibility to carbapenems fluctuating from 75% to 98%.

CONCLUSION This study demonstrated susceptibility rates among the most prevalent organisms for the private hospital in the Western Cape. Confirmed trends of carbapenem resistance were found among *Pseudomonas aeruginosa* and *Acinetobacter* spp.

Introduction

Monitoring of local resistance and susceptibility trends of prevalent hospital-specific pathogens can assist clinicians in choosing optimal empiric antimicrobial therapy for patients in a specific geographical area.¹⁻³ Basing empiric treatment on local susceptibility data is crucial since pathogens are continually evolving due to the changes in bacterial and host populations, the interaction between them and ecological conditions that affect survival of the organisms,⁴ resulting in varying geographical pathogen resistant patterns.¹ Hospitals are therefore in need of individualised antibiograms since national antibiograms do not necessarily provide adequate information for a specific hospital setting.²

The study conducted at a 173-bed private hospital in Worcester, Inland and Coastal District of the Western Cape, South Africa aimed to (i) identify the most prevalent pathogens isolated in the hospital and in each unit, (ii) determine the susceptibilities to the antimicrobial agents of pathogens isolated 30 times or more in total in the hospital in order to generate a cumulative antibiogram, and (iii) analyse the susceptibility of hospital-specific pathogens in order to predict antibiotic combinations that would provide adequate empiric therapy.

The Clinical and Laboratory Standards Institute (CLSI) developed clinical and epidemiological useful recommendations for the analysis and presentation of antimicrobial susceptibility data.⁵ The first guidelines (M39-A) were published in 2002 and revised in 2009 and 2014.^{6,7}

An earlier study by Brink et al. conducted in South Africa during 2006 using data collected from 12 laboratories of seven private hospitals pathology practices established that *Escherichia coli* showed high levels of resistance to ampicillin (84%) and

amoxicillin/clavulanic acid (37%) and 20% resistance to fluoroquinolones. These results were similar to results reported from Europe.⁸ *Klebsiella pneumoniae* showed high rates of cephalosporin resistance among blood culture isolates (44% to 52%) and a nationwide piperacillin/tazobactam resistance of 40%. Cefepime and ciprofloxacin showed 80% and 88% susceptibility respectively to *Enterobacter* spp. Tobramycin was the most effective agent against *Acinetobacter baumannii* with 81% susceptibility. No resistance to teicoplanin, vancomycin or linezolid among *Staphylococcus aureus* was detected; however, high sensitivity rates were found for fusidic acid (97%), rifampicin (89%), gentamycin (88%) and trimethoprim/sulfamethoxazole (71%). Tigecycline was found as the agent showing excellent activity against gram-negative pathogens (including extended spectrum beta-lactamases-producing isolates). Resistance among *Pseudomonas aeruginosa* was higher than in *Acinetobacter baumannii*. No single agent was found as suitable empirical monotherapy option for pseudomonal or *Acinetobacter* bacteraemia/septicaemia.⁸ Brink et al. concluded that significant regional differences in antibiotic resistance patterns in South Africa exist and individualised surveillance should be done in order to optimise empirical antibiotic treatment.⁸

Methods

Design and data source

A descriptive, quantitative cross-sectional design using retrospective data from medical records of patients admitted to the 173-bed private hospital located in Worcester in the Inland and Coastal District of the Western Cape of South Africa during 1 January 2014 to 31 December 2015 was performed. The study was conducted according to the Declaration of

Helsinki. Research commenced after ethical approval was obtained from a National Health Research Ethics Committee (HREC) - (Ethics number: 00355-15-A1).

Data collection

Only final isolates of patients 18 years and older admitted to the medical unit, orthopaedic unit, surgical unit, and critical care unit were included in the study. As in accordance with CLSI guidelines (i) only the first isolate from a patient was included irrespective of the specimen, (ii) only diagnostic isolates were included, and (iii) isolates for surveillance cultures were excluded.^{5,6}

Data were collected retrospectively using two databases, viz. PathProvider[®] V.1.4.2 and ICNet[®] Clinical Surveillance Software and included patients' information such as patient number, age, and the unit/ward admitted to. Clinical information collected included the source of specimen, date of specimen collection, organism cultured, and susceptibility to antibiotics as recommended by CLSI.⁶ The susceptibility of the pathogen to the antimicrobial agents tested was marked as R=resistant, I=intermediate, or S=sensitive.

Statistical analysis

Data were analysed using IBM[®] SPSS[®] Statistics for Windows[®], Version 24.0, and described using descriptive statistics. Pathogens isolated more than ten times during the study period in the hospital were identified. For the final cumulative antibiogram five or more most frequently isolated organisms for both gram-negative and gram-positive organisms were used. Susceptibility data for organisms with fewer than 30 isolates should normally be interpreted with caution; we therefore combined two years of data (01 January 2014 – 31 December 2015) to increase our sample size.

Where species with fewer than 30 isolates were included it was stated in a footnote as recommended by the CLSI.⁶ For *Escherichia coli*, a sufficient number of isolates were obtained to separate urine isolates from non-urine isolates. *Acinetobacter* species (*Acinetobacter baumannii*, *Acinetobacter haemolyticus*, *Acinetobacter johnsonii*, *Acinetobacter lwoffii*, *Acinetobacter* spp., *Acinetobacter ursingii*) were grouped together in the antibiogram. For gram-positive isolates, all coagulase-negative *Staphylococcus* species (i.e. *Staphylococcus capitis*, *Staphylococcus caprae*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Staphylococcus hominis* and *Staphylococcus lugdunensis*⁹) and methicillin-resistant *Staphylococcus* species (methicillin-resistant *Staphylococcus capitis*, methicillin-resistant *Staphylococcus cohnii*, methicillin-resistant *Staphylococcus haemolyticus*, methicillin-resistant *Staphylococcus hominis*, and methicillin-resistant *Staphylococcus epidermidis*) were grouped. Pathogens reported in the antibiogram that did not have 100% sensitivity against any antimicrobial were analysed in order to provide combination recommendations for appropriate empiric therapy. Appropriate empiric antimicrobial therapy was defined as antimicrobials administered as the first dose where the isolate bacterium is susceptible to at least one of the administered antimicrobials.¹⁰

Results

A total of 1424 bacterial isolates (908 gram-negative and 516 gram-positive organisms) were collected from patients aged 18 years and older. The total number of specimens obtained in the critical care unit for gram-negative organisms was 132 (14.5% of gram-negative isolates), 299 for the medical unit (32.9% of gram-negative isolates), 141 for the orthopaedic unit (15.5% of gram-negative isolates) and 336 for the surgical unit (37% of gram-negative isolates). Table 1 shows the prevalence of gram-negative organisms that were isolated more

than ten times during the study period by study site. The prevalence of organisms is expressed as the frequency (%) for each unit.

Gram-negative organisms isolated ten times or more in the hospital represented 86.01% (n = 781) of the total number of gram-negative isolates identified during the study period. Isolates mostly identified in the hospital included *Escherichia coli* (31.5%), *Klebsiella* spp. (7.6%), *Klebsiella pneumoniae* (6.7%), *Pseudomonas aeruginosa* (6.6%), *Proteus mirabilis* (4.4%), *Haemophilus influenzae* (4.1%), *Enterobacter cloacae* (3.6%), and *Bacteroides fragilis* (3.3%).

Table 2 shows the prevalence of gram-positive organisms that were isolated more than ten times during the study period. Specimens for gram-positive organisms isolated ten times or more in the hospital represented 79.8% (n = 412) of the total number of gram-positive isolated. Organisms isolated most in the hospital included *Staphylococcus aureus* (MSSA) (31.0%), *Enterococcus faecalis* (19.6%), *Streptococcus agalactiae* (7.1%), and methicillin-resistant *Staphylococcus aureus* (MRSA) (4.8%).

Table 3 depicts the cumulative antibiogram of gram-negative organisms isolated for 2014-2015. Urine isolates of *Escherichia coli* showed 100% sensitivity to fosfomycin and 97% to nitrofurantion. Non-urine isolates were 100% susceptible to doripenem, ertapenem, imipenem/cilastatin, meropenem, amikacin, and tigecycline. *Klebsiella* spp. had no sensitivity to amoxicillin and ampicillin, but high sensitivity (100%) to doripenem, ertapenem, imipenem/cilastatin, and meropenem. *Haemophilus parainfluenzae* showed 100% sensitivity to cefotaxime and ceftriaxone and 98% susceptibility to amoxicillin/clavulanic acid, cefuroxime and cefprozil. *Klebsiella pneumoniae* had no sensitivity to amoxicillin and ampicillin, but 100% sensitivity to doripenem, ertapenem, imipenem/cilastatin, and

meropenem. *Pseudomonas aeruginosa* demonstrated 98% sensitivity to amikacin and 97% sensitivity to tobramycin. *Proteus mirabilis* showed 100% sensitivity to ceftazidime (n = 26 isolates), doripenem (n = 28 isolates), ertapenem (n = 28 isolates), meropenem (n = 28 isolates), amikacin (n = 28 isolates), tobramycin (n = 26 isolates) and cefprozil (n = 21 isolates), and 98% sensitivity to ciprofloxacin. *Haemophilus influenzae* had 100% sensitivity to amoxicillin/clavulanic acid, cefuroxime, cefotaxime, ceftriaxone, cefprozil, and tetracycline. *Enterobacter cloacae* showed no sensitivity to amoxicillin, amoxicillin/clavulanic acid, ampicillin, cefoxitin, cefuroxime and cefprozil. High sensitivity (100%) was demonstrated to doripenem, ertapenem, imipenem/cilastatin, and meropenem. *Acinetobacter* spp. showed 100% sensitivity to tigecycline and 94% sensitivity to amikacin. *Bacteroides fragilis* had no sensitivity to penicillin; however, there was a 100% sensitivity to metronidazole.

The cumulative antibiogram of gram-positive organisms isolated 2014-2015 is depicted in Table 4. *Staphylococcus aureus* (MSSA) showed 100% sensitivity to cloxacillin, linezolid and vancomycin. *Enterococcus faecalis* demonstrated 100% susceptibility to amoxicillin, ampicillin, fosfomycin, linezolid, nitrofurantoin, teicoplanin, and vancomycin. No sensitivity was found among methicillin-resistant *Staphylococcus* spp. to cloxacillin and erythromycin. The organisms had 100% sensitivity to linezolid and vancomycin. Beta-haemolytic *Streptococcus* Group B (*Streptococcus agalactiae*) showed 100% sensitivity to amoxicillin, ampicillin, cefuroxime, ceftriaxone, levofloxacin (n = 29 isolates), trimethoprim/sulfamethoxazole (n = 17 isolates), vancomycin (n = 20 isolates), and cefprozil. Coagulase-negative *Staphylococcus* spp. demonstrated high sensitivity (100%) to cloxacillin, linezolid (n = 25 isolates), teicoplanin (n = 25 isolates), and vancomycin (n = 25 isolates). *Staphylococcus aureus* (MRSA) showed no sensitivity to cloxacillin, moxifloxacin (n = 23

isolates), and erythromycin (n = 24 isolates). The organism demonstrated 100% sensitivity to linezolid, teicoplanin and vancomycin. Beta-haemolytic *Streptococcus* Group A (*Streptococcus pyogenes*) demonstrated 100% sensitivity to amoxicillin, ampicillin, cefuroxime, cefotaxime, ceftriaxone, levofloxacin, erythromycin, clindamycin, vancomycin, and cefprozil. *Pseudomonas aeruginosa* had no antimicrobial agent to which it was 100% sensitive.

Discussion

Cumulative antibiogram reports contain important information that can be used as a basis for the selection of empirical antimicrobial therapy. The incidence of microbial resistance patterns varies geographically and it is therefore essential that any recommendations for empirical treatment be based on local susceptibility data.⁷

Liu et al. concluded that vancomycin should be prescribed empirically for patients with suspected *Staphylococcus aureus* bloodstream infections. Once the isolate is known to be MSSA, therapy should be switched to an antistaphylococcal penicillin or beta-lactam agent.¹² Vancomycin is therefore recommended to be used as empiric treatment if *Staphylococcus aureus* bloodstream infections are suspected and therapy should be reviewed once the sensitivity profile of the isolate is known. In support of this, isolates identified in the present study demonstrated 100% sensitivity to vancomycin. Thus making vancomycin a good empiric treatment option for suspected *Staphylococcus aureus* bloodstream infections according to the study.

Treatment of enterococcal infections is determined by the species, resistance patterns, the location and the severity of infection.¹³ Uncomplicated enterococcal infections can usually be

treated successfully with monotherapy, whereas ampicillin remains the preferred therapy for uncomplicated infections.¹³ In support of this, isolates from the results of the present study showed 100% sensitivity to ampicillin. Vancomycin illustrated 100% susceptibility in the present study and can be used as alternative empirical treatment option for patients with penicillin allergy.

Complicated enterococcal infections such as endocarditis requires the use of synergistic combinations in order to be effective.¹³ The combination usually includes a cell wall-active agent, such as a penicillin or glycopeptide with an aminoglycoside which results in a bactericidal activity against the organisms.¹⁴ In the present study gentamycin showed 84% susceptibility and can be added for complicated infections due to *Enterococcus faecalis*. Vancomycin can be added where high levels of aminoglycoside resistance are experienced - thus using both a penicillin and a glycopeptide.¹³ High levels of aminoglycoside resistance among enterococci eliminate this synergistic combination of a penicillin or glycopeptide plus an aminoglycoside.¹⁴ For enterococcal infections that are resistant to ampicillin and vancomycin, linezolid is recommended as choice of therapy.^{13,15,16} Isolates in the present study demonstrated 100% sensitivity to linezolid.

For uncomplicated lower urinary tract infections due to enterococci, nitrofurantoin and fosfomycin are recommended as choice of therapy.¹⁶ *Enterococcus faecalis* demonstrated 100% susceptibility to nitrofurantoin and fosfomycin in the present study in support of this.

A carbapenem is recommended as the drug of choice when treating carbapenem-susceptible MDR *Acinetobacter baumannii* infections.¹⁰ *Acinetobacter baumannii* has a drug-resistant nature and has unusual and unpredictable susceptibility patterns which make empirical and therapeutic decisions difficult. Usually *Acinetobacter baumannii* resistant to carbapenems are

also resistant to the majority of other antimicrobials (except the polymyxins or tigecycline). Aminoglycosides (amikacin and tobramycin) are shown to maintain their activity mostly against many *Acinetobacter baumannii* isolates.¹⁷ From the results of the present study amikacin, gentamycin and tigecycline could be good empiric treatment options when an infection due to *Acinetobacter baumannii* is suspected; however, treatment of tigecycline is associated with higher mortality rates.¹⁹

The effectiveness of combination therapy whether empirical or definitive against *Acinetobacter baumannii* has not yet been demonstrated.¹⁷ Combinations of colistin in combination with vancomycin, rifampicin, amikacin or gentamycin have been studied,¹⁸ showing high synergy among colistin plus rifampicin, colistin plus vancomycin¹⁸ and colistin and a carbapenem.¹⁷

In the present study *Enterobacter cloacae* showed the most resistance (100%) to second generation cephalosporins followed by *Klebsiella pneumoniae* (54%). Sensitivity of isolates in the present study to third and fourth generation cephalosporins ranged from 54% to 55% for *Klebsiella pneumoniae* and 82% to 85% for *Enterobacter cloacae*. No resistance to carbapenems was demonstrated by these organisms. For ESBL-producing *Escherichia coli*, *Klebsiella pneumoniae* or other Enterobacteriaceae resistant to all cephalosporins, trimethoprim/sulfamethoxazole, fluoroquinolones, aminoglycosides and a carbapenem remain the choice of therapy.^{15,20} Doripenem is not recommended for the treatment of pneumonia.¹⁵

Usually the microbial spectrum of uncomplicated urinary tract infections consists mainly of *Escherichia coli* and therefore local antimicrobial susceptibility patterns of *Escherichia coli* should be considered in empirical selection of antimicrobials for the treatment of

uncomplicated urinary tract infections.²¹ According to a study done in Gauteng, South Africa, gram-negative urinary tract pathogens showed 99% sensitivity to fosfomycin, 91% sensitivity to nitrofurantoin, 95% sensitivity to cefixime, 93% to cefuroxime, and 81% to amoxicillin/clavulanic acid.²¹ The susceptibility data of the present study are very similar to the susceptibility data of the study done by Van Schoor.²¹ Urinary isolates of *Escherichia coli* in the present study showed superior sensitivity to fosfomycin (100%), nitrofurantoin (97%), cefoxitin (93%), cefuroxime (93%), and amoxicillin/clavulanic acid (84%). Cephalosporins were recommended as the choice of therapy for the study by Van Schoor.²¹ Nitrofurantoin and fosfomycin are only suitable or recommended to treat lower urinary tract infections.²² Fosfomycin is recommended for the treatment of lower urinary tract infections caused by multi-drug resistant pathogens, including ESBL-producing Enterobacteriaceae and vancomycin-resistant enterococci.²³ To substantiate this, the results of the present study showed that cephalosporins can be used empirically for urinary tract infections and fosfomycin or nitrofurantoin for empirical treatment of lower urinary tract infections.

For suspected *Pseudomonas aeruginosa* infection carbapenems are usually used for empiric treatment since combination therapy for *Pseudomonas* species has been controversial.²⁴ For an infection due to multi-drug resistant *Pseudomonas* species the most used drug combination is an aminoglycoside with a beta-lactam agent. Other combinations with high synergy ratios include ceftazidime or piperacillin/tazobactam in combination with tobramycin.²⁴

Pseudomonas aeruginosa isolated in our study showed a degree of resistance developing against carbapenems. Doripenem, imipenem/cilastatin and meropenem illustrated resistance. Ertapenem in general lacks sufficient anti-pseudomonal activity and are not considered clinically useful for the treatment of *Pseudomonas aeruginosa* infections.²⁵ The susceptibility results of the present study showed that all organisms except *Pseudomonas aeruginosa* had a

single antimicrobial agent to which an organism was 100% sensitive. Therefore, combination empiric therapy is more appropriate when a Pseudomonal infection is suspected. From the results of the present study an aminoglycoside agent (amikacin, gentamycin, tobramycin) with a beta-lactam agent (piperacillin/tazobactam, ceftazidime, and cefepime) should be suggested.

When an infection is suspected due to mixed gram-positive and gram-negative organisms, combination therapy is recommended.²⁴ First-line therapy recommendations for suspected mixed infections include an anti-MRSA agent together with a carbapenem; or tigecycline (not for urinary tract infections) together with or without an antipseudomonal agent.

Recommendations for second-line therapy include an anti-MRSA agent together with piperacillin/tazobactam; or an anti-MRSA agent together with colistin.²⁴ According to the results of the present study, anti-MRSA agents included vancomycin, teicoplanin and linezolid showing 100% susceptibility to MRSA. Antipseudomonal agents demonstrated by the present study were ceftazidime, cefepime, piperacillin/tazobactam, carbapenems (imipenem/cilastatin, meropenem, doripenem), fluoroquinolones (ciprofloxacin and levofloxacin), and aminoglycosides.

The prevalence of gram-negative and gram-positive organisms for a private hospital in the Western Cape is demonstrated by this study. The study demonstrated the emergence of multi-drug resistant organisms (*Pseudomonas aeruginosa* and *Acinetobacter* spp.) for this geographical area. Furthermore, the findings of the study were in line with treatment recommendations.

Limitations of this study include the inclusion of two years of data and possible system errors. The standard cumulative antibiograms generated in the study do not take patient

factors into account, do not separate community and hospital acquired infections, do not include minimum inhibitory concentration (MIC) values, do not report on source of specimen and do include non-sterile site specimen types. Since the private hospital provides health services to a large population, the population may vary since private patients move between health care facilities. Despite these limitations, the facility-specific antibiogram developed for the specific geographical area in our study remains an excellent tool for guidance of therapy and should be used together with clinical parameters to choose optimal treatment for the suspected infection. Antibiogram data may furthermore serve as a baseline for further antimicrobial susceptibility studies.

Acknowledgements

Financial support: All authors declare that no financial support was provided.

Conflict of interest: No conflict of interest was reported by any of the authors relevant to this manuscript.

References:

1. Stein CR, Weber DJ, Kelley M. Using hospital antibiogram data to assess regional pneumococcal resistance to antibiotics. *Emerg Infect Dis* 2003;9:211-216.
2. Beardsley JR, Williamson JC, Johnson JW, Ohl CA, Karchmer TB, Bowton DL. Using local microbiologic data to develop institution-specific guidelines for the treatment of hospital-acquired pneumonia. *Chest* 2006;130:787-793.
3. Joshi S. Hospital antibiogram: A necessity. *Indian J Med Microbiol* 2010;28:277-280.
4. Sousa CPD. Pathogenicity mechanisms of prokaryotic cells: an evolutionary view. *Braz J Infect Dis* 2003;7:23-31.
5. Hindler JF, Stelling J. Analysis and presentation of cumulative antibiograms: a new consensus guideline from the Clinical and Laboratory Standards Institute. *Clin Infect Dis* 2007;44:867-873.
6. National Committee on Clinical Laboratory Standard. Analysis and presentation of cumulative antimicrobial susceptibility test data; approved M39-A guideline, 2002. National Committee on Clinical Laboratory Standard website. <http://clsi.org/> Published 2002. Accessed February 10, 2017.
7. Moehring RW, Hazen KC, Hawkins MR, Drew RH, Sexton DJ, Anderson DJ. Challenges in preparation of cumulative antibiogram reports for community hospitals. *J Clin Microbiol* 2015;53:2977-2982.
8. Brink A, Moolman J, Da Silva MC, Botha M. Antimicrobial susceptibility profile of selected bacteraemic pathogens from private institutions in South Africa. *SAfr Med J* 2007;97:273-279.
9. Becker K, Heilmann C, Peters G. Coagulase-negative staphylococci. *Clin Microbiol Rev* 2014;27:570-926.

10. Lueangarun S, Leelarasamee A. Impact of inappropriate empiric antimicrobial therapy on mortality of septic patients with bacteremia: a retrospective study. *Interdiscip Perspect Infect Dis* 2012;2012:1-13.
11. McDanel, JS, Perencevich, EN, Diekema, DJ, et al. Comparative effectiveness of beta-lactams versus vancomycin for treatment of methicillin-susceptible *Staphylococcus aureus* bloodstream infections among 122 hospitals. *Clin Infect Dis* 2015; 61:361-367.
12. Liu, C, Bayer, A, Cosgrove, SE. et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis* 2011;52:e18-e55.
13. Hollenbeck BL, Rice LB. Intrinsic and acquired resistance mechanisms in enterococcus. *Virulence* 2012;3:421-569.
14. Chow JW. Aminoglycoside resistance in enterococci. *Clin Infect Dis* 2000;31:586-589.
15. Gilbert DN, Chambers HF, Eliopoulos GM, Saag MS. *The Sanford Guide to Antimicrobial Therapy* 44th ed. Sperryville, VA: Antimicrobial Therapy; 2014.
16. Arias CA, Contreras GA, Murray BE. Management of multidrug-resistant enterococcal infections. *Clin Microbiol Infect* 2010;16:555-562.
17. Fishbain J, Peleg AY. Treatment of Acinetobacter infections. *Clin Infect Dis* 2010;51:79-84.
18. Leite GC, Oliveira MS, Perdigão-Neto LV, et al. Antimicrobial combinations against pan-resistant *Acinetobacter baumannii* isolates with different resistance mechanisms. *PloS One* 2016;11:e0151270.

19. Cheng A, Chuang YC, Sun HY, et al. Excess mortality associated with colistin-tigecycline compared with colistin-carbapenem combination therapy for extensively drug-resistant *Acinetobacter baumannii* bacteremia: a multicenter prospective observational study. *Crit Care Med* 2015;43:1194-1204.
20. Munoz-Price, LS. Extended-spectrum beta-lactamases, 2017. Published 2017. Up to date website. Accessed March 21, 2017.
21. Van Schoor J. Urinary tract infections in women. *S Afr Fam Pract* 2016;58:6-10.
22. Lewis DA, Gumede LYE, van der Hoven LA, et al. Antimicrobial susceptibility of organisms causing community-acquired urinary tract infections in Gauteng Province, South Africa. *S Afr Med J* 2013;103:377-381.
23. Falagas ME, Kastoris AC, Kapaskelis AM, Karageorgopoulos DE. Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum β -lactamase producing, Enterobacteriaceae infections: a systematic review. *Lancet Infect Dis* 2010;10:43-50.
24. Kanj SS, Kanafani ZA. Current concepts in antimicrobial therapy against resistant gram-negative organisms: extended-spectrum β -lactamase-producing enterobacteriaceae, carbapenem-resistant enterobacteriaceae, and multidrug-resistant *Pseudomonas aeruginosa*. *Mayo Clin Proc* 2011;86:250-259.
25. Zhanel GG, Wiebe R, Dilay L, et al. Comparative review of the carbapenems. *Drugs* 2007;67:1027-1052.

TABLE 1 Prevalence of gram-negative organisms isolated more than 10 times between 01 Jan. 2014 and 31 Dec. 2015

ORGANISM CULTURED (hospital level)	Critical care unit N = 132	Medical unit N=299	Orthopaedic unit N = 141	Surgical unit N = 336
	<i>n (%)</i>	<i>n (%)</i>	<i>n (%)</i>	<i>n (%)</i>
<i>Acinetobacter baumannii</i> (N = 23)	5 (3.8)	2 (0.7)	3 (2.1)	13 (3.9)
<i>Bacteroides fragilis</i> (N = 30)	4 (3.0)	4 (1.3)	3 (2.1)	19 (5.7)
<i>Campylobacter jejuni</i> (N = 12)	0 (0.0)	10 (3.3)	0 (0.0)	2 (0.6)
<i>Enterobacter cloacae</i> (N = 33)	9 (6.8)	5 (1.7)	6 (4.3)	13 (3.9)
<i>Escherichia coli</i> (N = 286)	34 (25.8)	93 (31.1)	55 (39.0)	104 (31.0)
<i>Haemophilus influenzae</i> (N = 37)	5 (3.8)	25 (8.4)	2 (1.4)	5 (1.5)
<i>Haemophilus parainfluenzae</i> (N = 63)	7 (5.3)	40 (13.4)	6 (4.3)	10 (3.0)
<i>Klebsiella oxytoca</i> (N = 15)	4 (3)	4 (1.3)	1 (0.7)	6 (1.8)
<i>Klebsiella pneumoniae</i> (N = 61)	15 (11.4)	19 (6.4)	3 (2.1)	24 (7.1)
<i>Klebsiella spp.</i> (N = 69)	9 (6.8)	27 (9.0)	18 (12.8)	15 (4.5)
<i>Morganella morganii</i> (N = 13)	1 (3.0)	0 (0.0)	3 (2.1)	6 (1.8)

ORGANISM CULTURED (hospital level)	Critical care unit N = 132	Medical unit N=299	Orthopaedic unit N = 141	Surgical unit N = 336
<i>Prevotella bivia</i> (N = 11)	0 (0.0)	1 (0.3)	1 (0.7)	9 (2.7)
<i>Proteus mirabilis</i> (N = 40)	3 (2.3)	8 (2.7)	10 (7.1)	19 (5.7)
<i>Pseudomonas aeruginosa</i> (N = 60)	11 (8.3)	17 (5.7)	8 (5.7)	24 (7.1)
<i>Serratia marcescens</i> (N = 17)	3 (2.3)	6 (2.0)	2 (1.4)	6 (1.8)
<i>Stenotrophomonas maltophilia</i> (N = 11)	8 (6.1)	2 (0.7)	0 (0.0)	1 (0.3)

Prevalence (n) is measured in frequency (%) with the total number (N) of isolates per unit as denominator.

TABLE 2 Prevalence of gram-positive organisms isolated more than 10 times between 01 Jan. 2014 and 31 Dec. 2015

ORGANISM CULTURED (hospital level)	Critical care unit N = 60	Medical unit N = 109	Orthopaedic unit N = 147	Surgical unit N = 200
	<i>n (%)</i>	<i>n (%)</i>	<i>n (%)</i>	<i>n (%)</i>
Beta-haemolytic Streptococcus Group A (Streptococcus pyogenes) (N = 21)	0 (0.0)	4 (3.7)	6 (4.1)	11 (5.5)
Beta-haemolytic Streptococcus Group B (Streptococcus agalactiae) (N = 37)	3 (5.0)	9 (8.3)	7 (4.8)	18 (9.0)
Enterococcus faecalis (N = 101)	13 (21.7)	23 (21.1)	22 (15.0)	43 (21.5)
Methicillin-resistant Staphylococcus epidermidis (MRSE) (N = 21)	7 (11.7)	3 (2.8)	8 (5.4)	3 (1.5)
Mycobacterium tuberculosis (N = 20)	1 (1.7)	15 (13.8)	2 (1.4)	2 (1.0)
Staphylococcus aureus (MRSA) (N = 25)	4 (6.7)	2 (1.8)	11 (7.5)	8 (4.0)
Staphylococcus aureus (MSSA) (N = 160)	9 (15.0)	18 (16.5)	55 (37.4)	78 (39.0)
Staphylococcus epidermidis (N = 12)	3 (5.0)	1 (0.9)	5 (3.4)	3 (1.5)
Streptococcus pneumoniae (N = 15)	5 (8.3)	7 (6.4)	2 (1.4)	1 (0.5)

Prevalence (n) is measured in frequency (%) with the total number (N) of isolates per unit as denominator. MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-susceptible *Staphylococcus aureus*

TABLE 3 Cumulative antibiogram of gram-negative organisms isolated 01 Jan. 2014 – 31 Dec. 2015 expressed as percentage susceptible

GRAM-NEGATIVE ORGANISMS	<i>Escherichia coli</i> (urine isolates)	<i>Escherichia coli</i> (non-urine isolates)	<i>Klebsiella</i> spp.	<i>Haemophilus parainfluenzae</i>	<i>Klebsiella pneumoniae</i>	<i>Pseudomonas aeruginosa</i>	<i>Proteus mirabilis</i>	<i>Haemophilus influenzae</i>	<i>Enterobacter cloacae</i>	<i>Acinetobacter</i> spp.	<i>Bacteroides fragilis</i>
Number of isolates	N = 212	N = 74	N = 69	N = 63	N = 61	N = 60	N = 40	N = 37	N = 33	N = 31	N = 28
<i>Amoxicillin</i>	26	28	0	84		-	60	95	0	-	-
<i>Amoxicillin/clavulanic acid</i>	84	68	65	98	54	-	93	100	0	-	-
<i>Ampicillin</i>	26	28	0	84	0	-	60	95	0	-	-
<i>Piperacillin/tazobactam</i>		86	73 (22)	-	54	92	96 (27)	-	82	68	-
<i>Cefoxitin</i>	93	84	67	-	54	-	95	-	0	-	-
<i>Cefuroxime</i>	93	82	67	98	54	-	95	100	0	-	-
<i>Cefotaxime</i>		95		100	54	-	96	100	82	-	-
<i>Ceftazidime</i>		96		-	55	93	100 (26)	-	82	42	-
<i>Ceftriaxone</i>		95	8 (24)	100	54	-	96 (28)	100	82	-	-
<i>Cefepime</i>		95	4 (23)	-	54	93	96 (28)	-	85	77	-
<i>Doripenem</i>		100	100 (23)	-	100	95	100 (28)	-	100	75 (28)	-
<i>Ertapenem</i>		100	100 (23)	-	100	-	100 (28)	-	100	-	-
<i>Imipenem/cilastatin</i>		100	100 (23)	-	100	87		-	100	81	-
<i>Meropenem</i>		100	100 (23)	-	100	93	100 (28)	-	100	77	-
<i>Amikacin</i>		100	100 (23)	-	97	98	100 (28)	-	97	94	-

GRAM-NEGATIVE ORGANISMS	<i>Escherichia coli</i> (urine isolates)	<i>Escherichia coli</i> (non-urine isolates)	<i>Klebsiella</i> spp.	<i>Haemophilus parainfluenzae</i>	<i>Klebsiella pneumoniae</i>	<i>Pseudomonas aeruginosa</i>	<i>Proteus mirabilis</i>	<i>Haemophilus influenzae</i>	<i>Enterobacter cloacae</i>	<i>Acinetobacter</i> spp.	<i>Bacteroides fragilis</i>
Gentamicin	92	91	64	-	64	92	97	-	91	81	-
Tobramycin		90		-	60	97	100 (26)	-	91	90	-
Ciprofloxacin	73	80	65	87	65	88	98	92	97	77	-
Levofloxacin	73		66	87				92	-	-	-
Moxifloxacin	-	-	-	84	-	-	-	92	-	-	-
Azithromycin	-	-	-	27	-	-	-	89	-	-	-
Clarithromycin	-	-	-	27	-	-	-	89	-	-	-
Telithromycin	-	-	-	29	-	-	-	89	-	-	-
Colistin	-	-	-	-	-		-	-			-
Trimethoprim/ sulfamethoxazole	48	45	49	67		-	77 (26)	57			-
Fosfomycin	100			-	-	-		-	-	-	-
Metronidazole	-	-	-	-	-	-	-	-	-	-	100 (28)
Nitrofurantoin	97		66	-		-		-	-	-	-
Tigecycline		100		-	96	-	0 (26)	-	94	100 (21)	-
Cefprozil	93	82	67	98	54	-	100 (21)	100	0	-	-
Tetracycline	-	-	-	97	-	-	-	100	-	-	-
Penicillin	-	-	-	-	-	-	-	-	-	-	0 (28)

Dash (-) = inappropriate drug or drug not tested; blank = <30 isolated tested; 0 = resistant. Number of isolates indicated in brackets (n) if < 30 isolates were obtained.

TABLE 4 Cumulative antibiogram of gram-positive organisms isolated 01 Jan. 2014 – 31 Dec. 2015 expressed as percentage susceptible

GRAM-POSITIVE ORGANISMS	<i>Staphylococcus aureus</i> (MSSA)	<i>Enterococcus faecalis</i>	Methicillin-resistant <i>Staphylococcus</i> spp.	Beta-haemolytic <i>Streptococcus</i> Group B-(<i>Streptococcus agalactiae</i>)	Coagulase-negative <i>Staphylococcus</i> spp.	<i>Staphylococcus aureus</i> (MRSA)	Beta-haemolytic <i>Streptococcus</i> Group A (<i>Streptococcus pyogenes</i>)
Number of isolates	N = 158	N = 100	N = 44	N = 37	N = 26	N = 25	N = 21
Amoxicillin	-	100	-	100	-	-	100 (21)
Amoxicillin/clavulanic acid		-		-			-
Ampicillin	-	100	-	100	-	-	100 (21)
Cloxacillin	100	-	0	-	100 (26)	0 (25)	-
Cefuroxime		-	-	100		-	100 (21)
Cefotaxime	-	-	-	100	-	-	100 (21)
Ceftriaxone	-	-	-	100	-	-	100 (21)
Gentamicin	92	84 (19)	55	-	96 (26)	84 (25)	-
Levofloxacin	-	87	-	100 (29)	-	-	100 (21)
Moxifloxacin	99	-		-	92 (12)	0 (23)	-
Erythromycin	94	-	0	95 (20)	68 (25)	0 (24)	100 (21)
Clindamycin	96	-	31	95 (20)	76 (25)	17 (24)	100 (21)
Trimethoprim / sulfamethoxazole	91	-	61	100 (17)	92 (26)	92 (25)	-
Fosfomycin	-	100	-	-	-	-	-
Fusidic acid	94	-	55	-	92 (25)	88 (24)	-

GRAM-POSITIVE ORGANISMS	<i>Staphylococcus aureus</i> (MSSA)	<i>Enterococcus faecalis</i>	Methicillin-resistant <i>Staphylococcus</i> spp.	Beta-haemolytic <i>Streptococcus</i> Group B- (<i>Streptococcus agalactiae</i>)	Coagulase-negative <i>Staphylococcus</i> spp.	<i>Staphylococcus aureus</i> (MRSA)	Beta-haemolytic <i>Streptococcus</i> Group A (<i>Streptococcus pyogenes</i>)
Linezolid	100	100	100	-	100 (25)	100 (25)	-
Nitrofurantoin		100					-
Rifampicin	98	-	84	-	96 (25)	83 (24)	-
Teicoplanin	100	100	98	-	100 (25)	100 (25)	-
Vancomycin	100	100	100	100 (20)	100 (25)	100 (25)	100 (21)
Cefprozil		-		100			100 (21)
Tetracycline	94	-		-		96 (23)	95 (21)

Dash (-) = inappropriate drug or drug not tested; blank = <30 isolated tested; 0 = resistant. Number of isolates indicated in brackets (n) if < 30 isolates were obtained. For coagulase-negative *Staphylococcus* spp.,

Staphylococcus aureus (MRSA) and Beta-haemolytic *Streptococcus* Group A less than 30 isolates were obtained. MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-susceptible *Staphylococcus*

aureus

3.3 Poster presentation

Title: Development and presentation of a facility-specific antibiogram for a private hospital in the Western Cape

SNYMAN HM, BPharm

DU PLESSIS JM, MPharm

BURGER JR, PhD (Pharmacy Practice)

Institutional affiliation: Medicine Usage in South Africa, Faculty of Health Sciences, North-West University, Potchefstroom, 2531, South Africa

Number of words:

Abstract: 269

Abstract

BACKGROUND Individualised antibiograms provide critical information on facility-specific susceptibility patterns that can assist prescribing healthcare professionals in their choice of empiric antimicrobial use. Empiric treatment should be based on local susceptibility data since pathogen susceptibility differs per hospital. The study therefore aimed at identifying the most prevalent pathogens in the specific hospital and to summarise the susceptibility profile of frequently tested pathogens to antimicrobials commonly used.

METHOD Retrospective quantitative descriptive research was conducted at a 173-bed private hospital positioned in Worcester in the Inland and Coastal District of the Western Cape of South Africa. Using the ICNet[®] Clinical Surveillance Software, documentation and analysis of the most prevalent pathogens on retrospective data between 1 January 2014 and 31 December 2015 took place. Retrospective analysis of pathogen susceptibility to antimicrobial agents was used in order to generate a cumulative antibiogram.

RESULTS A total of 1424 pathogens (908 gram-negative and 516 gram-positive) were isolated. The most prevalent gram-negative organism was *Escherichia coli* (34.5%) whereas *Staphylococcus aureus* (MSSA) (31%) was the most prevalent gram-positive organism. *Escherichia coli*, *Klebsiella* spp., *Klebsiella pneumoniae*, *Proteus mirabilis* and *Enterobacter cloacae* showed 100% sensitivity to carbapenems. Gram-positive organisms displayed 98 to 100 % sensitivity to linezolid, teicoplanin, and vancomycin. *Pseudomonas aeruginosa* demonstrated 87% to 95 % sensitivity to carbapenems. *Acinetobacter* spp. showed 72% sensitivity to doripenem (among the 28 isolates), 81% to imipenem/cilastatin and 77% to meropenem.

CONCLUSION The study demonstrates the prevalence of gram-negative and gram-positive organisms in a private hospital in the Western Cape. It showed the emergence of multi-drug resistant organisms for the geographical area (*Pseudomonas aeruginosa* and *Acinetobacter* spp. confirmed trends of carbapenem resistance).

Development and presentation of a facility-specific antibiogram for a private hospital in the Western Cape

SNYMAN HM, BPharm; DU PLESSIS JM, MBChB, MPharm; BURGER JR, BPharm, MPharm, PhD

Affiliation: Medicine Usage in South Africa, Faculty of Health Sciences, North-West University, Potchefstroom, 2531, South Africa

1. Background

Primary and opportunistic pathogens are continually evolving which brings forth changes in resistance and susceptibility trends for different geographical areas. Antibiograms are a summary of the susceptibility profile of pathogens towards antimicrobial agents for a specific period which serves as an essential tool for prescribing healthcare professionals.

2. Aim

To identify the most prevalent pathogens and their susceptibility towards commonly used antimicrobials, and to generate an antibiogram specific to the study hospital.

3. Methods

Setting: A 173-bed private hospital positioned in Worcester in the Inland and Coastal District of the Western Cape of South Africa.

Study design: A quantitative retrospective cross-sectional research was performed (ethics approval NWU-00355-15-A1).

Study population & Data source: Final isolates of male and female patients aged 18 years and older admitted to the medical unit, orthopaedic unit, surgical unit, and critical care unit from 1 January 2014 to 31 December 2015. Only the first positive cultured pathogen from a patient was included irrespective of the specimen except isolates for surveillance cultures.

Retrospective data from the databases ICNet® Clinical Surveillance Software and PathProvider® were used.

Data analysis: Descriptive statistics e.g. frequency, were calculated using SPSS Statistics for Windows, Version 24.0 and Microsoft® Office Excel 2007.

The cumulative antibiogram consisted of separate tables for gram-positive and gram-negative organisms which included the total number of isolates for each bacterial species and the susceptibility data expressed as percentage of strains susceptible to the antimicrobial agent.

Escherichia coli had sufficient number of isolates to separate urine isolates from non-urine isolates. Species that were included with less than 30 isolates were stated in a footnote as recommended by the CLSI.

4. Results

Table 1 and 2 depict the antibiograms respectively of gram-positive- and gram-negative organisms isolated during 2014 – 2015 from all the identified units of the hospital.

From the total of 1424 pathogens that were isolated 516 were gram-positive organisms and 908 were gram-negative organisms.

5. Limitations

- Patient factors were not taken into consideration
- Impossible to distinguish between community or hospital acquired infections
- Susceptibility data of isolates from various body sites were represented
- Usually MIC data are not included
- Susceptibility data of all the units of the hospital are combined
- Some isolates may represent contaminants and not true infections since all isolates are included
- This study included two years of data.

Table 1 Cumulative antibiogram of gram-positive organisms isolated 2014 – 2015

GRAM-POSITIVE ORGANISMS	Staphylococcus aureus (MSSA)	Enterococcus faecalis	Methicillin resistant Staphylococcus spp. (MRSA)	Beta-haemolytic Streptococcus Group A (Streptococcus pyogenes)	Coagulase-negative staphylococci spp. (Staphylococcus)	Staphylococcus aureus (MSSA)	Beta-haemolytic Streptococcus Group A (Streptococcus pyogenes)
Number of isolates	N=158	N=100	N=44	N=37	N=26	N=25	N=21
Amoxicillin	-	100	-	100	-	-	100(21)
Amoxicillin/clavulanic acid	-	-	-	-	-	-	100(21)
Ampicillin	-	100	-	100	-	-	100(21)
Cloxacillin	100	-	0	-	100(26)	0(25)	-
Cefuroxime	-	-	-	100	-	-	100(21)
Cefotaxime	-	-	-	100	-	-	100(21)
Ceftriaxone	-	-	-	100	-	-	100(21)
Gentamicin	92	84(19)	55	-	96(26)	84(25)	-
Levofloxacin	-	87	-	100(29)	-	-	100(21)
Moxifloxacin	99	-	-	-	92(22)	0(23)	-
Erythromycin	94	-	0	95(20)	68(25)	0(24)	100(21)
Clindamycin	96	-	31	95(20)	76(25)	17(24)	100(21)
Trimethoprim/sulfamethoxazole	91	-	51	100(17)	92(26)	92(25)	-
Positronium	-	100	-	-	-	-	-
Fusidic acid	94	-	55	-	92(25)	88(24)	-
Linezolid	100	100	100	-	100(26)	100(25)	-
Nitrofurantoin	100	-	-	-	-	-	-
Rifampicin	98	-	84	-	96(25)	83(24)	-
Teicoplanin	100	100	98	-	100(25)	100(25)	-
Nafcorylin	100	100	100	100(20)	100(25)	100(25)	-
Cefprozil	-	-	-	100	-	-	100(21)
Tetracycline	94	-	-	-	96(23)	95(21)	-

Dash (-) = inappropriate drug or drug not tested; blank = <30 isolated tested; 0 = resistant
Number of isolates indicated in brackets (n) if < 30 isolates were obtained
For Coagulase-negative Staphylococcus spp., Staphylococcus aureus (MSSA) and Beta-haemolytic Streptococcus Group A, less than 30 isolates were obtained
MSSA = Methicillin sensitive Staphylococcus aureus; MRSA = Methicillin resistant Staphylococcus aureus

Table 2 Cumulative antibiogram of gram-negative organisms isolated 2014 – 2015

GRAM-NEGATIVE ORGANISMS	Escherichia coli (urine isolates)	Escherichia coli (non-urine isolates)	Klebsiella spp.	Haemophilus parainfluenzae	Klebsiella pneumoniae	Pseudomonas aeruginosa	Proteus mirabilis	Haemophilus influenzae	Enterobacter cloacae	Acinetobacter spp.	Bacteroides fragilis
Number of isolates	N=212	N=74	N=69	N=53	N=51	N=60	N=40	N=37	N=33	N=31	N=28
Amoxicillin	26	28	0	84	-	60	95	0	-	-	-
Amoxicillin/clavulanic acid	84	68	65	98	54	-	93	100	0	-	-
Ampicillin	26	28	0	84	0	60	95	0	-	-	-
Piperacillin-tazobactam	86	73(22)	-	54	92	96(27)	-	82	68	-	-
Cefoxitin	93	84	67	-	54	-	95	-	0	-	-
Cefuroxime	53	82	67	98	54	-	95	100	0	-	-
Cefotaxime	-	100	54	-	96	100	82	-	-	-	-
Ceftazidime	96	-	-	55	53	100(25)	-	82	42	-	-
Ceftriaxone	95	8(24)	100	54	-	96(28)	100	82	-	-	-
Cefepime	95	4(23)	-	54	93	96(28)	-	85	77	-	-
Doripenem	100	100(23)	-	100	95	100(28)	-	100	75(28)	-	-
Ertapenem	100	100(23)	-	100	-	100(28)	-	100	-	-	-
Imipenem/clastatin	100	100(23)	-	100	87	-	-	100	81	-	-
Meropenem	100	100(23)	-	100	93	100(28)	-	100	77	-	-
Amikacin	100	100(23)	-	97	98	100(28)	-	97	94	-	-
Gentamicin	92	91	64	-	64	92	97	-	91	81	-
Tobramycin	90	90	-	60	97	100(26)	-	91	90	-	-
Siprofloxacin	73	60	65	87	95	98	92	97	77	-	-
Levofloxacin	73	-	66	87	-	-	92	-	-	-	-
Moxifloxacin	-	-	84	-	-	-	92	-	-	-	-
Azithromycin	-	-	27	-	-	-	89	-	-	-	-
Clarithromycin	-	-	27	-	-	-	89	-	-	-	-
Telithromycin	-	-	29	-	-	-	89	-	-	-	-
Colistin	-	-	-	-	-	-	-	-	-	-	-
Trimethoprim/sulfamethoxazole	48	45	49	67	-	77(26)	57	-	-	-	-
Fosfomycin	100	-	-	-	-	-	-	-	-	-	-
Metronidazole	-	-	-	-	-	-	-	-	-	100(28)	-
Nitrofurantoin	97	96	-	-	-	-	-	-	-	-	-
Tigecycline	100	-	-	-	-	-	-	-	-	-	-
Colistin	93	82	67	98	54	100(21)	100	0	-	-	-
Tetracycline	-	-	97	-	-	-	100	-	-	-	-
Penicillin	-	-	-	-	-	-	-	-	-	0(28)	-

Dash (-) = inappropriate drug or drug not tested; blank = <30 isolated tested; 0 = resistant
Number of isolates indicated in brackets (n) if < 30 isolates were obtained

6. Conclusion and Relevance

The sensitivity profile of the prevalent gram-positive- and gram-negative organisms for a private hospital in the Western Cape. Emergence of multi-drug resistant organisms for the geographical area is demonstrated by *Pseudomonas aeruginosa* and *Acinetobacter* spp. which confirm trends of carbapenem resistance. These cumulative antibiograms compiled from local data house important information regarding antimicrobial resistance and susceptibility in order to improve empiric antimicrobial treatment for the geographical area.

7. References

- Sousa, C.P.D. 2003. Pathogenicity mechanisms of prokaryotic cells: an evolutionary view. *Brazilian journal of infectious diseases*, 7(1):23-31.
- Joshi, S. 2010. Hospital antibiogram: A necessity. *Indian journal of medical microbiology*, 28(4):277-280. <http://www.ijmm.org/article.asp?issn=0255-0857;year=2010;volume=28;issue=4;page=277;epage=280;au=Joshi> Date of access: 28 April 2017.
- Hindler, J.F. & Stelling, J. 2007. Analysis and presentation of cumulative antibiograms: a new consensus guideline from the Clinical and Laboratory Standards Institute. *Clinical infectious diseases*, 44(6):867-873.
- NCCLS (National Committee on Clinical Laboratory Standards). 2002. Analysis and presentation of cumulative antimicrobial susceptibility test data; approved guidelines. *NCCLS document M39-A*, 22(8). <http://docs.clinical-laboratory-standards.org/docs/m39-a.html> Date of access: 12 Jun. 2015.



3.4 Chapter summary

In this chapter the results of the study were discussed and presented in the form of a manuscript and poster. Chapter 4 will include conclusions and recommendations for this study together with an assessment of limitations and strengths of the research.

CHAPTER 4: CONCLUSIONS AND RECOMMENDATIONS

4.1 Introduction

This chapter presents the conclusions and recommendations which are drawn regarding the specific objectives provided in Chapter 1 and are based on results obtained from the empirical investigation as well as the literature review. Limitations and strengths of the study are provided and recommendations for further studies are discussed.

The general aim of this study was to provide information using hospital data regarding the prevalence of pathogens in order to develop a facility-specific cumulative antibiogram.

4.2 Conclusions from the study

The study included a literature review and an empirical investigation. Specific research objectives were formulated and conclusions were drawn in order to achieve the general aim of the study. In the subsequent paragraphs the conclusions drawn from the study are tested against the literature review and the results obtained through the empirical investigation.

4.2.1 Conclusions from the literature review

A literature review was conducted and included in Chapter 2 in order to reach specific literature review objectives, as outlined in paragraph 1.3.2 of Chapter 1. The key findings are summarised in subsequent paragraphs.

4.2.1.1 Review antimicrobial agents

Through a literature overview, the main concepts regarding antimicrobial agents were investigated. The principal focus was on the characterisation and classification of antimicrobial agents, such as the mechanism of action, spectrum of activity, adverse effects, and common indications (refer to Chapter 2, section 2.2).

4.2.1.2 Investigate resistance trends of pathogens

This objective was approached through a literature review of the main different resistant mechanisms produced by different bacterial pathogens. Literature indicated that the efficiency of antimicrobials in treating common infections is diminishing due to the emergence of untreatable strains (Laxminarayan *et al.*, 2013:1057). With the increase of antimicrobial use the level and

complexity of resistance mechanisms of pathogens increases (Tenover, 2006:S3). Resistance of pathogens develops through the formation of microbe mutations (refer to Chapter 2, section 2.5). Mechanisms by which bacteria develop multi-drug resistance include trends of using multi-drug efflux pumps which can pump out more than one drug type, and/or through the increase of resistance plasmids or transposons of genes that each code for resistance to a specific agent (Nikaido, 2009:120).

4.2.1.3 Determine the development and use of antibiograms in the hospital setting

This objective was approached via an assessment of the literature on the development and use of antibiograms in a hospital. The CLSI published guidelines for the preparation of cumulative antibiograms in 2002. These guidelines were revised in 2009 and 2014 and include the recommendations for the collection, analysis and presentation of cumulative antimicrobial susceptibility test data. Literature indicated that the main goals of developing a cumulative antibiogram are to guide clinicians in the selection of antimicrobials for empiric treatment and to promote the monitoring of bacterial resistance to antimicrobial agents (Hindler & Stelling, 2007:867; Lautenbach & Nachamkin, 2006:409).

Through a literature review the recommendations of the CLSI for the development and presentation of susceptibility data were stipulated (refer to Chapter 2, section 2.8.2). The final antibiogram should include at least five most frequently isolated organisms for gram-positive and gram-negative organisms. The percentage sensitivity of organisms to antimicrobials should be presented in a tabular form. Literature accentuates the necessity of antibiograms. Antibiograms are indispensable for monitoring resistance trends over time within an institution and comparing susceptibility rates across institutions.

4.2.1.4 Determine empirical treatment suggestions for multi-resistant gram-negative organisms

Through a literature review, empiric treatment suggestions for multi-drug organisms were identified (refer to Chapter 2, section 2.10). Gram-negative organisms of concern include *Acinetobacter baumannii*, ESBL-producing *Escherichia coli*, *Klebsiella pneumoniae* and Enterobacteriaceae; and carbapenemase producing aerobic gram-negative bacilli or *Pseudomonas aeruginosa*. This objective concluded that there are several regimens for treating infections caused by multi-drug resistant organisms. For infections due to ESBL-producing bacteria carbapenems remains the choice of empirical treatment. Research supported the use of combination therapy for infections caused by carbapenem resistant gram-negative bacteria.

Common antibiotics used in combinations include tigecycline, polymyxins, carbapenems, aminoglycosides, fluoroquinolones (ciprofloxacin, levofloxacin), fosfomycin, rifampicin, ampicillin, piperacillin/tazobactam, and tetracyclines (minocycline and doxycycline) (Izadpanah & Khalili, 2015:111).

4.2.2 Conclusions from the empirical study objectives

The empirical investigation was presented in the form of a manuscript and poster presentation (refer to Chapter 3). The objectives as outlined in paragraph 1.3.2 of Chapter 1 were achieved by using local hospital data from two databases, viz. PathProvider® V.1.4.2 and ICNet® Clinical Surveillance Software. The key findings of the empirical investigation are summarised in the following paragraphs:

4.2.2.1 Identification of pathogens isolated more than ten times during the study period in the hospital in order to identify the most prevalent pathogens in each unit of the hospital

Surveillance of pathogens in a hospital according to literature do contribute to improving empiric therapy for infected patients (Bamford, 2011:579). Overall a total of 1424 pathogens were isolated in the hospital of which 63.7% (n = 908) represented gram-negative organisms and 36.24% (n = 516) gram-positive organisms. A Europe one-day prospective point prevalent study (European Prevalence of Infection in Intensive Care II (EPIC II)) found gram-negative organisms more prevalent (62%) than gram-positive organisms (47%). The most frequently isolated organisms in the EPIC II study were *Pseudomonas* spp., *Escherichia coli* and *Klebsiella* spp. among gram-negative organisms and *Staphylococcus aureus* among gram-positive organisms (Vincent *et al.*, 2009:2325-2326). *Escherichia coli* (n = 286), *Staphylococcus aureus* (MSSA) (n = 160) and *Enterococcus faecalis* (n = 101) were the three most frequently isolated organisms identified in the hospital. For the critical care unit of the hospital *Enterococcus faecalis*, *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were the most frequently isolated organisms.

Gram-negative pathogens isolated more than ten times during the study period included *Escherichia coli* (n = 286), *Klebsiella* spp. (n = 69), *Haemophilus parainfluenzae* (n = 63), *Klebsiella pneumoniae* (n = 61), *Pseudomonas aeruginosa* (n = 60), *Proteus mirabilis* (n = 40), *Haemophilus influenzae* (n = 37), *Enterobacter cloacae* (n = 33), *Bacteroides fragilis* (n = 30), *Acinetobacter baumannii* (n = 23), *Serratia marcescens* (n = 17), *Klebsiella oxytoca* (n = 15), *Morganella morganii* (n = 13), *Campylobacter jejuni* (n = 12), *Prevotella bivia* (n = 11), and

Stenotrophomonas maltophilia (n = 11) (refer to manuscript, Table 1). Gram-positive pathogens isolated more than ten times during the study period in the hospital included *Staphylococcus aureus* (MSSA) (n = 160), *Enterococcus faecalis* (n = 101), Beta-haemolytic *Streptococcus* Group B (*Streptococcus agalactiae*) (n = 37), *Staphylococcus aureus* (MRSA) (n = 25), Beta-haemolytic *Streptococcus* Group A (*Streptococcus pyogenes*) (n = 21), methicillin-resistant *Staphylococcus epidermidis* (MRSE) (n = 21), *Mycobacterium tuberculosis* (n = 20), *Streptococcus pneumoniae* (n = 15), and *Staphylococcus epidermidis* (n = 12) (refer to manuscript, Table 2).

A total of 192 pathogens were isolated in the critical CCU, 408 in the medical unit, 288 in the orthopaedic unit and 536 in the surgical unit of the hospital (refer to manuscript, Table 1 and Table 2).

4.2.2.2 Determination of susceptibilities of pathogens isolated 30 times or more in the hospital to antimicrobial agents

During the study pathogens were identified that were isolated 30 times or more in the hospital in order to generate a cumulative antibiogram since susceptibility data of organisms with less than 30 isolates should be interpreted with caution (NCCLS, 2002:10-12). The susceptibilities of these pathogens were determined by using PathProvider[®] V.1.4.1, and ICNet[®] Clinical Surveillance Software. The susceptibility of each pathogen to the antimicrobial agents tested was reported as R=resistant, I=intermediate or S=sensitive (NCCLS, 2002:3-6). Intermediate susceptibility was categorised as resistant. *Streptococcus pneumoniae* and *Viridans streptococci* did not have enough isolates to be included in the antibiogram (refer to Chapter 2, section 2.8.2).

The results of the susceptibility were expressed as percentage (%) sensitivity of the pathogen to the specific antimicrobials (NCCLS, 2002:11). The susceptibility was calculated by summing the number of times the isolate was sensitive to a specific antimicrobial agent divided by the total number of times it was tested against the specific antimicrobial agent. In order to express the value in percentage the quotient was multiplied by 100 (Adorka *et al.*, 2013:1031).

4.2.2.3 Generation of a cumulative antibiogram using the local data of pathogens isolated 30 times or more and their susceptibilities to antimicrobial agents

The results of this study are formulated in a cumulative antibiogram which includes five or more frequently isolated organisms for gram-negative and gram-positive (see manuscript, Table 3 and Table 4). Two years of data (2014 - 2015) were combined since one year of data did not provide enough isolates for the generation of a cumulative antibiogram. Sufficient numbers of *Escherichia coli* were isolated for gram-negative organisms in order to separate urine isolates from non-urine isolates as recommended by the NCCLS (2002:11). In the study *Acinetobacter* spp., methicillin-resistant *Staphylococcus* spp. and coagulase-negative *Staphylococcus* spp. were grouped together as recommended by the CLSI in order to have adequate isolates to be included in the antibiogram (NCCLS, 2002:10-12).

Gram-positive organisms included in the cumulative antibiogram are MSSA (n = 158), *Enterococcus faecalis* (n = 100), methicillin-resistant *Staphylococcus* spp. (n = 44), Beta-haemolytic *Streptococcus* Group B (*Streptococcus agalactiae*) (n = 37), coagulase-negative *Staphylococcus* spp. (n = 26), MRSA (n = 25), and Beta-haemolytic *Streptococcus* Group A (*Streptococcus pyogenes*) (n = 21). Gram-negative organisms included in the cumulative antibiogram are *Escherichia coli* urine isolates (n = 212), *Escherichia coli* non-urine isolates (n = 74), *Klebsiella* spp. (n = 69), *Haemophilus parainfluenzae* (n = 63), *Klebsiella pneumoniae* (n = 61), *Pseudomonas aeruginosa* (n = 60), *Proteus mirabilis* (n = 40), *Haemophilus influenzae* (n = 37), *Enterobacter cloacae* (n = 33), *Acinetobacter* spp. (n = 31), and *Bacteroides fragilis* (n = 28). For the study a footnote was added which stated which organisms included in the antibiogram had fewer than 30 isolates for the study period, as recommended by the CLSI (NCCLS, 2002:10-12).

4.2.2.4 Analysis of the susceptibility of hospital-specific pathogens in order to predict antibiotic combinations that would provide adequate empiric therapy when a multidrug-resistant organism is suspected

The susceptibility results of this study showed that only *Pseudomonas aeruginosa* had no single antimicrobial agent to which an organism was 100% sensitive (refer to manuscript, Table 3). *Pseudomonas aeruginosa* isolated in the study showed a degree of resistance developing against carbapenems. All other organisms demonstrated excellent sensitivity (100%) to antimicrobials. Monotherapy should therefore be recommended rather than combination therapy for the empiric treatment when one of these organisms is suspected. Empiric treatment for this

geographical area should be based on the local susceptibility patterns as demonstrated by the results of the study. Combination empiric therapy is more appropriate according to the results of the study when a Pseudomonal infection is suspected since trends of carbapenem resistance are confirmed. Recommendations for empiric therapy according to the susceptibility data include an aminoglycoside agent (amikacin, gentamycin, tobramycin) with a beta-lactam agent (piperacillin/tazobactam, ceftazidime, and cefepime). Other combinations with high synergy ratios that could be suggested include ceftazidime or piperacillin/tazobactam in combination with tobramycin (Kanj & Kanafani, 2011:254-256).

Combination empiric therapy is also suggested when mixed gram-positive and gram-negative infection are suspected. Recommendations for first-line therapy include an anti-MRSA agent together with a carbapenem; or tigecycline (not for urinary tract infections) together with or without an antipseudomonal agent. Second-line therapy recommendations include an anti-MRSA agent together with piperacillin/tazobactam; or an anti-MRSA agent together with colistin (Kanj & Kanafani, 2011:254). In this study anti-MRSA agents include vancomycin, teicoplanin and linezolid (100% susceptibility). Agents that showed superior antipseudomonal activity in the study included amikacin, gentamycin, tobramycin, doripenem, imipenem/cilastatin, meropenem, cefepime, ceftazidime, piperacillin/tazobactam, ciprofloxacin and levofloxacin.

4.3 Limitations of the study

This research had several limitations and shortcomings, which included:

- Antibigrams do not take patient factors into consideration. These include factors such as previous infection history and antimicrobial usage. Resistance patterns for certain drugs can be influenced by a patient's underlying medical condition and may affect how well an antimicrobial works.
- Timing of the isolate in relation to the admission of the patient to the hospital is not revealed on the antibiogram, in order to determine whether it was community or healthcare acquired infections. Thus making the data not a good reflection of either alone.
- The antibiogram in the study represents the susceptibility data of isolates from various body sites. Resistant patterns may vary for different sites of infection. Possible inclusion of colonisations may be excluded by only documenting sterile body sites.
- System errors or laboratory errors could have influenced results.
- The MIC data were not included on the antibiogram and trends below the resistance threshold were not reflected. Increasing resistance cannot be identified.
- The antibiogram combined susceptibility data across the entire hospital. Normally resistance to antimicrobials is more prevalent in the CCU than in the other units of the hospital.

Resistant patterns for CCU may be masked or susceptibility patterns of the other wards may appear to show more resistance if the CCU data is included.

- Two years of data were required to develop the cumulative antibiogram. Normally annual data are necessary since resistance patterns change over time.

4.4 Strengths of the study

The strengths of the study include awareness of prevalence and susceptibility/resistance patterns of pathogens for a private facility in the Inland Coastal District of the Western Cape. The study showed benefits to the prescribing healthcare provider and to future patients receiving antimicrobial treatment. Data were presented to the prescribers in a poster format and placed on the institution's intranet. The anticipated risks associated with this study were classified as medium risk, therefore the benefits outweighed the risks for this study since a retrospective study design was used.

The anticipated benefits of this study included:

- Increased knowledge about antimicrobial resistance and susceptibility in order to improve empiric antimicrobial treatment for the geographical area.
- Added value to healthcare practices and valuable data for future patients.
- Information obtained can be used to guide future patients' empiric antibiotic treatment to improve their outcome when admitted to the facility.
- The results of this study contributed to Antimicrobial Stewardship in South Africa.

4.5 Recommendations

The study recommends that future studies should be conducted to monitor surveillance on a regular basis and on the incorporation of the MIC values into the antibiogram. The susceptibility data should be incorporated in the antimicrobial stewardship program and identify targets for education. Unit specific antibiograms should be compiled for a more accurate reflection of susceptibility data. Further research should be done on combination antibiograms, cross-resistance trends of organisms and synergistic properties of antimicrobial combinations for this geographical area.

4.6 Chapter summary

This chapter provided a brief summary of the conclusions drawn from specific research objects of both the literature review and empirical study. Also noted in this chapter were the limitations, strengths and recommendations made for future studies.

4.7 Study reflection

This dissertation consisted of four chapters. The introduction of the study was provided in Chapter 1. Chapter 2 provided a literature review on antimicrobial therapy, resistance of pathogens and antibiograms. In Chapter 3 the results of the study were presented in the form of a manuscript and chapter 4 provided the conclusions and recommendations of the study.

REFERENCES

- Adorka, M., Lubbe, M., Serfontein, J., Allen, K. & Kabwebwe, M. 2013. Making antibiotic choices: formula derivation and usage in the rational selection of antibiotics in the empirical treatment of infections. *Tropical journal of pharmaceutical research*, 12(6):1029-1034.
- Ahmed, A., Azim, A., Gurjar, M. & Baronia, A.K. 2014. Current concepts in combination antibiotic therapy for critically ill patients. *Indian journal of critical care medicine*, 18(5):310. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4047693/> Date of access: 15 Nov. 2016.
- Alanis, A.J. 2005. Resistance to antibiotics: are we in the post-antibiotic era? *Archives of medical research*, 36(6):697-705.
- Alavijeh, M.S., Chishty, M., Qaiser, M.Z. & Palmer, A.M. 2005. Drug metabolism and pharmacokinetics, the blood-brain barrier, and central nervous system drug discovery. *The journal of the American Society for Experimental Neurotherapeutics*, 2(4):554-571.
- Alekshun, M.N. & Levy, S.B. 2007. Molecular mechanisms of antibacterial multidrug resistance. *Cell*, 128(6):1037-1050.
- American Thoracic Society and Infectious Diseases Society of America. 2005. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *American journal of respiratory and critical care medicine*, 171(4):388-416.
- Andes, D. & Craig, W.A. 2002. Animal model pharmacokinetics and pharmacodynamics: a critical review. *International journal of antimicrobial agents*, 19(4):261-268.
- Antimicrobial Therapy, Inc. 2016. Sanford guide: antimicrobial Rx. Version 1.0.25. (Mobile application software). <https://play.google.com/store/apps/details?id=com.sanfordguide.amt> Date of access: 13 Feb. 2016.
- Arias, C.A., Contreras, G.A. & Murry, B.E. 2010. Management of multidrug-resistant enterococcal infections. *Clinical microbiology and infection*, 16(6):555-562.

Armahizer, M.J., Kane-Gill, S.L., Smithburger, P.L., Anthes, A.M. & Seybert, A.L. 2012. Comparing drug-drug interaction severity ratings between bedside clinicians and proprietary databases. *International scholarly research notices critical care*, 2013. <http://dx.doi.org/10.5402/2013/347346> Date of access: 7 Feb. 2016.

Ashley, E.S.D., Kaye, K.S., DePestel, D.D. & Hermsen, E.D. 2014. Antimicrobial stewardship: philosophy versus practice. *Clinical infectious diseases*, 59(Suppl. 3):S112-S121.

Asín-Prieto, E., Rodríguez-Gascón, A. & Isla, A. 2015. Applications of the pharmacokinetic/pharmacodynamic (PK/PD) analysis of antimicrobial agents. *Journal of infection and chemotherapy*, 21(5):319-329.

Astellas Pharma Incorporated. 2007. Mycamine[®]. (Package insert). http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021506s009lbl.pdf Date of access: 1 Jan. 2017.

AstraZeneca Pharmaceuticals. 2014. Merrem[®]. (Prescribing information). http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/050706s036lbl.pdf Date of access: 31 Dec. 2016.

B. Braun Medical Incorporated. 2000. Cefazolin. (Package insert). http://www.accessdata.fda.gov/drugsatfda_docs/label/2000/50779lbl.pdf Date of access: 31 Dec. 2016.

B. Braun Medical Incorporated. 2006. Cefepime. (Package insert). <http://www.fda.gov/ohrms/dockets/dockets/06p0461/06p-0461-cp00001-04-attachment-03-vol1.pdf> Date of access: 31 Dec. 2016.

B. Braun Medical Incorporated. 2007a. Cefuroxime. (Package insert). http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/065214s013lbl.pdf Date of access: 31 Dec. 2016.

B. Braun Medical Incorporated. 2007b. Cefotaxime. (Package Insert). http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/050792s002lbl.pdf Date of access: 31 Dec. 2016.

B. Braun Medical Incorporated. 2009. Ceftriaxone. (Package insert).
http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/050796Orig1s011bledt.pdf Date of access: 31 Dec. 2016.

B. Braun Medical Incorporated. 2013. Cefoxitin. (Package insert).
http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/065214s013lbl.pdf Date of access: 31 Dec. 2016.

Bakheet, T.M. & Doig, A.J. 2010. Properties and identification of antibiotic drug targets. *BioMed central bioinformatics*, 11(195).
<http://bmcbioinformatics.biomedcentral.com/articles/10.1186/1471-2105-11-195> Date of access: 9 Jan. 2017.

Bakry, M.A., Hakim, A.S., Nagwa, S. & Zaki, M.S. 2014. Role played by gene factor in initiation of bacterial antibiotic resistance. *Life science journal*, 11(6):154-160.

Balkhy, H.H., Cunningham, G., Chew, F.K., Francis, C., Al Nakhli, D.J., Almuneef, M.A. & Memish, Z.A. 2006. Hospital-and community-acquired infections: a point prevalence and risk factors survey in a tertiary care center in Saudi Arabia. *International journal of infectious diseases*, 10(4):326-333.

Bamford, C., Brink, A., Govender, N., Lewis, D.A., Perovic, O., Botha, M., Harris, B., Keddy, K.H., Gelband, H. & Duse, A.G. 2011. Part V. surveillance activities. *South African medical journal*, 101(8 Part 2):579-582.

Banerjee, A. & Chaudhury, S. 2010. Statistics without tears: Populations and samples. *Industrial psychiatry journal*, 19(1):60-65.

Baorto, E.P. 2016. *Staphylococcus aureus* infection.
<http://emedicine.medscape.com/article/971358-overview> Date of access: 20 Nov. 2016.

Baron, E.J., Miller, J.M., Weinstein, M.P., Richter, S.S., Gilligan, P.H., Thomson, R.B., Bourbeau, P., Carroll, K.C., Kehl, S.C., Dunne, M., Robinson-Dunn, B., Schwartzman, J.D., Chapin, K.C., Snyder, J.W., Forbes, B.A., Patel, R., Rosenblatt, J.E. & Pritt, B.S. 2013. A guide to utilization of the microbiology laboratory for diagnosis of infectious diseases: 2013 recommendations by the Infectious Diseases Society of America (IDSA) and the American Society for Microbiology (ASM). *Clinical infectious diseases*, 57(4):1-100.

Bateman, D.N. & Eddleston, M. 2008. Clinical pharmacology: the basics. *Medicine*, 36(7):339-343.

Bauer, L.A. 2008. Applied clinical pharmacokinetics. 2nd ed. New York, NY: McGraw Hill.

Bayer Limited. 2003a. Ciprobay®. (Package insert).

<http://home.intekom.com/pharm/bayer/ciprobay.html> Date of access: 31 Dec. 2016.

Bayer Limited. 2003b. Avelon®. (Package insert).

<http://home.intekom.com/pharm/bayer/avelon.html> Date of access: 31 Dec. 2016.

Beardsley, J.R., Williamson, J.C., Johnson, J.W., Ohl, C.A., Karchmer, T.B. & Bowton, D.L. 2006. Using local microbiologic data to develop institution-specific guidelines for the treatment of hospital-acquired pneumonia. *Chest journal*, 130(3):787-793.

Beberok, A., Otręba, M., Wrześniok, D. & Buszman, E. 2013. Cytotoxic effect of lomefloxacin in culture of human epidermal melanocytes. *Pharmacological reports*, 65(3):689-699.

Becker, K., Heilmann, C. & Peters, G. 2014. Coagulase-negative staphylococci. *Clinical microbiology reviews*, 27(4):870-926.

Belley, A., Neesham-Grenon, E., Arhin, F.F., McKay, G.A., Parr, T.R. & Moeck, G. 2008. Assessment by time-kill methodology of the synergistic effects of oritavancin in combination with other antimicrobial agents against *Staphylococcus aureus*. *Antimicrobial agents and chemotherapy*, 52(10):3820-3822.

Benet, L.Z. & Zia-Amirhosseini, P. 1995. Basic principles of pharmacokinetics. *Toxicologic pathology*, 23(2):115-123.

Beveridge, T.J. 2001. Use of the Gram stain in microbiology. *Biotechnic & histochemistry*, 76(3):111-118. (Abstract).

Bill, R.L. 2017. Clinical pharmacology and therapeutics for veterinary technicians. 5th ed. St. Louis, Mo: Mosby/Elsevier.

Bittner, E.A., Shank, E., Woodson, L. & Martyn, J.J. 2015. Acute and perioperative care of the burn-injured patient. *The journal of the American Society of Anesthesiologists*, 122(2):448-464.

Blanchet, B., Jullien, V., Vinsonneau, C. & Tod, M. 2008. Influence of burns on pharmacokinetics and pharmacodynamics of drugs used in the care of burn patients. *Clinical pharmacokinetics*, 47(10):635-654.

Blot, S.I., Pea, F. & Lipman, J. 2014. The effect of pathophysiology on pharmacokinetics in the critically ill patient: concepts appraised by the example of antimicrobial agents. *Advanced drug delivery reviews*, 77:3-11.

Bodene Limited. 2006. Gentamycin-Fresenius®. (Package insert).
<http://home.intekom.com/pharm/intramed/gent-fre.html> Date of access: 31 Dec. 2016.

Boehme, M.S., Somsel, P.A. & Downes, F.P. 2010. Systematic review of antibiograms: a national laboratory system approach for improving antimicrobial susceptibility testing practices in Michigan. *Public health reports*, 125(Suppl. 2):63-72.

Boggan, J.C., Navar-Boggan, A.M. & Jhaveri, R. 2012. Pediatric-specific antimicrobial susceptibility data and empiric antibiotic selection. *Pediatrics*, 130(3):e615-e622.

Bollenbach, T., Quan, S., Chait, R. & Kishony, R. 2009. Nonoptimal microbial response to antibiotics underlies suppressive drug interactions. *Cell*, 139(4):707-718.

Boyd, N. & Nailor, M.D. 2011. Combination antibiotic therapy for empiric and definitive treatment of gram-negative infections: Insights from the Society of Infectious Diseases Pharmacists. *Pharmacotherapy: The journal of human pharmacology and drug therapy*, 31(11):1073-1084.

Braden, C.D. 2016. Neutropenia. <http://emedicine.medscape.com/article/204821-overview>
Date of access: 12 Sep. 2016.

Brink, A., Moolman, J., Da Silva, M.C. & Botha, M. 2007. Antimicrobial susceptibility profile of selected bacteraemic pathogens from private institutions in South Africa. *South African medical journal*, 97(4):273-279.

Brink, H., ed. 2011. Fundamentals of research methodology for health care professionals. 2nd ed. Cape Town: Juta.

Bristol-Myers Squibb Limited. 1993. Duracef®. (Package insert).
http://home.intekom.com/pharm/bm_squib/duracef.html Date of access: 31 Dec. 2016.

- Bristol-Myers Squibb Limited. 2001a. Azactam®. (Package insert).
http://home.intekom.com/pharm/bm_squib/azactam.html Date of access: 31 Dec. 2016.
- Bristol-Myers Squibb Limited. 2001b. Amikin®. (Package insert).
http://home.intekom.com/pharm/bm_squib/amikin.html Date of access: 31 Dec. 2016.
- Bristol-Myers Squibb Limited. 2005a. Proze®. (Package insert).
http://home.intekom.com/pharm/bm_squib/proze.html Date of access: 31 Dec. 2016.
- Bristol-Myers Squibb Limited. 2005b. Tequin®. (Package insert).
http://home.intekom.com/pharm/bm_squib/tequin.html Date of access: 31 Dec. 2016.
- Bristol-Myers Squibb Limited. 2005c. Fungi zone®. (Package insert).
http://home.intekom.com/pharm/bm_squib/fungiz-i.html Date of access: 1 Jan. 2017.
- Brouwer, M.C., Tunkel, A.R. & Van de Beek, D. 2010. Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. *Clinical microbiology reviews*, 23(3):467-492.
- Büdingen, F.V., Gonzalez, D., Tucker, A.N. & Derendorf, H. 2014. Relevance of liver failure for anti-infective agents: from pharmacokinetic alterations to dosage adjustments. *Therapeutic advances in infectious disease*, 2(1):17-42.
- Burgess, D.S. 2005. Use of pharmacokinetics and pharmacodynamics to optimize antimicrobial treatment of *Pseudomonas aeruginosa* infections. *Clinical infectious diseases*, 40(Suppl. 2):S99-S104.
- Burke, A. & Cunha, M.D. 2011. Antibiotic essentials. 10th ed. New York, NY: Physicians' Press.
- Bushardt, R.L., Massey, E.B., Simpson, T.W., Ariail, J.C. & Simpson, K.N. 2008. Polypharmacy: misleading, but manageable. *Clinical interventions in aging*, 3(2):383-389.
- Bushra, R., Aslam, N. & Khan, A.Y. 2011. Food-drug interactions. *Oman medical journal*, 26(2):77-83.
- Butler, M.S. & Buss, A.D. 2006. Natural products — the future scaffolds for novel antibiotics? *Biochemical pharmacology*, 71(7):919-929.

Buyck, J.M., Tulkens, P.M. & van Bambeke, F. 2014. Activity of antibiotic combinations towards resistant strains of *Pseudomonas aeruginosa* in a model of infected THP-1 monocytes. *Antimicrobial agents and chemotherapy*, 59(1):258-268.

Calderwood, S.B. 2016a. Beta-lactam antibiotics: Mechanisms of action and resistance and adverse effects. http://hpm.healthsoc.co.za/contents/beta-lactam-antibiotics-mechanisms-of-action-and-resistance-and-adverse-effects?source=search_result&search=beta-lactamase+sensitive+penicillins&selectedTitle=2~150 Date of access: 14 Mar. 2016.

Calderwood, S.B. 2016b. Cephalosporins. <http://hpm.healthsoc.co.za/contents/cephalosporins?source=machineLearning&search=cephalosporins&selectedTitle=1~150§ionRank=1&anchor=H4#H4> Date of access: 22 May 2016.

Cardoso, T., Almeida, M., Friedman, N.D., Aragão, I., Costa-Pereira, A., Sarmento, A.E. & Azevedo, L. 2014. Classification of healthcare-associated infection: a systematic review 10 years after the first proposal. *BioMed central medicine*, 12(40):1-13.

Carlet, J., Collignon, P., Goldmann, D., Goossens, H., Gyssens, I.C., Harbarth, S., Jarlier, V., Levy, S.B., N'Doye, B., Pittet, D., Richtmann, R., Sete, W.H., Van der Meer, J.W.M. & Voss, A. 2011. Society's failure to protect a precious resource: antibiotics. *The lancet*, 378(9788):369-371.

Carlet, J., Jarlier, V., Harbarth, S., Voss, A., Goossens, H. & Pittet, D. 2012. Ready for a world without antibiotics? The penières antibiotic resistance call to action. *Antimicrobial resistance and infection control*, 1(11):1-13. <https://aricjournal.biomedcentral.com/articles/10.1186/2047-2994-1-11>. Date of access: 14 Jan. 2017.

Casadevall, A. & Pirofski, L.A. 2000. Host-pathogen interactions: basic concepts of microbial commensalism, colonization, infection, and disease. *Infection and immunity*, 68(12):6511-6518.

Cassiere, H.A. 1998. Antibiotic therapy in community acquired pneumonia: switch and step down therapy. http://www.medscape.com/viewarticle/715529_4 Date of access: 24 Jan. 2016.

Centers for Disease Control and Prevention. 2017a. CDC/NHSN surveillance definitions for specific types of infections. Atlanta, GA.

Centers for Disease Control and Prevention. 2017b. Evaluation and diagnosis of penicillin allergy for Healthcare professionals. <https://www.cdc.gov/antibiotic-use/community/for-hcp/Penicillin-Allergy.html> Date of access: 6 Feb. 2018.

Chamot, E., El Amari, E.B., Rohner, P. & van Delden, C. 2003. Effectiveness of combination antimicrobial therapy for *Pseudomonas aeruginosa* bacteremia. *Antimicrobial agents and chemotherapy*, 47(9):2756-2764.

Cheng, A., Chuang, Y.C., Sun, H.Y., Sheng, W.H., Yang, C.J., Liao, C.H., Hsueh, P.R., Yang, J.L., Shen, N.J., Wang, J.T., Hung, C.C., Chen, Y.C. & Chang, S.C. 2015. Excess mortality associated with colistin-tigecycline compared with colistin-carbapenem combination therapy for extensively drug-resistant *Acinetobacter baumannii* bacteremia: a multicenter prospective observational study. *Critical care medicine*, 43(6):1194-1204.

Chow, J.W. 2000. Aminoglycoside resistance in enterococci. *Clinical infectious diseases*, 31(2):586-589.

Christoff, J., Tolentino, J., Mawdsley, E., Matushek, S., Pitrak, D. & Weber, S.G. 2010. Optimizing empirical antimicrobial therapy for infection due to gram-negative pathogens in the intensive care unit: utility of a combination antibiogram. *Infection control & hospital epidemiology*, 31(3):256-261.

Cipla-Medpro Limited. 2001. Utin-400[®]. (Package insert). <http://home.intekom.com/pharm/cipla/utin400.html> Date of access: 31 Dec. 2016.

Coates, A.R., Halls, G. & Hu, Y. 2011. Novel classes of antibiotics or more of the same? *British journal of pharmacology*, 163(1):184-194.

Cockeran, M. 2017. Statistical analysis [email]. 22 May 2017.

Coculescu, B.I. 2009. Antimicrobial resistance induced by genetic changes. *Journal of medicine and life*, 2(2):114-123.

Conly, J.M. & Johnston, B.L. 2005. Where are all the new antibiotics? The new antibiotic paradox. *Canadian journal of infectious diseases & medical microbiology*, 16(3):159-160.

Craig, W.A. 2001. Pharmacodynamics of antimicrobials: general concepts and applications. (In Nightingale, C.H., Murakawa, T. & Ambrose, P.G., eds. *Antimicrobial pharmacodynamics in theory and clinical practice*. New York, NY: Marcel Dekker. p. 103-104).

Critchley, I.A. & Karlowsky, J.A. 2004. Optimal use of antibiotic resistance surveillance systems. *Clinical microbiology and infection*, 10(6):502-511.

Cubist Pharmaceuticals Incorporated. 2015. Cubicin®. (Package insert).
http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021572Orig1s048lbletdt.pdf Date of access: 31 Dec. 2016.

Currie, C.J., Berni, E., Jenkins-Jones, S., Poole, C. D., Ouwens, M., Driessen, S., De Voogd, H., Butler, C.C. & Morgan, C.L. 2014. Antibiotic treatment failure in four common infections in UK primary care 1991-2012: longitudinal analysis. *The British medical journal*, 349:g5493.
<http://www.bmj.com/content/bmj/349/bmj.g5493.full.pdf> Date of access: 27 Dec. 2016.

Cyriac, J. M. & James, E. 2014. Switch over from intravenous to oral therapy: a concise overview. *Journal of pharmacology and pharmacotherapeutics*, 5(2):83.
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4008927/> Date of access: 7 Feb. 2016

Daikos, G.L. & Markogiannakis, A. 2011. Carbapenemase-producing *Klebsiella pneumoniae*: (when) might we still consider treating with carbapenems? *Clinical microbiology and infection*, 17(8):1135-1141.

Darley, E.S. & MacGowan, A.P. 2004. Antibiotic treatment of gram-positive bone and joint infections. *Journal of antimicrobial chemotherapy*, 503(6):928-935.

Das, S. & Kataria, V.K. 2010. Bioterrorism: a public health perspective. *Medical journal, Armed Forces India*, 66(3):255-260.

Davey, P.G. & Marwick, C. 2008. Appropriate vs. inappropriate antimicrobial therapy. *Clinical microbiology and infection*, 14(Suppl. 3):S15-S21.

David, M. & Sutton, C.D. 2004. Social research: The basics. London: SAGE.

Davies, J. & Davies, D. 2010. Origins and evolution of antibiotic resistance. *Microbiology and molecular biology reviews*, 74(3):417-433.

De Paepe, P., Belpaire, F.M. & Buylaert, W.A. 2002. Pharmacokinetic and pharmacodynamic considerations when treating patients with sepsis and septic shock. *Clinical pharmacokinetics*, 41(14):1135-1151.

Delattre, I.K., Musuamba, F.T., Verbeeck, R.K., Dugernier, T., Spapen, H., Laterre, P., Wittebole, X., Cumps, J., Taccone, F.S. Vincent, J., Jacobs, F. & Wallemacq, P.E. 2010. Empirical models for dosage optimization of four β -lactams in critically ill septic patients based on therapeutic drug monitoring of amikacin. *Clinical biochemistry*, 43(6):589-598.

Dellinger, R.P., Levy, M.M., Carlet, J.M., Bion, J., Parker, M.M., Jaeschke, R., Reinhart, K., Angus, D.C., Brun-Buisson C., Beale, R., Calandra, T., Dhainaut, J., Gerlach, H., Harvey, M., Marini, J.J., Marshall J., Ranieri, M., Ramsay, G., Sevransky, J., Thompson, B.T., Townsend, S., Vender, J.S., Zimmerman J.L. & Vincent, J. 2008. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Intensive care medicine*, 34(1):17-60.

Dellinger, R.P., Levy, M.M., Rhodes, A., Annane, D., Gerlach, H., Opal, S.M., Sevransky, J.E., Sprung, C.L., Douglas, I.S., Jaeschke, R., Osborn, T.M., Nunnally, M.E., Townsend, S.R., Reinhart, K., Kleinpell, R.M., Angus, D.C., Deutschman, C.S., Machado, F.R., Rubenfeld, G.D., Webb, S., Beale, R.J., Vincent, J. & Moreno, R. 2013. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive care medicine*, 39(2):165-228.

Dellit, T.H., Owens, R.C., McGowan, J.E., Gerding, D.N., Weinstein, R.A., Burke, J.P., Huskins, W.C., Paterson, D.L., Fishman, N.O., Carpenter, C.F., Brennan, P.J., Billeter, M. & Hooton, T.M. 2007. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clinical infectious diseases*, 44(2):159-177.

Deresinski, S. 2007. Principles of antibiotic therapy in severe infections: optimizing the therapeutic approach by use of laboratory and clinical data. *Clinical infectious diseases*, 45(Suppl. 3):S177-S183.

Dictionary.com. 2016a. Age. <http://www.dictionary.com/browse/age> Date of access: 13 Dec. 2016.

Dictionary.com. 2016b. Specimen. <http://www.dictionary.com/browse/specimen> Date of access: 13 Dec. 2016.

Doogue, M.P. & Polasek, T.M. 2011. Drug dosing in renal disease. *Clinical biochemist reviews*, 32(2):69-73.

Dorland's Illustrated Medical Dictionary. 2012. 32nd ed. Philadelphia, PA: Elsevier.

Doron, S. & Davidson, L.E. 2011. Antimicrobial stewardship. *Mayo Clinic proceedings*, 86(11):1113-1123.

Driskell, R.R., Jahoda, C.A., Chuong, C.M., Watt, F. M. & Horsley, V. 2014. Defining dermal adipose tissue. *Experimental dermatology*, 23(9):629-631.

Džidić, S., Šušković, J. & Kos, B. 2008. Antibiotic resistance mechanisms in bacteria: biochemical and genetic aspects. *Food technology and biotechnology*, 46(1):11-21.

El-Halim, H.F.A., Mohamed, G.G., El-Dessouky, M.M. & Mahmoud, W.H. 2011. Ligational behaviour of lomefloxacin drug towards Cr (III), Mn (II), Fe (III), Co (II), Ni (II), Cu (II), Zn (II), Th (IV) and UO₂ (VI) ions: synthesis, structural characterization and biological activity studies. *Spectrochimica acta part A: molecular and biomolecular spectroscopy*, 82(1):8-19.

Ellis, L.B. & Wackett, L.P. 2012. Use of the University of Minnesota biocatalysis/biodegradation database for study of microbial degradation. *Microbial informatics and experimentation*, 2(1):1-10.

Engelkirk, P.G. & Duben-Engelkirk, J.L. 2008. Laboratory diagnosis of infectious diseases: essentials of diagnostic microbiology. Philadelphia, PA: Lippincott Williams & Wilkins.

Engelkirk, P.G., Duben-Engelkirk, J.L. & Burton, G.R.W. 2011. Burton's microbiology for the health sciences. 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins.

Enzler, M.J., Berbari, E. & Osmon, D.R. 2011. Antimicrobial prophylaxis in adults. *Mayo Clinic proceedings*, 86(7):686-701.

Ernst, E.J., Diekema, D.J., BootsMiller, B.J., Vaughn, T., Yankey, J.W., Flach, S.D., Ward, M.M., Franciscusb, C.L.J., Acosta, E., Pfaller, M.A. & Doebbeling, B.N. 2004. Are United States hospitals following national guidelines for the analysis and presentation of cumulative antimicrobial susceptibility data? *Diagnostic microbiology and infectious disease*, 49(2):141-145.

Ezeanolue, E., Ezeanolue, C. & Slavin, K. 2006. What bug, which drug? Optimizing empiric antimicrobial therapy. *Contemporary pediatrics*, 23(3):64-72.

Farlex partner medical dictionary. 2012. Ward. <http://medical-dictionary.thefreedictionary.com/ward> Date of access: 13 Dec. 2016.

Faulkner, C.M., Cox, H.L. & Williamson, J.C. 2005. Unique aspects of antimicrobial use in older adults. *Clinical infectious diseases*, 40(7):997-1004.

Ferguson, C.J. 2009. An effect size primer: a guide for clinicians and researchers. *Professional psychology: research and practice*, 40(5):532-538.

Fernández, L. & Hancock, R.E. 2012. Adaptive and mutational resistance: role of porins and efflux pumps in drug resistance. *Clinical microbiology reviews*, 25(4):661-681.

File, T.M. 2016. Treatment of community-acquired pneumonia in adults who require hospitalization. <http://www.uptodate.com/contents/treatment-of-community-acquired-pneumonia-in-adults-who-require-hospitalization> Date of access: 13 Nov. 2016.

Filho, L.S, Kuti, J.L. & Nicolau, D.P. 2007. Employing pharmacokinetic and pharmacodynamic principles to optimize antimicrobial treatment in the face of emerging resistance. *Brazilian journal of microbiology*, 38(2):183-193.

Fischbach, M.A. 2011. Combination therapies for combating antimicrobial resistance. *Current opinion in microbiology*, 14(5):519-523.

Fishbain, J. & Peleg, A.Y. 2010. Treatment of Acinetobacter infections. *Clinical infectious diseases*, 51(1):79-84.

Fox, B.C., Shenk, G., Peterson, D., Spiegel, C.A. & Maki, D.G. 2008. Choosing more effective antimicrobial combinations for empiric antimicrobial therapy of serious gram-negative rod infections using a dual cross-table antibiogram. *American journal of infection control*, 36(3 Suppl.):S57-S61.

Fraser, S.L. 2015. Enterobacter infections treatment & management. <http://emedicine.medscape.com/article/216845-treatment> Date of access: 5 Oct. 2016.

Fraser, S.L. 2016. Enterococcal infections treatment & management. <http://emedicine.medscape.com/article/216993-treatment> Date of access: 3 Oct. 2016.

Freifeld, A.G., Bow, E.J., Sepkowitz, K.A., Boeckh, M.J., Ito, J.I., Mullen, C.A., Raad, I.I., Rolston, K.V. Young, J.H. & Wingard, J.R. 2011. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clinical infectious diseases*, 52(4):e56-e93.

Gallagher, J.C. & MacDougall, C. 2013. Antibiotics simplified. Burlington, VT: Jones & Bartlett.

García, M.S. 2009. Early antibiotic treatment failure. *International journal of antimicrobial agents*, 34(Suppl. 3):S14-S19.

Gauer, R.L. & Braun, M.M. 2012. Thrombocytopenia. *American family physician*, 85(6):612-622.

Generix International SA Limited. 2005. Taziject®. (Package Insert).

Gilbert, D.N., Chambers, H.F., Eliopoulos, G.M. & Saag, M.S. 2014. The Sanford Guide to Antimicrobial Therapy 2014. 44th ed. Sperryville, VA: Antimicrobial Therapy.

Gilbert, G.L. 2015. Knowing when to stop antibiotic therapy. *The medical journal of Australia*, 202(11):121-122.

GlaxoSmithKline. 2005. Floxapen®. (Package insert).

http://home.intekom.com/pharm/smith_kb/floxapen.html Date of access: 30 Dec. 2016.

GlaxoSmithKline. 2006a. Amoxil®. (Package insert).

http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/050760s11,050761s11,050754s12,050542s25lbl.pdf Date of access: 30 Dec. 2016.

GlaxoSmithKline. 2006b. Augmentin®. (Package insert).

http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/050564s051lbl.pdf Date of access: 30 Dec. 2016.

Goff, D.A. & Rybak, M.J. 2012. Introduction to the special issue on antimicrobial stewardship. *Pharmacotherapy: The journal of human pharmacology and drug therapy*, 32(8):663-664.

Golan, D.E., Tashjian, A.H., Armstrong, E.J. & Armstrong, A.W., eds. 2008. Principles of pharmacology: the pathophysiologic basis of drug therapy. 2nd ed. Baltimore, MD: Lippincott Williams & Wilkins.

Gregory, K.E. & Radovinsky, L. 2012. Research strategies that result in optimal data collection from the patient medical record. *Applied nursing research*, 25(2):108-116.

Griffith, M., Postelnick, M. & Scheetz, M. 2012. Antimicrobial stewardship programs. *Expert review of anti-infective therapy*, 10(1):63-73.

Grohmann, E., Muth, G. & Espinosa, M. 2003. Conjugative plasmid transfer in gram-positive bacteria. *Microbiology and molecular biology reviews*, 67(2): 277-301.

Gurevich, K.G. 2013. Effect of blood protein concentrations on drug-dosing regimes: practical guidance. *Theoretical biology and medical modelling*, 10(20).

<https://tbiomed.biomedcentral.com/articles/10.1186/1742-4682-10-20> Date of access: 5 Jan. 2017.

Gyssens, I.C. 2011. Antibiotic policy. *International journal of antimicrobial agents*, 38(Suppl.):11-20.

Hall, K.K. & Lyman, J.A. 2006. Updated review of blood culture contamination. *Clinical microbiology reviews*, 19(4):788-802.

Hawkyard, C.V. & Koerner, R.J. 2007. The use of erythromycin as a gastrointestinal prokinetic agent in adult critical care: benefits versus risks. *Journal of antimicrobial chemotherapy*, 59(3):347-358.

Heifets, L.B. 1991. Drug susceptibility in the chemotherapy of mycobacterial infections. Boca Raton, FL: CRC press.

Helms, J.B., Kaloyanova, D.V., Strating, J.R., van Hellemond, J.J., Van der Schaar, H.M., Tielens, A.G., Van Kuppeveld, F.J. & Brouwers, J.F. 2015. Targeting of the hydrophobic metabolome by pathogens. *Traffic*, 16(5):439-460.

Heuker, M., Gomes, A., van Dijk, J.M., van Dam, G.M., Friedrich, A.W., Sinha, B. & van Oosten, M. 2016. Preclinical studies and prospective clinical applications for bacteria-targeted imaging: the future is bright. *Clinical and translational imaging*, 4(4):253-264.

Hexal Pharma Limited. 2000a. CEC[®] 500. (Package insert).

<http://home.intekom.com/pharm/hexal/cec-tab.html> Date of access: 31 Dec. 2016.

Hexal Pharma Limited. 2000b. Minot abs[®]. (Package insert).

<http://home.intekom.com/pharm/hexal/minotb50.html> Date of access: 31 Dec. 2016.

Hexal Pharma Limited. 2005. Clindahexa[®]. (Package insert).

<http://home.intekom.com/pharm/hexal/clindhex.html> Date of access: 31 Dec. 2016.

Hickman, R.A., Hughes, D., Cars, T., Malmberg, C. & Cars, O. 2014. Cell-wall-inhibiting antibiotic combinations with activity against multidrug-resistant *Klebsiella pneumoniae* and *Escherichia coli*. *Clinical microbiology and infection*, 20(4):O267-O273.

Hightower, C. & Scott, K. 2012. Infer more, describe less: more powerful survey conclusions through easy inferential tests. *Issues in science and technology librarianship*, 69.

<http://www.istl.org/12-spring/article1.html> Date of access: 16 Dec. 2016.

Hill, J.N., Suda, K.J., Ramanathan, S. & Evans, C.T. 2015. Development of a unit-specific antibiogram and planning for implementation: preimplementation findings. *American journal of infection control*, 43(11):1264-1267.

Hindler, J.F. & Stelling, J. 2007. Analysis and presentation of cumulative antibiograms: a new consensus guideline from the Clinical and Laboratory Standards Institute. *Clinical infectious diseases*, 44(6):867-873.

Hollenbeck, B.L. & Rice, L.B. 2012. Intrinsic and acquired resistance mechanisms in enterococcus. *Virulence*, 3(5):421-569.

Horvat, R.T. 2010. Review of antibiogram preparation and susceptibility testing systems. *Hospital pharmacy*, 45(Suppl. 1):S6-S9.

Hospira Incorporated. 2011. Tobramycin[®]. (Package insert).

http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/063116s010lbl.pdf Date of access: 31 Dec. 2016.

Impilo Drugs Limited. 2003. Meditrim[®]. (Package insert).

<http://home.intekom.com/pharm/xeragen/meditrim.html> Date of access: 31 Dec. 2016.

Infectious Diseases Society of America. 2011. Combating antimicrobial resistance: policy recommendations to save lives. *Clinical infectious diseases*, 52(Suppl. 5):S397-S428.

Izadpanah, M. & Khalili, H. 2015. Antibiotic regimens for treatment of infections due to multidrug-resistant gram-negative pathogens: an evidence-based literature review. *Journal of research in pharmacy practice*, 4(3):105-114.

Jansen Pharmaceutica Limited. 2004. Sporanox[®]. (Package insert).
<http://home.intekom.com/pharm/janssen/sporanox.html> Date of access: 1 Jan. 2017.

Janssen Pharmaceuticals Incorporated. 2013. Nizoral[®]. (Package insert).
https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/018533s040lbl.pdf Date of access: 1 Jan. 2017.

Jin, J.F., Zhu, L.L., Chen, M., Xu, H.M., Wang, H.F., Feng, X.Q., Zhu, X. & Zhou, Q. 2015. The optimal choice of medication administration route regarding intravenous, intramuscular, and subcutaneous injection. *Patient preference and adherence*, 9:923-942.

Jindal, A.K., Pandya, K. & Khan, I.D. 2015. Antimicrobial resistance: a public health challenge. *Medical journal, Armed Forces India*, 71(2):178-181.

Johnson, A.P., Uttley, A.H., Woodford, N. & George, R.C. 1990. Resistance to vancomycin and teicoplanin: an emerging clinical problem. *Clinical microbiology reviews*, 3(3):280-291.

Jones, R.N. 2001. Resistance patterns among nosocomial pathogens: trends over the past few years. *Chest journal*, 119(Suppl. 2):397S-404S.

Joshi, S. 2010. Hospital antibiogram: A necessity. *Indian journal of medical microbiology*, 28(4):277-280.

Joubert, G. & Ehrlich, R., eds. 2012. Epidemiology a research manual for South Africa. 2nd ed. Cape Town: Oxford.

Kalil, A.C., Metersky, M.L., Klompas, M., Muscedere, J., Sweeney, D.A., Palmer, L.B., Napolitano, L.M., O'Grady, N.P., Bartlett, J.G., Carratalà, J., El Solh, A.A., Ewig, S., Fey, P.D., File, T.M., Restrepo, M.I., Roberts, J.A., Waterer, G.W., Cruse, P., Knight, S.L. & Brozek, J.L. 2016. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016: Clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clinical infectious diseases*, 63(5):e61-e111.

Kanafani, Z.A. & Kanji, S.S. 2016. Acinetobacter infection: treatment and prevention. http://hpm.healthsoc.co.za/contents/acinetobacter-infection-treatment-and-prevention?source=search_result&search=multidrug+resistant+organisms&selectedTitle=3%7E150#H699838553 Date of access: 26 Sep. 2016.

Kanj, S.S. & Kanafani, Z.A. 2011. Current concepts in antimicrobial therapy against resistant gram-negative organisms: extended-spectrum β -lactamase-producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae, and multidrug-resistant *Pseudomonas aeruginosa*. *Mayo Clinic proceedings*, 86(3):250-259.

Karlowsky, J.A. & Sahm, D.F. 2002. Antibiotic resistance: is resistance detected by surveillance relevant to predicting resistance in the clinical setting? *Current opinion in pharmacology*, 2(5):487-492.

Kefala, G., Ahn, C., Krupa, M., Esquivies, L., Maslennikov, I., Kwiatkowski, W. & Choe, S. 2010. Structures of the OmpF porin crystallized in the presence of foscholine-12. *Protein science*, 19(5):1117-1125.

Kelkar, D. & Galwankar, S. 2013. State of the globe: antimicrobial stewardship guides rationale use of antimicrobials to enable faster cure and prevent drug resistance. *Journal of global infectious diseases*, 5(2):43-44.

Khan, H.A., Ahmad, A. & Mehboob, R. 2015. Nosocomial infections and their control strategies. *Asian pacific journal of tropical biomedicine*, 5(7):509-514.

Kimberlin, C.L. & Winterstein, A.G. 2008. Validity and reliability of measurement instruments used in research. *American Society of Health-system Pharmacists*, 65(23):2276-2284.

Klugman, K.P. 2003. Implications for antimicrobial prescribing of strategies based on bacterial eradication. *International journal of infectious diseases*, 7(Suppl. 1):S27-S31.

Koenig, S.M. & Truwit, J.D. 2006. Ventilator-associated pneumonia: diagnosis, treatment, and prevention. *Clinical microbiology reviews*, 19(4):637-657.

Kohanski, M.A., Dwyer, D.J. & Collins, J.J. 2010. How antibiotics kill bacteria: from targets to networks. *Nature reviews microbiology*, 8(6):423-435.

Kohanski, M.A., Dwyer, D.J., Hayete, B., Lawrence, C.A. & Collins, J.J. 2007. A common mechanism of cellular death induced by bactericidal antibiotics. *Cell*, 130(5):797-810.

Kollef, M.H. 2006. The intensive care unit as a research laboratory: developing strategies to prevent antimicrobial resistance. *Surgical infections*, 7(2):85-99.

Kristich, C.J., Rice, L.B. & Arias, C.A. 2014. Enterococcal infection - Treatment and antibiotic resistance. (In Gilmore, M.S., Clewell, D.B., Ike, Y. & Shankar, N., eds. Enterococci: From commensals to leading causes of drug resistant infection. Boston: Massachusetts Eye and Ear Infirmary. p. 123-184).

Kumar, A., Roberts, D., Wood, K.E., Light, B., Parrillo, J.E., Sharma, S., Suppes, R., Feinstein, D., Zanotti, S., Taiberg, L., Gurka, D., Kumar, A. & Cheang, M. 2006. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Critical care medicine*, 34(6):1589-1596.

Kuster, S.P., Ruef, C., Zbinden, R., Gottschalk, J., Ledergerber, B., Neuber, L. & Weber, R. 2008. Stratification of cumulative antibiograms in hospitals for hospital unit, specimen type, isolate sequence and duration of hospital stay. *Journal of antimicrobial chemotherapy*, 62(6):1451-1461.

Labuschagne, Q., Schellack, N., Gous, A., Bronkhorst, E., Schellack, G., Van Tonder, L., Truter, A, Smith, C., Lancaster, R. & Kolman, S. 2016. Colistin: adult and paediatric guideline for South Africa, 2016. *Southern African journal of infectious diseases*, 31(1):3-7.

Laupland, K.B. & Church, D.L. 2014. Population-based epidemiology and microbiology of community-onset bloodstream infections. *Clinical microbiology reviews*, 27(4):647-664.

Lautenbach, E. & Nachamkin, I. 2006. Analysis and presentation of cumulative antimicrobial susceptibility data (antibiograms): substantial variability across medical centers in the United States. *Infection control*, 27(04):409-412.

Laxminarayan, R., Duse, A., Wattal, C., Zaidi, A. K., Wertheim, H. F.I., Sumpradit, N., Vlieghe, E., Hara, G.L., Gould, I.M., Goossens, H, Greko, C., So, A.D., Bigdeli, M., Tomson, G., Woodhouse, W., Ombaka, E., Peralta, A.Q., Qamar, F.N., Mir, F., Kariuki, S., Bhutta, Z.A., Coates, A., Bergstrom, R., Wright, G.D., Brown, E.D. & Cars, O. 2013. Antibiotic resistance: the need for global solutions. *The lancet infectious diseases*, 13(12):1057-1098.

Leekha, S., Terrell, C.L. & Edson, R.S. 2011. General principles of antimicrobial therapy. *Mayo Clinic proceedings*, 86(2):156-167.

Lehman, L.S. 2007. Which antibiotics are time-or concentration-dependent?

<http://www.medscape.com/viewarticle/563444> Date of access: 26 Dec. 2016.

Leite, G.C., Oliveira, M.S., Perdigão-Neto, L.V., Rocha, C.K.D., Guimarães, T., Rizek, C., Levin, A.S. & Costa, S.F. 2016. Antimicrobial combinations against pan-resistant *Acinetobacter baumannii* isolates with different resistance mechanisms. *Plos one*, 11(3):e0151270.

<http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0151270> Date of access: 23 Apr. 2017.

Lennon Limited. 1996. Len V.K[®] tablets. (Package insert).

<http://home.intekom.com/pharm/lennon/len-vk.html> Date of access: 29 Dec. 2016.

Levison, M.E. & Levison, J.H. 2009. Pharmacokinetics and pharmacodynamics of antibacterial agents. *Infectious Disease Clinics of North America*, 23(4):791-815.

Llewelyn, M.J., Fitzpatrick, J.M., Darwin, E., Tonkin-Crine, S., Gorton, C., Paul, J., Peto, T.E.A., Yardley, L., Hopkins, S. & Walker, A.S. 2017. The antibiotic course has had its day. *British medical journal*, 358(j3418):1-5.

Lewis, D.A., Gumede, L.Y.E., van der Hoven, L.A., de Gita, G.N., de Kock, E.J., de Lange, T., Maseko, V., Kekana, V., Smuts, F.P. & Perovic, O. 2013. Antimicrobial susceptibility of organisms causing community-acquired urinary tract infections in Gauteng Province, South Africa. *South African medical journal*, 103(6):377-381.

Ligon, B.L. 2004. Sir Alexander Fleming: Scottish researcher who discovered penicillin. *Seminars in pediatric infectious diseases*, 15(1):58-64.

Lim, S.M. & Webb, S.A.R. 2005. Nosocomial bacterial infections in Intensive Care Units. I: Organisms and mechanisms of antibiotic resistance. *Anaesthesia*, 60(9):887-902.

Lin, J.H. & Lu, A.Y. 1997. Role of pharmacokinetics and metabolism in drug discovery and development. *Pharmacological reviews*, 49(4):403-449.

Lindblad, C.I., Hanlon, J.T., Gross, C.R., Sloane, R.J., Pieper, C.F., Hajjar, E.R., Ruby, C.M., Schmader, K.E. & Panel, M.C. 2006. Clinically important drug-disease interactions and their prevalence in older adults. *Clinical therapeutics*, 28(8):1133-1143.

Lister, P.D., Wolter, D.J. & Hanson, N.D. 2009. Antibacterial-resistant *Pseudomonas aeruginosa*: clinical impact and complex regulation of chromosomally encoded resistance mechanisms. *Clinical microbiology reviews*, 22(4):582-610.

Litha Pharma. 2012. Litha Piperacillin Co. (Package insert).
<http://home.intekom.com/pharm/litha/l-pipco.html> Date of access: 30 Dec. 2016.

Liu, C., Bayer, A., Cosgrove, S.E., Daum, R.S., Fridkin, S.K., Gorwitz, R.J., Kaplan, S.L., Karchmer, A.W., Levine, D.P., Murray, B.E., Rybak, M.J., Talan, D.A. & Chambers, H.F. 2011. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clinical infectious diseases*, 52(3):e18-e55.

Llarrull, L.I., Fisher, J.F. & Mobashery, S. 2009. Molecular basis and phenotype of methicillin resistance in *Staphylococcus aureus* and insights into new β -lactams that meet the challenge. *Antimicrobial agents and chemotherapy*, 53(10):4051-4063.

Lobritz, M.A., Belenky, P., Porter, C.B., Gutierrez, A., Yang, J.H., Schwarz, E.G., Dwyerh, D.J., Khalila, A.S. & Collins, J.J. 2015. Antibiotic efficacy is linked to bacterial cellular respiration. *Proceedings of the National Academy of Sciences*, 112(27):8173-8180.

Lode, H. 2005. Management of serious nosocomial bacterial infections: do current therapeutic options meet the need? *Clinical microbiology and infection*, 11(10):778-787.

Lueangarun, S. & Leelarasamee, A. 2012. Impact of inappropriate empiric antimicrobial therapy on mortality of septic patients with bacteremia: a retrospective study. *Interdisciplinary perspectives on infectious diseases*, 2012:1-13.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3419419/pdf/IPID2012-765205.pdf> Date of access: 18 Aug. 2017.

MacDougall, C. & Polk, R.E. 2005. Antimicrobial stewardship programs in health care systems. *Clinical microbiology reviews*, 18(4):638-656.

Macedo, R.S., Onita, J.H., Wille, M.P. & Furtado, G.H.C. 2013. Pharmacokinetics and pharmacodynamics of antimicrobial drugs in intensive care unit patients. *Shock*, 39(Suppl. 1):24-28.

- Madappa, T. 2016. *Escherichia coli* infections treatment & management. <http://emedicine.medscape.com/article/217485-treatment> Date of access: 5 Oct. 2016.
- Magill, S.S., Edwards, J.R., Bamberg, W., Beldavs, Z.G., Dumyati, G., Kainer, M.A., Lynfield, R., Maloney, M., McAllister-Hollod, L., Nadle, J., Ray, S.M., Thompson, D.L., Wilson, L.E. & Fridkin, S.K. 2014. Multistate point-prevalence survey of health care–associated infections. *The New England journal of medicine*, 370(13):1198-1208.
- Mandell, L A., Ball, P. & Tillotson, G. 2001. Antimicrobial safety and tolerability: differences and dilemmas. *Clinical infectious diseases*, 32(Suppl. 1):S72-S79.
- Mandell, L.A., Wunderink, R.G., Anzueto, A., Bartlett, J.G., Campbell, G.D., Dean, N.C., Dowell, S.F., File, T.M., Musher, D.M., Niederman, M.S., Torres, A. & Whitney, C.G. 2007. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clinical infectious diseases*, 44(Suppl. 2):S27-S72.
- Mann, C.J. 2003. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. *Emergency medicine journal*, 20(1):54-60.
- Maree, K., ed. 2014. First steps in research. 2nd ed. Pretoria: Van Schaik.
- Marquet, K., Liesenborgs, A., Bergs, J., Vleugels, A. & Claes, N. 2015. Incidence and outcome of inappropriate in-hospital empiric antibiotics for severe infection: a systematic review and meta-analysis. *Critical care*, 19(1):1-12.
- Martínez, J.L. & Baquero, F. 2002. Interactions among strategies associated with bacterial infection: pathogenicity, epidemicity, and antibiotic resistance. *Clinical microbiology reviews*, 15(4):647-679.
- Masterton, R. 2008. The importance and future of antimicrobial surveillance studies. *Clinical infectious diseases*, 47(Suppl. 1):S21-S31.
- Maurin, M. & Gyuranecz, M. 2016. Tularaemia: clinical aspects in Europe. *The lancet infectious diseases*, 16(1):113-124.
- Maurin, M. & Raoult, D. 2001. Use of aminoglycosides in treatment of infections due to intracellular bacteria. *Antimicrobial agents and chemotherapy*, 45(11):2977-2986.

- McDanel, J.S., Perencevich, E.N., Diekema, D.J., Herwaldt, L.A., Smith, T.C., Chrischilles, E.A., Dawson, J.D., Jiang, L., Goto, M. & Schweizer, M.L. 2015. Comparative effectiveness of beta-lactams versus vancomycin for treatment of methicillin-susceptible *Staphylococcus aureus* bloodstream infections among 122 hospitals. *Clinical infectious diseases*, 61(3):361-367.
- McHugh, M.L. 2013. The chi-square test of independence. *Biochemia medica*, 23(2):143-149.
- McKenzie, C. 2011. Antibiotic dosing in critical illness. *Journal of antimicrobial chemotherapy*, 66(Suppl. 2):ii25-ii31.
- McKinnon, P.S. & Davis, S.L. 2004. Pharmacokinetic and pharmacodynamic issues in the treatment of bacterial infectious diseases. *European journal of clinical microbiology and infectious diseases*, 23(4):271-288.
- McKinnon, P.S. & Yu, V.L. 2004. Pharmacologic considerations in antimicrobial therapy, with emphasis on pharmacokinetics and pharmacodynamics: reviews for the practicing clinician. *European journal of clinical microbiology & infectious diseases*, 23(4):231-232.
- Medical Dictionary for the Health Professions and Nursing. 2012. Bacterial infection. <http://medical-dictionary.thefreedictionary.com/bacterial+infection> Date of access: 28 Jan. 2016.
- Medscape. 2016a. Penicillin VK (Rx). <http://reference.medscape.com/drug/pen-vee-k-penicillin-v-penicillin-vk-342483> Date of access: 8 Jan. 2016.
- Medscape. 2016aa. Tigecycline (Rx). <http://reference.medscape.com/drug/tygacil-tigecycline-342527> Date of access: 9 Jul. 2016.
- Medscape. 2016ab. Gatifloxacin (Rx). <http://reference.medscape.com/drug/zymar-zymaxid-gatifloxacin-ophthalmic-343570> Date of access: 18 Nov. 2016.
- Medscape. 2016b. Penicillin G aqueous (Rx). <http://reference.medscape.com/drug/pfizerpen-penicillin-g-potassium-penicillin-g-aqueous-342482> Date of access: 9 Jan. 2016.
- Medscape. 2016ba. Azithromycin (Rx). <http://reference.medscape.com/drug/zithromax-zmax-azithromycin-342523> Date of access: 10 Jul. 2016.
- Medscape. 2016c. Amoxicillin (Rx). <http://reference.medscape.com/drug/amoxil-moxatag-amoxicillin-342473> Date of access: 10 Jan. 2016.

Medscape. 2016ca. Clarithromycin (Rx). <http://reference.medscape.com/drug/biaxin-xl-clarithromycin-342524> Date of access: 10 Jul. 2016.

Medscape. 2016d. Amoxicillin/clavulanate (Rx). <http://reference.medscape.com/drug/augmentin-amoxicillin-clavulanate-342474> Date of access: 10 Jan. 2016.

Medscape. 2016da. Telithromycin (Rx). <http://reference.medscape.com/drug/ketek-telithromycin-342572> Date of access: 10 Jul. 2016.

Medscape. 2016e. Ampicillin (Rx). <http://reference.medscape.com/drug/ampi-omnipen-ampicillin-342475> Date of access: 10 Jan. 2016.

Medscape. 2016ea. Linezolid (Rx). <http://reference.medscape.com/drug/zyvox-linezolid-342574> Date of access: 10 Jul. 2016.

Medscape. 2016f. Piperacillin/tazobactam (Rx). <http://reference.medscape.com/drug/zosyn-piperacillin-tazobactam-342485> Date of access: 14 Feb. 2016.

Medscape. 2016fa. Metronidazole (Rx). <http://reference.medscape.com/drug/flagyl-metronidazole-342566> Date of access: 10 Jul. 2016.

Medscape. 2016g. Cefazolin (Rx). <http://reference.medscape.com/drug/kefzol-cefazolin-342492> Date of access: 4 Apr. 2016.

Medscape. 2016ga. Nitrofurantoin (Rx). <http://reference.medscape.com/drug/macrobid-macrodantin-nitrofurantoin-342567> Date of access: 17 Jul. 2016.

Medscape. 2016h. Cefixime (Rx). <http://reference.medscape.com/drug/suprax-cefixime-342503> Date of access: 26 Jun. 2016.

Medscape. 2016ha. Fosfomycin (Rx). <http://reference.medscape.com/drug/monurol-fosfomycin-342560> Date of access: 17 Jul. 2016

Medscape. 2016i. Cefotaxime (Rx). <http://reference.medscape.com/drug/claforan-cefotaxime-342506> Date of access: 26 Jun. 2016.

Medscape. 2016ia. Daptomycin (Rx). <http://reference.medscape.com/drug/cubicin-daptomycin-342576> Date of access: 17 Jul. 2016

Medscape. 2016j. Ceftazidime (Rx). <http://reference.medscape.com/drug/fortaz-tazicef-ceftazidime-342507> Date of access: 26 Jun. 2016.

Medscape. 2016ja. Trimethoprim/sulfamethoxazole (Rx). <http://reference.medscape.com/drug/bactrim-trimethoprim-sulfamethoxazole-342543> Date of access: 17 Jul. 2016.

Medscape. 2016k. Ceftriaxone (Rx). <http://reference.medscape.com/drug/rocephin-ceftriaxone-342510> Date of access: 26 Jun. 2016.

Medscape. 2016ka. Dapsone (Rx). <http://reference.medscape.com/drug/dapsone-342559> Date of access: 17 Jul. 2016.

Medscape. 2016l. Cefpodoxime (Rx). <http://reference.medscape.com/drug/vantin-cefpodoxime-342498> Date of access: 26 Jun. 2016.

Medscape. 2016la. Clindamycin (Rx). <http://reference.medscape.com/drug/cleocin-clindesse-clindamycin-342558> Date of access: 20 Jul. 2016.

Medscape. 2016m. Cefepime (Rx). <http://reference.medscape.com/drug/maxipime-cefepime-342511> Date of access: 28 Jun. 2016.

Medscape. 2016ma. Colistin (Rx). <http://reference.medscape.com/drug/colistimethate-sodium-coly-mycin-m-colistin-342578> Date of access: 21 Jul. 2016.

Medscape. 2016n. Cefpirome (Rx). <http://reference.medscape.com/drug/cefpirome-342512> Date of access: 29 Jun. 2016.

Medscape. 2016na. Amphotericin B phospholipid complex (Rx). <http://reference.medscape.com/drug/abelcet-amphoterin-b-phospholipid-complex-999575#0> Date of access: 2 Sep. 2016.

Medscape. 2016o. Imipenem/cilastatin (Rx). <http://reference.medscape.com/drug/primaxin-imipenem-cilastatin-342562> Date of access: 1 Jul. 2016.

Medscape. 2016oa. Ketoconazole (Rx). <http://reference.medscape.com/drug/nizoral-ketoconazole-342592> Date of access: 2 Sep. 2016.

Medscape. 2016p. Meropenem (Rx). <http://reference.medscape.com/drug/merrem-iv-meropenem-342565> Date of access: 2 Jul. 2016.

Medscape. 2016pa. Fluconazole (Rx). <http://reference.medscape.com/drug/diflucan-fluconazole-342587> Date of access: 2 Sep. 2016.

Medscape. 2016q. Aztreonam (Rx). <http://reference.medscape.com/drug/azactam-aztreonam-342553> Date of access: 2 Jul. 2016.

Medscape. 2016qa. Itraconazole (Rx). <http://reference.medscape.com/drug/sporanox-omnel-itraconazole-342591> Date of access: 2 Sep. 2016.

Medscape. 2016r. Vancomycin (Rx). <http://reference.medscape.com/drug/vancocin-vancomycin-342573> Date of access: 3 Jul. 2016.

Medscape. 2016ra. Voriconazole (Rx). <http://reference.medscape.com/drug/vfend-voriconazole-342598> Date of access: 2 Sep. 2016.

Medscape. 2016s. Levofloxacin (Rx). <http://reference.medscape.com/drug/levaquin-levofloxacin-systemic-levofloxacin-342532> Date of access: 3 Jul. 2016.

Medscape. 2016sa. Caspofungin (Rx). <http://reference.medscape.com/drug/cancidas-caspofungin-342584> Date of access: 2 Sep. 2016.

Medscape. 2016t. Moxifloxacin (Rx). <http://reference.medscape.com/drug/avelox-moxifloxacin-systemic-moxifloxacin-342537> Date of access: 4 Jul. 2016.

Medscape. 2016ta. Micafungin (Rx). <http://reference.medscape.com/drug/mycamine-micafungin-342585> Date of access: 2 Sep. 2016.

Medscape. 2016u. Gemifloxacin (Rx). <http://reference.medscape.com/drug/factive-gemifloxacin-342529> Date of access: 4 Jul. 2016.

Medscape. 2016ua. Anidulafungin (Rx). <http://reference.medscape.com/drug/ecalta-eraxis-anidulafungin-342599> Date of access: 2 Sep. 2016.

Medscape. 2016v. Tobramycin (Rx). <http://reference.medscape.com/drug/nebcin-injection-tobramycin-342521> Date of access: 9 Jul. 2016.

Medscape. 2016va. Revamping (Rx). <http://reference.medscape.com/drug/rifadin-rimactane-rifampin-342570> Date of access: 2 Sep. 2016.

Medscape. 2016w. Amikacin (Rx). <http://reference.medscape.com/drug/amikin-amikacin-342516> Date of access: 9 Jul. 2016.

Medscape. 2016wa. Isoniazid (Rx). <http://reference.medscape.com/drug/isoniazid-342564> Date of access: 2 Sep. 2016.

Medscape. 2016x. Streptomycin (Rx). <http://reference.medscape.com/drug/streptomycin-342682> Date of access: 9 Jul. 2016.

Medscape. 2016xa. Ceftaroline (Rx). <http://reference.medscape.com/drug/teflaro-ceftaroline-999606> Date of access: 17 Nov. 2016.

Medscape. 2016y. Doxycycline (Rx). <http://reference.medscape.com/drug/vibramycin-monodox-doxycycline-342548> Date of access: 9 Jul. 2016.

Medscape. 2016ya. Gentamycin (Rx). <http://reference.medscape.com/drug/gentak-garamycin-gentamicin-342517> Date of access: 18 Nov. 2016.

Medscape. 2016z. Minocycline (Rx). <http://reference.medscape.com/drug/dynacin-minocin-minocycline-342549> Date of access: 9 Jul. 2016.

Medscape. 2016za. Norfloxacin (Rx). <http://reference.medscape.com/drug/noroxin-norfloxacin-systemic-342535> Date of access: 18 Nov. 2016.

Meghani, S.H., Buck, H.G., Dickson, V.V., Hammer, M.J., Rabelo-Silva, E.R., Clark, R. & Naylor, M.D. 2013. The conceptualization and measurement of comorbidity: a review of the interprofessional discourse. *Nursing research and practice*, 2013:1-10.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3800641/> Date of access: 24 Feb. 2016.

Merck & Co Incorporated. 2005. Cancidas®. (Package insert).

http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/21227s015lbl.pdf Date of access: 1 Dec. 2017.

Merck & Co Incorporated. 2013. Invanz®. (Prescribing information).

http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021337s041lbl.pdf Date of access: 31 Dec. 2016.

Merck & Co. Incorporated. 2016. Primaxin[®]. (Prescribing information).
http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/050587s074lbl.pdf Date of access:
31 Dec. 2016.

Merck Limited. 1992. Fixime[®]. (Package insert).
<http://home.intekom.com/pharm/merckp/fixime.html> Date of access: 31 Dec. 2016

Mermel, L.A., Allon, M., Bouza, E., Craven, D.E., Flynn, P., O'Grady, N.P., Raad, I.I., Rijnders, B.J.A., Sherertz, R.J. & Warren, D.K. 2009. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clinical infectious diseases*, 49(1):1-45.

Merriam-Webster's Medical Dictionary. 2015c. Comorbid. <http://www.merriam-webster.com/dictionary/comorbid> Date of access: 24 Jan. 2016.

Merriam-Webster's Medical Dictionary. 2015d. Lethal. <http://www.merriam-webster.com/dictionary/lethal>. Date of access: 31 Jan. 2016.

Merriam-Webster's Medical Dictionary. 2016a. Prokaryote. <http://www.merriam-webster.com/dictionary/prokaryote> Date of access: 27 Sep. 2016.

Merriam-Webster's Medical Dictionary. 2017. Sensitivity. <https://www.merriam-webster.com/dictionary/sensitivity#medicalDictionary> Date of access: 24 Feb. 2017.

Merriam-Webster's Medical Dictionary. 2015a. Antibiotics. <http://www.merriam-webster.com/medical/antibiotics> Date of access: 13 Aug. 2015.

Merriam-Webster's Medical Dictionary. 2015b. Pathogen. <http://www.merriam-webster.com/medical/pathogen> Date of access: 13 Aug. 2015.

Merriam-Webster's Medical Dictionary. 2016b. Frequency. <https://www.merriam-webster.com/dictionary/frequency#medicalDictionary> Date of access: 16 Dec. 2016.

Mertz, D., Koller, M., Haller, P., Lampert, M.L., Plagge, H., Hug, B., Koch, G., Battegay, M., Flückiger, U. & Bassetti, S. 2009. Outcomes of early switching from intravenous to oral antibiotics on medical wards. *Journal of antimicrobial chemotherapy*, 64(1):188-199.

Mettler, J., Simcock, M., Sendi, P., Widmer, A.F., Bingisser, R., Battegay, M., Fluckiger, U. & Bassetti, S. 2007. Empirical use of antibiotics and adjustment of empirical antibiotic therapies in a university hospital: a prospective observational study. *BioMed central infectious diseases*, 7(1). <http://bmcinfectdis.biomedcentral.com/articles/10.1186/1471-2334-7-21> Date of access: 10 Sep. 2016.

Mizuta, M., Linkin, D.R., Nachamkin, I., Fishman, N.O., Weiner, M.G., Sheridan, A. & Lautenbach, E. 2006. Identification of optimal combinations for empirical dual antimicrobial therapy of *Pseudomonas aeruginosa* infection: potential role of a combination antibiogram. *Infection control and hospital epidemiology*, 27(4):413-415.

Moehring, R.W., Hazen, K.C., Hawkins, M.R., Drew, R.H., Sexton, D.J. & Anderson, D.J. 2015. Challenges in preparation of cumulative antibiogram reports for community hospitals. *Journal of clinical microbiology*, 53(9):2977-2982.

Mosby's Dictionary of Medicine, Nursing & Health Professions. 2006. 7th ed. St. Louis, MO: Mosby/Elsevier.

Mosby's Drug Reference for Health Professions. 2014. 5th ed. St. Louis, MO: Mosby/Elsevier.

Mouton, J.W., Ambrose, P.G., Canton, R., Drusano, G.L., Harbarth, S., MacGowan, A., Theuretzbacher, U. & Turnidge, J. 2011. Conserving antibiotics for the future: new ways to use old and new drugs from a pharmacokinetic and pharmacodynamic perspective. *Drug resistance updates*, 14(2):107-117.

Mouton, J.W., Dudley, M.N., Cars, O., Derendorf, H. & Drusano, G.L. 2005. Standardization of pharmacokinetic/pharmacodynamic (PK/PD) terminology for anti-infective drugs: an update. *Journal of antimicrobial chemotherapy*, 55(5):601-607.

Mueller, M., de la Peña, A. & Derendorf, H. 2004. Issues in pharmacokinetics and pharmacodynamics of anti-infective agents: kill curves versus MIC. *Antimicrobial agents and chemotherapy*, 48(2):369-377.

Müller, M., eds. 2010. Clinical pharmacology: current topics and case studies. 2nd ed. New York, NY: Springer.

Muñoz-López, M. & García-Pérez, J.L. 2010. DNA transposons: nature and applications in genomics. *Current genomics*, 11(2):115-128.

Munoz-Price, L.S. 2017. Extended-spectrum beta-lactamases.

<http://www.uptodate.com/contents/extended-spectrum-beta-lactamases> Date of access: 21 March. 2017.

Murray, P.R., Rosenthal, K.S. & Pfaller, M.A. 2015. Medical microbiology. 8th ed. Philadelphia, PA: Elsevier.

Naber, K.G. 2002. Lomefloxacin versus ciprofloxacin in the treatment of chronic bacterial prostatitis. *International journal of antimicrobial agents*, 20(1):18-27.

NCCLS (National Committee on Clinical Laboratory Standards). 2002. Analysis and presentation of cumulative antimicrobial susceptibility test data; approved guidelines. *NCCLS document M39-A*, 22(8):1-30. <http://docslide.us/documents/m39-a.html> Date of access: 12 Jun. 2015.

Nebeker, J.R., Barach, P. & Samore, M.H. 2004. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. *Annals of internal medicine*, 140(10):795-801.

Nigo, M., Munita, J.M., Arias, C.A. & Murray, B.E. 2014. What's new in the treatment of Enterococcal Endocarditis? *Current infectious disease reports*, 16(10):1-10.

Nikaido, H. 2009. Multidrug resistance in bacteria. *Annual review of biochemistry*, 78(1):119-146.

Nix, D.E., Matthias, K.R. & Ferguson, E.C. 2004. Effect of ertapenem protein binding on killing of bacteria. *Antimicrobial agents and chemotherapy*, 48(9):3419-3424.

Onwuamaegbu, M.E., Belcher, R.A. & Soare, C. 2005. Cell wall-deficient bacteria as a cause of infections: a review of the clinical significance. *Journal of international medical research*, 33(1):1-20.

Otto, M. 2013. Community-associated MRSA: what makes them special? *International journal of medical microbiology*, 303(6):324-330.

Pakyz, A.L. 2007. The utility of hospital antibiograms as tools for guiding empiric therapy and tracking resistance: insights from the Society of Infectious Diseases Pharmacists. *Pharmacotherapy: The journal of human pharmacology and drug therapy*, 27(9):1306-1312.

Parija, S.C. 2014. Textbook of microbiology & immunology. Haryana: Elsevier Health Sciences.

Pasquale, T.R. & Tan, J.S. 2005. Nonantimicrobial effects of antibacterial agents. *Clinical infectious diseases*, 40(1):127-135.

Paterson, D.L. 2008. Impact of antibiotic resistance in gram-negative bacilli on empirical and definitive antibiotic therapy. *Clinical infectious diseases*, 47(Suppl. 1):S14-S20.

Pathcare. 2007. Microbiology. <http://www.pathcare.co.za/pages/pathcare-microbiology.html> Date of access: 13 Aug. 2015.

Peeling, R.W., Smith, P.G. & Bossuyt, P.M. 2010. A guide for diagnostic evaluations. *Nature reviews microbiology*, 8:S2-S6.
http://www.nature.com/nrmicro/journal/v8/n12_suppl/full/nrmicro1522.html Date of access: 14 Jan. 2017.

Perez-Jorge, E.V. & Burdette, S.D. 2014. Antibiotic therapy for positive blood cultures. <http://www.antimicrobe.org/new/e38rev2.asp> Date of access: 10 Sep. 2016.

Peterson, L.R. 2008. Currently available antimicrobial agents and their potential for use as monotherapy. *Clinical microbiology and infection*, 14(Suppl. 6):30-45.

Pfizer Incorporated. 2000. Zithromax[®]. (Package insert).
http://www.accessdata.fda.gov/drugsatfda_docs/label/2001/50733s5lbl.pdf Date of access: 31 Dec. 2016.

Pfizer Incorporated. 2007. Unasyn[®]. (Package insert).
http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/050608s029lbl.pdf Date of access: 30 Dec. 2016.

Pfizer Incorporated. 2008. Zyvox[®]. (Package insert).
http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021130s016,021131s013,021132s014lbl.pdf Date of access: 31 Dec. 2016.

Pfizer Incorporated. 2011. Diflucan[®]. (Package insert).
http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/019949s051lbl.pdf Date of access: 1 Jan. 2017.

- Pfizer Incorporated. 2012. Eraxis[®]. (Package insert).
http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021632s011lbl.pdf Date of access: 1 Jan. 2017.
- Pfizer Incorporated. 2015. Vfend[®]. (Package insert).
<http://labeling.pfizer.com/ShowLabeling.aspx?id=618> Date of access: 1 Jan. 2017.
- Pharmacare Limited. 1999. Cloxin[®]. (Package insert).
<http://home.intekom.com/pharm/lennon/cloxin-i.html> Date of access: 30 Dec. 2016.
- Pharmacare Limited. 2000a. Trichazole[®]. (Package insert).
<http://home.intekom.com/pharm/lennon/trichazl.html> Date of access: 31 Dec. 2016.
- Pharmacare Limited. 2000b. Lennon-Dapsone[®]. (Package insert).
<http://home.intekom.com/pharm/lennon/dapsone.html> Date of access: 31 Dec. 2016.
- Pharmacare Limited. 2001. Maxaquin[®]. (Package insert).
<http://home.intekom.com/pharm/lennon/maxaquin.html> Date of access: 31 Dec. 2016.
- Pharmacare Limited. 2004. Purmycin[®]. (Package insert).
<http://home.intekom.com/pharm/lennon/purmycn.html> Date of access: 31 Dec. 2016.
- Pharmacare Limited. 2008. Aspen Levofloxacin[®]. (Package insert).
<http://home.intekom.com/pharm/aspen-p/a-levofl.html> Date of access: 31 Dec. 2016.
- Pharmacare Limited. 2014. Factive[®]. (Package insert).
<http://home.intekom.com/pharm/aspen-p/factive.html> Date of access: 31 Dec. 2016.
- Pirofski, L.A. & Casadevall, A. 2012. Q&A: What is a pathogen? A question that begs the point. *BioMed Central biology*, 10(1):6. <http://bmcbiol.biomedcentral.com/articles/10.1186/1741-7007-10-6> Date of access: 24 Feb. 2017.
- Pommerville, J. 2012. Alcamo's fundamentals of microbiology: body systems. Burlington: Jones & Bartlett.
- Powers, J.H. 2004. Antimicrobial drug development – the past, the present, and the future. *Clinical microbiology and infection*, 10(Suppl. 4):23-31.

- Prado, C.A.N. 2016. Pneumococcal infections medication.
<http://emedicine.medscape.com/article/225811-medication#1> Date of access: 4 Oct. 2016.
- Quatromed Limited. 2000. Noritet®. (Package insert).
<http://home.intekom.com/pharm/quatrom/noritet.html> Date of access: 31 Dec. 2016.
- Qureshi, S. 2015. Klebsiella infections treatment & management.
<http://emedicine.medscape.com/article/219907-treatment> Date of access: 5 Oct. 2016.
- Ranbaxy Limited. 2003. Cepodem®. (Package insert).
<http://home.intekom.com/pharm/ranbaxy/cephodem.html> Date of access: 31 Dec. 2016.
- Ranbaxy Limited. 2005. Ranceph®. (Package insert).
<http://home.intekom.com/pharm/ranbaxy/ranceph.html>. Date of access: 31 Dec. 2016.
- Ranbaxy Limited. 2007. Klarithran®. (Package insert).
<http://home.intekom.com/pharm/ranbaxy/klarithr.html>. Date of access: 31 Dec. 2016.
- Randhawa, V., Sarwar, S., Walker, S., Elligsen, M., Palmay, L. & Daneman, N. 2014. Weighted-incidence syndromic combination antibiograms to guide empiric treatment of critical care infections: a retrospective cohort study. *Critical care*, 18(3):1-10.
- Rayner, C. & Munckhof, W.J. 2005. Antibiotics currently used in the treatment of infections caused by *Staphylococcus aureus*. *Internal medicine journal*, 35(Suppl. 2):S3-S16.
- Relman, D.A. & Falkow, S. 2014. Basic principles in the diagnosis and management of infectious diseases. (In Bennett, J.E., Dolin, R. & Blaser, M.J., eds. *Principles and practice of infectious diseases* (Vol. 1). 8th ed. Philadelphia, PA: Elsevier. p. 1-25).
- Roberts, J.A., Joynt, G.M., Choi, G.Y., Gomersall, C.D. & Lipman, J. 2012. How to optimise antimicrobial prescriptions in the intensive care unit: principles of individualised dosing using pharmacokinetics and pharmacodynamics. *International journal of antimicrobial agents*, 39(3):187-192.
- Rodloff, A., Bauer, T., Ewig, S., Kujath, P. & Müller, E. 2008. Susceptible, intermediate, and resistant — the Intensity of antibiotic action. *Deutsches ärzteblatt international*, 105(39):657-662.

Rodrigues, A.T., Stahlschmidt, R., Granja, S., Falcão, A.L.E., Moriel, P. & Mazzola, P.G. 2015. Clinical relevancy and risks of potential drug–drug interactions in intensive therapy. *Saudi pharmaceutical journal*, 23(4):366-370.

Rogers, G.B., Hoffman, L.R. & Döring, G. 2011. Novel concepts in evaluating antimicrobial therapy for bacterial lung infections in patients with cystic fibrosis. *Journal of cystic fibrosis*, 10(6):387-400.

Rossiter, D., ed. 2010. South African medicines formulary. 9th ed. Cape Town: Health and Medical Publishing Group of the South African Medical Association.

Rossolini, G.M. & Thaller, M.C. 2010. Coping with antibiotic resistance: contributions from genomics. *Genome medicine*, 2(15):1-5.

Roussel Laboratories Limited. 1994. Targocid®. (Package insert).
<http://home.intekom.com/pharm/roussel/targocid.html> Date of access: 31 Dec. 2016.

Sahoo, S., Haraldsdóttir, H.S., Fleming, R.M. & Thiele, I. 2015. Modeling the effects of commonly used drugs on human metabolism. *Federation of European Biochemical Societies journal*, 282(2):297-317.

Sakoulas, G., Moise, P.A., Casapao, A.M., Nonejuie, P., Olson, J., Okumura, C.Y., Rybak, M.J., Kullar, R., Dhand, A., Rose, W.E., Goff, D.A., Bressler, A.M., Lee, Y., Pogliano, J., Johns, S., Kaatz, G.W., Ebright, J.R. & Nizet, V. 2014. Antimicrobial salvage therapy for persistent staphylococcal bacteremia using daptomycin plus ceftaroline. *Clinical therapeutics*, 36(10):1317-1333.

Sandoz. 2012. Penicillin G Sodium for Injection. (Package insert).
http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/065068s013lbl.pdf Date of access: 29 Dec. 2016.

Sanofi-Aventis. 2007. Ketek®. (Package insert).
http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021144s012lbl.pdf Date of access: 31 Dec. 2016.

Sanofi-Aventis. 2013. Rifadin®. (Package insert). <http://products.sanofi.us/rifadin/rifadin.pdf>
Date of access: 1 Jan. 2017.

- Scheinfeld, N.S. 2015. Intravenous-to-oral switch therapy. <http://emedicine.medscape.com/article/237521-overview> Date of access: 26. Jan. 2016.
- Schmidt, S., Röck, K., Sahre, M., Burkhardt, O., Brunner, M., Lobmeyer, M.T. & Derendorf, H. 2008. Effect of protein binding on the pharmacological activity of highly bound antibiotics. *Antimicrobial agents and chemotherapy*, 52(11):3994-4000.
- Sefton, A.M. 2002. Mechanisms of antimicrobial resistance. *Drugs*, 62(4):557-566.
- Septimus, E.J. 2012. Optimizing dosing strategies: the key to antimicrobial stewardship. <http://www.medscape.org/viewarticle/767071> Date of access: 26 Dec. 2016.
- Sethi, M.L. 2002. Antiviral agents and protease inhibitors. (In David, A.W. & Thomas, L.L., eds. Foye's principles of medicinal chemistry. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins. p. 925-980).
- Shaikh, S., Fatima, J., Shakil, S., Rizvi, S.M.D. & Kamal, M.A. 2015. Antibiotic resistance and extended spectrum beta-lactamases: types, epidemiology and treatment. *Saudi journal of biological sciences*, 22(1):90-101.
- Sharma, M., Chauhan, G., Kwarkwal, H. & Varma, A. 2009. Medically important members of family Enterobacteriaceae: identification techniques. (In Chauhan, A.K. & Varma, A., eds. A textbook of molecular biotechnology. New Delhi: I.K. International Pvt. p. 1169-1180).
- Shionogi & Co. Limited. 2009. Doribax®. (Prescribing information). http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022106s002s005lbl.pdf Date of access: 31 Dec. 2016.
- Silhavy, T.J., Kahne, D. & Walker, S. 2010. The bacterial cell envelope. *Cold spring harbor perspectives in biology*, 2(5):1-16.
- Silva, F., Lourenço, O., Queiroz, J.A. & Domingues, F.C. 2011. Bacteriostatic versus bactericidal activity of ciprofloxacin in *Escherichia coli* assessed by flow cytometry using a novel far-red dye. *The journal of antibiotics*, 64(4):321-325.
- Singh, A., Bhat, T.K. & Sharma, O.P. 2011. Clinical biochemistry of hepatotoxicity. *Journal of clinical toxicology*, S4(001):1-19.
- Sivagnanam, S. & Deleu, D. 2002. Red man syndrome. *Critical care*, 7(2):119-121.

Smith, L.H. 2012. Torsade de pointes, prolonged QT intervals, and patients with cancer. *Clinical journal of oncology nursing*, 16(2):125-128.

Smith, W. 2013. Medications: Adverse drug reactions: Allergy? Side-effect? Intolerance? *Australian family physician*, 42(1&2):12-16.

Smith, R.P., Baltch, A.L., Michelsen, P.B., Ritz, W.J. & Alteri, R. 2003. Use of the microbial growth curve in postantibiotic effect studies of *Legionella pneumophila*. *Antimicrobial agents and chemotherapy*, 47(3):1081-1087.

SmithKline Beecham Pharmaceuticals Limited. 1991. Furadantin®. (Package insert). http://home.intekom.com/pharm/smith_kb/furadant.html Date of access: 31 Dec. 2016.

So, A.D. & Shah, T.A. 2014. New business models for antibiotic innovation. *Uppsala journal of medical sciences*, 119(2):176-180.

Soares, G.M.S., Figueiredo, L.C., Faveri, M., Cortelli, S.C., Duarte, P.M. & Feres, M. 2012. Mechanisms of action of systemic antibiotics used in periodontal treatment and mechanisms of bacterial resistance to these drugs. *Journal of applied oral science*, 20(3):295-309.

Song, J.H. 2003. Introduction: the goals of antimicrobial therapy. *International journal of infectious diseases*, 7(Suppl. 1):S1-S4.

Sousa, C.P.D. 2003. Pathogenicity mechanisms of prokaryotic cells: an evolutionary view. *Brazilian journal of infectious diseases*, 7(1):23-31.

South Africa. 2004. National Health Act, 2004 (Act no. 61 of 2003). (Proclamation no. 869). *Government gazette*, 26595:25-26, 23 Jul.

Spellberg, B., Powers, J.H., Brass, E.P., Miller, L.G. & Edwards, J.E. 2004. Trends in antimicrobial drug development: implications for the future. *Clinical infectious diseases*, 38(9):1279-1286.

Sriratanaviriyakul, N., Nguyen, L.P., Henderson, M.C. & Albertson, T.E. 2014. Drug reaction with eosinophilia and systemic symptoms syndrome (DRESS) syndrome associated with azithromycin presenting like septic shock: a case report. *Journal of medical case reports*, 8(1):332. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4196465/pdf/1752-1947-8-332.pdf> Date of access: 26 Dec. 2016.

- Stein, C.R., Weber, D.J. & Kelley, M. 2003. Using hospital antibiogram data to assess regional pneumococcal resistance to antibiotics. *Emerging infectious diseases*, 9(2):211-216.
- Street, T. 2014. Antimicrobial susceptibility. <http://emedicine.medscape.com/article/2103786-overview> Date of access: 12 Jan. 2016.
- Sydnor, E.R. & Perl, T.M. 2011. Hospital epidemiology and infection control in acute-care settings. *Clinical microbiology reviews*, 24(1):141-173.
- Szumilas, M. 2010. Explaining Odds ratios. *Journal of the Canadian Academy of Child and Adolescent Psychiatry*, 19(3):227-229.
- Tamma, P.D., Cosgrove, S.E. & Maragakis, L.L. 2012. Combination therapy for treatment of infections with gram-negative bacteria. *Clinical microbiology reviews*, 25(3):450-470.
- Tängdén, T. 2014. Combination antibiotic therapy for multidrug-resistant Gram-negative bacteria. *Uppsala journal of medical sciences*, 119(2):149-153.
- Tay Pharmaceuticals Limited. 2011. Colistin®. (Package insert). <http://tajpharma.com/colistin/Colistin-Colistimethate%20sodium%20for%20injection%20and%20inhalation.pdf> Date of access: 31 Dec. 2016.
- Tenover, F.C. 2001. Development and spread of bacterial resistance to antimicrobial agents: an overview. *Clinical infectious diseases*, 33(Suppl. 3):S108-S115.
- Tenover, F.C. 2006. Mechanisms of antimicrobial resistance in bacteria. *The American journal of medicine*, 119(6 Suppl. 1):S3-S10.
- Ternent, L., Dyson, R.J., Krachler, A.M. & Jabbari, S. 2015. Bacterial fitness shapes the population dynamics of antibiotic-resistant and-susceptible bacteria in a model of combined antibiotic and anti-virulence treatment. *Journal of theoretical biology*, 372:1-11.
- The Free Dictionary. 2016a. Genera. <http://www.thefreedictionary.com/genera> Date of access: 27 Sep. 2016.
- The Free Dictionary. 2016b. Thrombocytopenia. <http://medical-dictionary.thefreedictionary.com/blood> Date of access: 27 Sep. 2016.

The Free Dictionary. 2017a. Prevalence. <http://www.thefreedictionary.com/prevalence> Date of access: 14 Sep. 2017.

The Free Dictionary. 2017b. Specimen. <http://medical-dictionary.thefreedictionary.com/specimen> Date of access: 14 Sep. 2017.

The Free Dictionary. 2018a. Inpatient. <https://www.thefreedictionary.com/inpatient> Date of access: 2 Feb. 2018.

Thiese, M.S. 2014. Observational and interventional study design types; an overview. *Biochemia medica*, 24(2):199-210.

Thompson, R.L. & Wright, A.J. 1998. General principles of antimicrobial therapy. *Mayo Clinic proceedings*, 73(10):995-1006.

Tille, P. 2014. Bailey & Scott's diagnostic microbiology. 13th ed. St. Louis, Mo: Elsevier.

Ting, Y.W. & Miles, D. 2002. Developing a web-based tool using hospital-specific cumulative antibiogram data. *Hospital pharmacy*, 37(11):1190-1195.

Tiwari, V.K. 2012. Burn wound: how it differs from other wounds? *Indian journal of plastic surgery*, 45(2):364. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3495387/> Date of access: 17 Nov. 2016.

Tseng, Y.J., Wu, J.H., Ping, X.O., Lin, H.C., Chen, Y.Y., Shang, R.J., Chen, M.Y., Lai, F. & Chen, Y.C. 2012. A web-based multidrug-resistant organisms surveillance and outbreak detection system with rule-based classification and clustering. *Journal of medical internet research*, 14(5):e131. <http://doi.org/10.2196/jmir.2056> Date of access: 15 Jan. 2016.

Tsering, D.C., Das, S., Adhiakari, L., Pal, R. & Singh, T.S. 2009. Extended spectrum beta-lactamase detection in gram-negative bacilli of nosocomial origin. *Journal of global infectious diseases*, 1(2):87. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2840957/> Date of access: 19 Nov. 2016.

Tunkel, A.R., Hartman, B.J., Kaplan, S.L., Kaufman, B.A., Roos, K.L., Scheld, W.M. & Whitley, R.J. 2004. Practice guidelines for the management of bacterial meningitis. *Clinical infectious diseases*, 39(9):1267-1284.

Udy, A.A., Roberts, J.A. & Lipman, J. 2013. Clinical implications of antibiotic pharmacokinetic principles in the critically ill. *Intensive care medicine*, 39(12):2070-2082.

UpToDate. 2016a. Penicillin V potassium (oral): drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/penicillin-v-potassium-oral-drug-information?source=search_result&search=phenoxymethylpenicillin&selectedTitle=1~35 Date of access: 6 Feb. 2016.

UpToDate. 2016aa. Doripenem: drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/doripenem-drug-information?source=search_result&search=doripenem&selectedTitle=1%7E22 Date of access: 2 Jul. 2016.

UpToDate. 2016ab. Clindamycin (systemic): drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/clindamycin-systemic-drug-information?source=search_result&search=clindamycin&selectedTitle=1%7E148#F8008044 Date of access: 20 Jul. 2016.

UpToDate. 2016b. Penicillin G (parenteral): drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/penicillin-g-parenteral-drug-information?source=search_result&search=benzylpenicillin&selectedTitle=1~112 Date of access: 14 Feb. 2016.

UpToDate. 2016ba. Aztreonam (systemic): drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/aztreonam-systemic-drug-information?source=search_result&search=aztreonam&selectedTitle=1%7E61#F29768899 Date of access: 2 Jul. 2016.

UpToDate. 2016bb. Colistin (colistinmethate): drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/colistin-colistimethate-drug-information?source=search_result&search=colistin&selectedTitle=1%7E59 Date of access: 21 Jul. 2016.

UpToDate. 2016c. Amoxicillin: drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/amoxicillin-drug-information?source=search_result&search=amoxicillin&selectedTitle=1~150 Date of access: 14 Feb. 2016.

UpToDate. 2016ca. Vancomycin: drug information Lexicomp.
http://hpm.healthsc.co.za/contents/vancomycin-drug-information?source=search_result&search=vancomycin&selectedTitle=1%7E150 Date of access: 3 Jul. 2016.

UpToDate. 2016cb. Amphotericin B (conventional): drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/amphotericin-b-conventional-drug-information?source=search_result&search=amphotericin+b+adult&selectedTitle=4%7E150#F134707 Date of access: 2 Sep. 2016.

UpToDate. 2016d. Amoxicillin and clavulanate: drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/amoxicillin-and-clavulanate-drug-information?source=search_result&search=amoxicillin+clavulanate&selectedTitle=1~134 Date of access: 14 Feb. 2016.

UpToDate. 2016da. Teicoplanin: international drug information (concise) Lexicomp.
http://hpm.healthsoc.co.za/contents/teicoplanin-international-drug-information-concise?source=search_result&search=teicoplanin&selectedTitle=1%7E19#F1980200 Date of access: 3 Jul. 2016.

UpToDate. 2016db. Liposomal amphotericin B: drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/liposomal-amphotericin-b-drug-information?source=search_result&search=amphotericin+b+adult&selectedTitle=5%7E150#F134868 Date of access: 2 Sep. 2016.

UpToDate. 2016e. Ampicillin: drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/ampicillin-drug-information?source=search_result&search=ampicillin&selectedTitle=1~150 Date of access: 14 Feb. 2016.

UpToDate. 2016ea. Ciprofloxacin (systemic): drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/ciprofloxacin-systemic-drug-information?source=search_result&search=ciprofloxacin+adult&selectedTitle=1%7E150 Date of access: 3 Jul. 2016.

UpToDate. 2016eb. Ketoconazole (systemic): drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/ketoconazole-systemic-drug-information?source=search_result&search=ketoconazole&selectedTitle=1%7E148 Date of access: 2 Sep. 2016.

UpToDate. 2016f. Piperacillin and tazobactam sodium: drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/piperacillin-and-tazobactam-sodium-drug-information?source=search_result&search=piperacillin+tazobactam+adult&selectedTitle=1~81
Date of access: 14 Feb. 2016.

UpToDate. 2016fa. Levofloxacin (systemic): drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/levofloxacin-systemic-drug-information?source=search_result&search=levofloxacin&selectedTitle=1%7E143 Date of access: 3 Jul. 2016.

UpToDate. 2016fb. Fluconazole: drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/fluconazole-drug-information?source=search_result&search=fluconazole&selectedTitle=1%7E150 Date of access: 2 Sep. 2016.

UpToDate. 2016g. Cloxacillin: drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/cloxacillin-drug-information?source=search_result&search=cloxacillin+adult&selectedTitle=1~15#F153887
Date of access: 14 Feb. 2015.

UpToDate. 2016ga. Moxifloxacin (systemic): drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/moxifloxacin-systemic-drug-information?source=search_result&search=moxifloxacin&selectedTitle=1%7E92 Date of access: 4 Jul. 2016.

UpToDate. 2016gb. Itraconazole: drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/itraconazole-drug-information?source=search_result&search=itraconazole+drug+information&selectedTitle=1%7E150 Date of access: 2 Sep. 2016.

UpToDate. 2016h. Flucloxacillin: international drug information (concise).
http://hpm.healthsoc.co.za/contents/flucloxacillin-international-drug-information-concise?source=search_result&search=flucloxacillin+adult&selectedTitle=1~12 Date of access: 14 Feb. 2016.

UpToDate. 2016ha. Gemifloxacin: drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/gemifloxacin-drug-information?source=search_result&search=gemifloxacin&selectedTitle=1%7E18#F175794
Date of access: 4 Jul. 2016.

UpToDate. 2016hb. Voriconazole: drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/voriconazole-drug-information?source=search_result&search=voriconazole+adult&selectedTitle=1%7E150 Date of access: 2 Sep. 2016.

UpToDate. 2016i. Cefazolin: drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/cefazolin-drug-information?source=search_result&search=cefazolin+adult&selectedTitle=1~112 Date of access: 4 Apr. 2016.

UpToDate. 2016ia. Gentamycin: drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/gentamicin-systemic-drug-information?source=search_result&search=gentamicin&selectedTitle=1%7E145#F8107118
Date of access: 9 Jul. 2016.

UpToDate. 2016ib. Caspofungin: drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/caspofungin-drug-information?source=search_result&search=caspofungin+adult&selectedTitle=1%7E50#F146770 Date of access: 2 Sep. 2016.

UpToDate. 2016j. Cephalexin: drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/cephalexin-drug-information?source=search_result&search=cephalexin&selectedTitle=1%7E83 Date of access: 27 May 2016.

UpToDate. 2016ja. Tobramycin (systemic): drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/tobramycin-systemic-drug-information?source=search_result&search=tobramycin&selectedTitle=1%7E103#F45031135
Date of access: 9 Jul. 2016.

UpToDate. 2016jb. Micafungin: drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/micafungin-drug-information?source=search_result&search=micafungin&selectedTitle=1%7E41 Date of access:
2 Sep. 2016.

UpToDate. 2016k. Cefadroxil: drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/cefadroxil-drug-information?source=search_result&search=cefadroxil&selectedTitle=1%7E17 Date of access:
27 May 2016.

UpToDate. 2016ka. Amikacin: drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/amikacin-drug-information?source=search_result&search=amikacin&selectedTitle=1%7E102 Date of access:
9 Jul. 2016.

UpToDate. 2016kb. Anidulafungin: drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/anidulafungin-drug-information?source=search_result&search=anidulafungin&selectedTitle=1%7E30#F2649588
Date of access: 2 Sep. 2016.

UpToDate. 2016l. Cefaclor: drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/cefaclor-drug-information?source=search_result&search=cefaclor&selectedTitle=1%7E15#F146877 Date of
access: 28 May 2016.

UpToDate. 2016la. Streptomycin: drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/streptomycin-drug-information?source=search_result&search=streptomycin&selectedTitle=1%7E100 Date of
access: 9 Jul. 2016.

UpToDate. 2016lb. Revamping (rifampicin): drug information Lexicomp.

http://hpm.healthsoc.co.za/contents/rifampin-rifampicin-drug-information?source=search_result&search=rifampicin+adult&selectedTitle=1%7E150 Date of access: 2 Sep. 2016.

UpToDate. 2016m. Cefoxitin: drug information Lexicomp.

http://hpm.healthsoc.co.za/contents/cefoxitin-drug-information?source=search_result&search=cefoxitin&selectedTitle=1%7E63 Date of access: 28 May 2016.

UpToDate. 2016ma. Doxycycline: drug information Lexicomp.

http://hpm.healthsoc.co.za/contents/doxycycline-drug-information?source=search_result&search=doxycycline&selectedTitle=1%7E150#F163304 Date of access: 9 Jul. 2016.

UpToDate. 2016mb. Isoniazid: drug information Lexicomp.

http://hpm.healthsoc.co.za/contents/isoniazid-drug-information?source=search_result&search=isoniazid+adult&selectedTitle=1%7E150#F184759 Date of access: 2 Sep. 2016.

UpToDate. 2016n. Cefuroxime: drug information Lexicomp.

http://hpm.healthsoc.co.za/contents/cefuroxime-drug-information?source=search_result&search=cefuroxime&selectedTitle=1%7E75 Date of access: 28 May 2016.

UpToDate. 2016na. Minocycline: drug information Lexicomp.

http://hpm.healthsoc.co.za/contents/minocycline-drug-information?source=search_result&search=minocycline&selectedTitle=1%7E146 Date of access: 9 Jul. 2016.

UpToDate. 2016o. Cefprozil: drug information Lexicomp.

http://hpm.healthsoc.co.za/contents/cefprozil-drug-information?source=search_result&search=cefprozil&selectedTitle=1%7E12 Date of access: 28 May 2016.

UpToDate. 2016oa. Tigecycline: drug information Lexicomp.

[http://hpm.healthsoc.co.za/contents/tigecycline-drug-](http://hpm.healthsoc.co.za/contents/tigecycline-drug-information?source=search_result&search=tigecycline&selectedTitle=1%7E37)

[information?source=search_result&search=tigecycline&selectedTitle=1%7E37](http://hpm.healthsoc.co.za/contents/tigecycline-drug-information?source=search_result&search=tigecycline&selectedTitle=1%7E37) Date of access: 7 July 2016.

UpToDate. 2016p. Cefixime: drug information Lexicomp.

[http://hpm.healthsoc.co.za/contents/cefixime-drug-](http://hpm.healthsoc.co.za/contents/cefixime-drug-information?source=search_result&search=cefixime&selectedTitle=1%7E34)

[information?source=search_result&search=cefixime&selectedTitle=1%7E34](http://hpm.healthsoc.co.za/contents/cefixime-drug-information?source=search_result&search=cefixime&selectedTitle=1%7E34) Date of access: 28 Jun. 2016.

UpToDate. 2016pa. Erythromycin (systemic): drug information Lexicomp.

[http://hpm.healthsoc.co.za/contents/erythromycin-systemic-drug-](http://hpm.healthsoc.co.za/contents/erythromycin-systemic-drug-information?source=search_result&search=erythromycin&selectedTitle=1%7E145#F8086260)

[information?source=search_result&search=erythromycin&selectedTitle=1%7E145#F8086260](http://hpm.healthsoc.co.za/contents/erythromycin-systemic-drug-information?source=search_result&search=erythromycin&selectedTitle=1%7E145#F8086260) Date of access: 10 Jul. 2016.

UpToDate. 2016q. Cefotaxime: drug information Lexicomp.

[http://hpm.healthsoc.co.za/contents/cefotaxime-drug-](http://hpm.healthsoc.co.za/contents/cefotaxime-drug-information?source=search_result&search=cefotaxime&selectedTitle=1%7E115#F147475)

[information?source=search_result&search=cefotaxime&selectedTitle=1%7E115#F147475](http://hpm.healthsoc.co.za/contents/cefotaxime-drug-information?source=search_result&search=cefotaxime&selectedTitle=1%7E115#F147475) Date of access: 28 Jun. 2016.

UpToDate. 2016qa. Telithromycin: drug information Lexicomp.

[http://hpm.healthsoc.co.za/contents/telithromycin-drug-](http://hpm.healthsoc.co.za/contents/telithromycin-drug-information?source=search_result&search=telithromycin&selectedTitle=1%7E60#F225034)

[information?source=search_result&search=telithromycin&selectedTitle=1%7E60#F225034](http://hpm.healthsoc.co.za/contents/telithromycin-drug-information?source=search_result&search=telithromycin&selectedTitle=1%7E60#F225034) Date of access: 10 Jul. 2016.

UpToDate. 2016r. Ceftazidime: drug information Lexicomp.

[http://hpm.healthsoc.co.za/contents/ceftazidime-drug-](http://hpm.healthsoc.co.za/contents/ceftazidime-drug-information?source=search_result&search=ceftazidime&selectedTitle=1%7E105)

[information?source=search_result&search=ceftazidime&selectedTitle=1%7E105](http://hpm.healthsoc.co.za/contents/ceftazidime-drug-information?source=search_result&search=ceftazidime&selectedTitle=1%7E105) Date of access: 28 Jun. 2016.

UpToDate. 2016ra. Clarithromycin: drug information Lexicomp.

[http://hpm.healthsoc.co.za/contents/clarithromycin-drug-](http://hpm.healthsoc.co.za/contents/clarithromycin-drug-information?source=search_result&search=clarithromycin&selectedTitle=1%7E150#F152348)

[information?source=search_result&search=clarithromycin&selectedTitle=1%7E150#F152348](http://hpm.healthsoc.co.za/contents/clarithromycin-drug-information?source=search_result&search=clarithromycin&selectedTitle=1%7E150#F152348) Date of access: 10 Jul. 2016.

UpToDate. 2016s. Ceftriaxone: drug information Lexicomp.

[http://hpm.healthsoc.co.za/contents/ceftriaxone-drug-](http://hpm.healthsoc.co.za/contents/ceftriaxone-drug-information?source=search_result&search=ceftriaxone&selectedTitle=1%7E150#F148178)

[information?source=search_result&search=ceftriaxone&selectedTitle=1%7E150#F148178](http://hpm.healthsoc.co.za/contents/ceftriaxone-drug-information?source=search_result&search=ceftriaxone&selectedTitle=1%7E150#F148178)

Date of access: 28 Jun. 2016.

UpToDate. 2016sa. Azithromycin (systemic): drug information Lexicomp.

[http://hpm.healthsoc.co.za/contents/azithromycin-systemic-drug-](http://hpm.healthsoc.co.za/contents/azithromycin-systemic-drug-information?source=search_result&search=Azithromycin+%28systemic%29%3A+Drug+informa)

[information?source=search_result&search=Azithromycin+%28systemic%29%3A+Drug+informa](http://hpm.healthsoc.co.za/contents/azithromycin-systemic-drug-information?source=search_result&search=Azithromycin+%28systemic%29%3A+Drug+information&selectedTitle=1%7E148#F7983211)
[tion&selectedTitle=1%7E148#F7983211](http://hpm.healthsoc.co.za/contents/azithromycin-systemic-drug-information?source=search_result&search=Azithromycin+%28systemic%29%3A+Drug+information&selectedTitle=1%7E148#F7983211) Date of access: 10 Jul. 2016.

UpToDate. 2016t. Cefpodoxime: drug information Lexicomp.

[http://hpm.healthsoc.co.za/contents/cefpodoxime-drug-](http://hpm.healthsoc.co.za/contents/cefpodoxime-drug-information?source=search_result&search=cefpodoxime&selectedTitle=1%7E29#F147751)

[information?source=search_result&search=cefpodoxime&selectedTitle=1%7E29#F147751](http://hpm.healthsoc.co.za/contents/cefpodoxime-drug-information?source=search_result&search=cefpodoxime&selectedTitle=1%7E29#F147751)

Date of access: 28 Jun. 2016.

UpToDate. 2016ta. Linezolid: drug information Lexicomp.

[http://hpm.healthsoc.co.za/contents/linezolid-drug-](http://hpm.healthsoc.co.za/contents/linezolid-drug-information?source=search_result&search=linezolid&selectedTitle=1%7E150#F188943)

[information?source=search_result&search=linezolid&selectedTitle=1%7E150#F188943](http://hpm.healthsoc.co.za/contents/linezolid-drug-information?source=search_result&search=linezolid&selectedTitle=1%7E150#F188943) Date of
access: 10 Jul. 2016.

UpToDate. 2016u. Cefepime: drug information Lexicomp.

[http://hpm.healthsoc.co.za/contents/cefepime-drug-](http://hpm.healthsoc.co.za/contents/cefepime-drug-information?source=search_result&search=cefepime&selectedTitle=1%7E75#F147297)

[information?source=search_result&search=cefepime&selectedTitle=1%7E75#F147297](http://hpm.healthsoc.co.za/contents/cefepime-drug-information?source=search_result&search=cefepime&selectedTitle=1%7E75#F147297) Date of
access: 28 Jun. 2016.

UpToDate. 2016ua. Metronidazole (systemic): drug information Lexicomp.

[http://hpm.healthsoc.co.za/contents/metronidazole-systemic-drug-](http://hpm.healthsoc.co.za/contents/metronidazole-systemic-drug-information?source=search_result&search=metronidazole&selectedTitle=1%7E148)

[information?source=search_result&search=metronidazole&selectedTitle=1%7E148](http://hpm.healthsoc.co.za/contents/metronidazole-systemic-drug-information?source=search_result&search=metronidazole&selectedTitle=1%7E148) Date of
access: 10 Jul. 2016.

UpToDate. 2016v. Cefpirome: international drug information (concise) Lexicomp.

[http://hpm.healthsoc.co.za/contents/cefpirome-international-drug-information-](http://hpm.healthsoc.co.za/contents/cefpirome-international-drug-information-concise?source=search_result&search=cefpirome&selectedTitle=1%7E4#F1978203)

[concise?source=search_result&search=cefpirome&selectedTitle=1%7E4#F1978203](http://hpm.healthsoc.co.za/contents/cefpirome-international-drug-information-concise?source=search_result&search=cefpirome&selectedTitle=1%7E4#F1978203) Date of
access: 29 Jun. 2016.

UpToDate. 2016va. Nitrofurantoin: drug information Lexicomp.

[http://hpm.healthsoc.co.za/contents/nitrofurantoin-drug-](http://hpm.healthsoc.co.za/contents/nitrofurantoin-drug-information?source=search_result&search=nitrofurantoin&selectedTitle=1%7E57#F201984)

[information?source=search_result&search=nitrofurantoin&selectedTitle=1%7E57#F201984](http://hpm.healthsoc.co.za/contents/nitrofurantoin-drug-information?source=search_result&search=nitrofurantoin&selectedTitle=1%7E57#F201984)

Date of access: 17 Jul. 2016.

UpToDate. 2016w. Ceftaroline: drug information Lexicomp.

[http://hpm.healthsoc.co.za/contents/ceftaroline-drug-](http://hpm.healthsoc.co.za/contents/ceftaroline-drug-information?source=search_result&search=ceftaroline&selectedTitle=1%7E28#F10953360)

[information?source=search_result&search=ceftaroline&selectedTitle=1%7E28#F10953360](http://hpm.healthsoc.co.za/contents/ceftaroline-drug-information?source=search_result&search=ceftaroline&selectedTitle=1%7E28#F10953360)

Date of access: 29 Jun. 2016. UpToDate. 2016wa. Fosfomycin: drug information Lexicomp.

[http://hpm.healthsoc.co.za/contents/fosfomycin-drug-](http://hpm.healthsoc.co.za/contents/fosfomycin-drug-information?source=search_result&search=fosfomycin&selectedTitle=1%7E17#F174299)

[information?source=search_result&search=fosfomycin&selectedTitle=1%7E17#F174299](http://hpm.healthsoc.co.za/contents/fosfomycin-drug-information?source=search_result&search=fosfomycin&selectedTitle=1%7E17#F174299) Date

of access: 17 Jul. 2016.

UpToDate. 2016x. Imipenem and cilastatin: drug information Lexicomp.

[http://hpm.healthsoc.co.za/contents/imipenem-and-cilastatin-drug-](http://hpm.healthsoc.co.za/contents/imipenem-and-cilastatin-drug-information?source=search_result&search=imipenem+and+cilastatin+drug+information&selectedTitle=1%7E150#F182046)

[information?source=search_result&search=imipenem+and+cilastatin+drug+information&selected](http://hpm.healthsoc.co.za/contents/imipenem-and-cilastatin-drug-information?source=search_result&search=imipenem+and+cilastatin+drug+information&selectedTitle=1%7E150#F182046)

[dTitle=1%7E150#F182046](http://hpm.healthsoc.co.za/contents/imipenem-and-cilastatin-drug-information?source=search_result&search=imipenem+and+cilastatin+drug+information&selectedTitle=1%7E150#F182046) Date of access: 1 Jul. 2016.

UpToDate. 2016xa. Daptomycin: drug information Lexicomp.

[http://hpm.healthsoc.co.za/contents/daptomycin-drug-](http://hpm.healthsoc.co.za/contents/daptomycin-drug-information?source=search_result&search=daptomycin&selectedTitle=1%7E59)

[information?source=search_result&search=daptomycin&selectedTitle=1%7E59](http://hpm.healthsoc.co.za/contents/daptomycin-drug-information?source=search_result&search=daptomycin&selectedTitle=1%7E59) Date of

access: 17 Jul. 2016.

UpToDate. 2016y. Meropenem: drug information Lexicomp.

[http://hpm.healthsoc.co.za/contents/meropenem-drug-](http://hpm.healthsoc.co.za/contents/meropenem-drug-information?source=search_result&search=meropenem&selectedTitle=1%7E87#F193301)

[information?source=search_result&search=meropenem&selectedTitle=1%7E87#F193301](http://hpm.healthsoc.co.za/contents/meropenem-drug-information?source=search_result&search=meropenem&selectedTitle=1%7E87#F193301) Date

of access: 2 Jul. 2016.

UpToDate. 2016ya. Trimethoprim-sulfamethoxazole (co-trim oxazole): drug information

Lexicomp. [http://hpm.healthsoc.co.za/contents/trimethoprim-sulfamethoxazole-co-trimoxazole-](http://hpm.healthsoc.co.za/contents/trimethoprim-sulfamethoxazole-co-trimoxazole-drug-information?source=search_result&search=trimethoprim+sulfamethoxazole&selectedTitle=1%7E150)

[drug-](http://hpm.healthsoc.co.za/contents/trimethoprim-sulfamethoxazole-co-trimoxazole-drug-information?source=search_result&search=trimethoprim+sulfamethoxazole&selectedTitle=1%7E150)

[information?source=search_result&search=trimethoprim+sulfamethoxazole&selectedTitle=1%7](http://hpm.healthsoc.co.za/contents/trimethoprim-sulfamethoxazole-co-trimoxazole-drug-information?source=search_result&search=trimethoprim+sulfamethoxazole&selectedTitle=1%7E150)

[E150](http://hpm.healthsoc.co.za/contents/trimethoprim-sulfamethoxazole-co-trimoxazole-drug-information?source=search_result&search=trimethoprim+sulfamethoxazole&selectedTitle=1%7E150) Date of access: 17 Jul. 2016.

- UpToDate. 2016z. Ertapenem: drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/ertapenem-drug-information?source=search_result&search=ertapenem&selectedTitle=1%7E40#F166511 Date of access: 2 Jul. 2016.
- UpToDate. 2016za. Dapsone (systemic): drug information Lexicomp.
http://hpm.healthsoc.co.za/contents/dapsone-systemic-drug-information?source=search_result&search=dapsone&selectedTitle=1%7E147 Date of access: 17 Jul. 2016.
- Van Schoor, J. 2016. Urinary tract infections in women. *South African family practice*, 58:6-10.
- Velissaris, D., Karamouzos, V., Marangos, M., Pierrakos, C. & Karanikolas, M. 2014. Pharmacokinetic changes and dosing modification of aminoglycosides in critically ill obese patients: a literature review. *Journal of clinical medicine research*, 6(4):227-233.
- Ventola, C.L. 2015. The antibiotic resistance crisis: part 1: causes and threats. *Pharmacy and therapeutics*, 40(4):277-283.
- Verbeeck, R.K. 2008. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. *European journal of clinical pharmacology*, 64(12):1147-1161.
- Vincent, J.L., Rello, J., Marshall, J., Silva, E., Anzueto, A., Martin, C.D., Moreno, R., Lipman, J., Gomersall, C., Sakr, Y. & Reinhart, K. 2009. International study of prevalence and outcomes of infection in intensive care units. *The journal of the American Medical Association*, 302(21):2323-2329.
- Wagenstroom, G. 2015. Bed occupancy statistics [personal correspondence]. 30 Jul., Worcester.
- Wakshlak, R.B.K., Pedahzur, R. & Avnir, D. 2015. Antibacterial activity of silver-killed bacteria: the. *Scientific reports*, 5(9555). <http://www.nature.com/articles/srep09555> Date of access: 5 Jan. 2017.
- Walia, K., Ohri, V.C. & Mathai, D. 2015. Antimicrobial stewardship programme (AMSP) practices in India. *The Indian journal of medical research*, 142(2):130-138.

- Watkins, R.R., David, M.Z. & Salata, R.A. 2012. Current concepts on the virulence mechanisms of methicillin-resistant *Staphylococcus aureus*. *Journal of medical microbiology*, 61(9):1179-1193.
- WHO (World Health Organization). 2011. Step-by-step approach for development and implementation of hospital antibiotic policy and standard treatment guidelines. http://www.searo.who.int/entity/world_health_day/media/2011/whd-11_ha-policy.pdf Date of access: 12 Jun. 2015.
- WHO (World Health Organization). 2017. Plague. <http://www.who.int/mediacentre/factsheets/fs267/en/> Date of access: 23 Feb. 2018.
- Wiegand, I., Hilpert, K. & Hancock, R.E. 2008. Agar and broth dilution methods to determine the minimal inhibitory concentration (MIC) of antimicrobial substances. *Nature protocols*, 3(2):163-175.
- Williams, C. 2011. Research methods. *Journal of business & economics research*, 5(3):65-72.
- Wilson, G., Badarudeen, S. & Godwin, A. 2010. Real-time validation and presentation of the cumulative antibiogram and implications of presenting a standard format using a novel in-house software: ABSOFT. *American journal of infection control*, 38(9):e25-e30.
- Wong, D., Wong, T., Romney, M. & Leung, V. 2016. Comparative effectiveness of β -lactam versus vancomycin empiric therapy in patients with methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteremia. *Annals of clinical microbiology and antimicrobials*, 16(1):224-232.
- Woolhouse, M., Ward, M., van Bunnik, B. & Farrar, J. 2015. Antimicrobial resistance in humans, livestock and the wider environment. *Philosophical transactions of the Royal Society B*, 370(1670). <http://rstb.royalsocietypublishing.org/content/royptb/370/1670/20140083.full.pdf> Date of access: 19 Nov. 2016.
- Wyeth Pharmaceuticals Incorporated. 2013. Tygacil®. (Prescribing information). http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021821s026s031lbl.pdf Date of access: 31 Dec. 2016.
- X-Gen Pharmaceuticals Incorporated. 2011. Streptomycin. (Package insert). http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/064210s009lbl.pdf Date of access: 31 Dec. 2016.

- Yahav, D., Farbman, L., Leibovici, L. & Paul, M. 2012. Colistin: new lessons on an old antibiotic. *Clinical microbiology and infection*, 18(1):18-29.
- Yardena, S.I., Boaz, F., Ruth, O.W., Yoav, G., Aliza, N., David, S. & Michael, G. 2002. Reappraisal of community-acquired bacteremia: a proposal of a new classification for the spectrum of acquisition of bacteremia. *Clinical infectious diseases*, 34(11):1431-1439.
- Yim, G., Thaker, M.N., Koteva, K. & Wright, G. 2014. Glycopeptide antibiotic biosynthesis. *The journal of antibiotics*, 67(1):31-41.
- Young, K.D. 2006. The selective value of bacterial shape. *Microbiology and molecular biology reviews*, 70(3):660-703.
- Zapantis, A., Lacy, M.K., Horvat, R.T., Grauer, D., Barnes, B.J., O'Neal, B. & Couldry, R. 2005. Nationwide antibiogram analysis using NCCLS M39-A guidelines. *Journal of clinical microbiology*, 43(6):2629-2634.
- Zavascki, A.P., Bulitta, J.B. & Landersdorfer, C.B. 2013. Combination therapy for carbapenem-resistant Gram-negative bacteria. *Expert review of anti-infective therapy*, 11(12).
<http://revistaamicac.com/resistenciabacteriana.pdf> Date of access: 5 Oct. 2016.
- Zhanel, G.G., Wiebe, R., Dilay, L., Thomson, K., Rubinstein, E., Hoban, D.J., Noreddin, A.M. & Karlowsky, J.A. 2007. Comparative review of the carbapenems. *Drugs*, 67(7):1027-1052.
- Zur Wiesch, P.A., Kouyos, R., Abel, S., Viechtbauer, W. & Bonhoeffer, S. 2014. Cycling empirical antibiotic therapy in hospitals: meta-analysis and models. *PLOS pathogens*, 10(6):1-13.

ANNEXURE A: ELECTRONIC DATA COLLECTION SHEET A

[illegible]

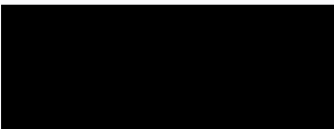
ANNEXURE B: ELECTRONIC DATA COLLECTION SHEET B

WARD:	ORGANISM CULTURED:	SOURCE OF SPECIMEN:	AGE: ≥18years
Patient number:	ANTIBIOTICS TESTED:		
	PENICILLINS CERIVALSPOPIINS CARBAPENEMS AMINOGLYCOSIDES FLUOROQUINOLONES, TETRACYCLINES MACROLIDES, LINCOSAMIDES, KETOIDES MISCELLANEOUS ANTIFUNGALS OTHER		
	Amoxicillin Amoxicillin/Clavulanic acid Ampicillin Clasacillin Flucloxacillin Piperacillin tazobactam Cefazolin Cefoxitin Cefuroxime Ceftriaxime Cefepime Ceftazidime Ceftioxcide Cefepime Doripenem Ertapenem Imipenem Mertapenem Meropenem Amikacin Gentamicin Tobramycin Ciprofloxacin Levofloxacin Moxifloxacin Doxycyclines Clarithromycin Clarithromycin Erythromycin Telithromycin Clindamycin Colistin Co-trimoxazole Daptomycin Doxycycline Erythromycin Fusidic acid Linezolid Metronidazole Nitrofurantoin Rifampicin Ticagrelorin Tigecycline Vancomycin Amphotericin B Fluconazole Itraconazole Voriconazole Isavuconazole Caspofungin		
MIC recommendations:			

ANNEXURE C: TABLE OF STATISTICAL ANALYSIS

Objective	Measurement	Variables		Statistics
		Dependant	Independent	Descriptive
Identify most prevalent pathogens in each hospital unit	Determine the prevalence of pathogens in each hospital unit	Pathogens	Hospital units	Frequency (%)
Determine susceptibilities to antimicrobials of prevalent pathogens in each unit	Determine susceptibility and prevalent pathogens	Susceptibility	Prevalent pathogens	Frequency (%)
To determine the best antimicrobial therapy combination to the most prevalent pathogens	Determine combination of antibiotics for the prevalent pathogens	Combination of antibiotics	Pathogens	Frequency (%)

ANNEXURE D: GOODWILL PERMISSION




CONSENT: Hospital data

Using hospital data to generate a facility-specific antibiogram for a private hospital in the Western Cape
INVESTIGATOR: HM HAVENGA (Bpharm)

The purpose of this study is to generate a facility-specific antibiogram for our hospital setting and to incorporate it as a tool for Antimicrobial Stewardship.

The potential benefit of the study is to improve knowledge about the prevalence of pathogens within our hospital setting in order to support empiric treatment and support Antimicrobial Stewardship.

There will be no risks or discomforts to the patients, since it will be a retrospective study using hospital data. All data will be transformed into a statistical analysis. It will be unable to link any data to the patients' identity. All data will be stored in a secure place and no one except the researcher will have access to the information.

If you have any questions about the study please feel free to ask me (Maryka Havenga). You may call me at 072 597 4634 or 023 348 1717.

I hereby freely give consent for the researcher to use the relevant hospital data.



Signature


Name and Surname



Date

CONSENT: Laboratory data

Using hospital data to generate a facility-specific antibiogram
for a private hospital in the Western Cape
INVESTIGATOR: HM HAVENGA (Bpharm)

The purpose of this study is to generate a facility-specific antibiogram for our hospital setting and to incorporate it as a tool for Antimicrobial Stewardship.

The potential benefit of the study is to improve knowledge about the prevalence of pathogens within our hospital setting in order to support empiric treatment and support Antimicrobial Stewardship.

There will be no risks or discomforts to the patients, since it will be a retrospective study using hospital data. All data will be transformed into a statistical analysis. It will be unable to link any data to the patients' identity. All data will be stored in a secure place and no one except the researcher will have access to the information.

If you have any questions about the study please feel free to ask me (Maryka Havenga).
You may call me at 072 597 4634 or 023 348 1717.

I hereby freely give consent for the researcher to use the relevant hospital data.


Signature

21/09/2015
Date


Name and Surname

15 October 2015

Ms M Havenga
PO Box 238
WORCESTER
6849

E-mail:

Cc:

Dear Maryka,

**USING HOSPITAL DATA TO GENERATE A FACILITY-SPECIFIC ANTIBIOGRAM FOR A PRIVATE HOSPITAL IN
THE WESTERN CAPE**

Please be advised that [REDACTED] hereby approves the above-mentioned research, subject to ethical approval.

Yours sincerely,

[REDACTED]

CHIEF CLINICAL OFFICER

ANNEXURE E: AUTHORS' GUIDELINES

AUTHORS' GUIDELINES FOR INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY

Obtained from: <https://www.cambridge.org/core/journals/infection-control-and-hospital-epidemiology/information/instructions-contributors>.

ARTICLE TYPES

Original articles should include a title page, a structured abstract of no more than 250 words (see below), a text of no more than 3,000 words, no more than 7 tables and figures, and no more than 40 references.

Concise communications should include a title page, a narrative abstract of no more than 50 words, a text of no more than 1,200 words, no more than 2 tables or figures, and no more than 10 references.

Research briefs should include a title page, a text of no more than 900 words, no more than 1 table or figure, and no more than 10 references. This category of article is intended for the presentation of short, focused, and evidence-based experimental observations: substantial preliminary and novel results of importance to the journal readership but not substantial enough in content to warrant a longer presentation. Research Briefs undergo the same peer review as longer article types.

Letters to the Editor should not exceed 900 words and should include no more than 1 table or figure and no more than 10 references.

Invited Reviews, including guidelines and position papers: committees, task forces, and authors under the auspices of the Society for Healthcare Epidemiology of America, and all others considering the preparation of a review, should contact the Editorial Office during the very earliest phases of development. The Editor-in-Chief will verify that there are no similar or overlapping documents under development. Anticipated length, format, number of citations, and mechanisms for peer review and publication by *ICHE* and the involvement of any other organizations will be negotiated with the journal and publisher

well in advance of submission.

Commentaries are by invitation only. Please contact the journal office if you are interested in writing a Commentary.

MANUSCRIPT PREPARATION

Authors are encouraged to follow the Uniform Requirements for Manuscripts Submitted to Biomedical Journals; this is the format used in PubMed/MEDLINE. They should strive for a concise article that is unencumbered by excessive detail. Authors who are not fluent in English should have their manuscript checked by a native speaker of English and/or an editing service that provides such assistance. Manuscripts that do not follow the required format or are poorly prepared may be rejected for that reason.

For guidance regarding the reporting of randomized (CONSORT), observational (STROBE), meta-analyses (PRISMA), and other clinical trials, please consult www.equator-network.org.

Double space the entire manuscript, including title page, abstract, body, references, tables, and figure legends. Use left justification only, so that the right margin is ragged. Number pages consecutively, beginning with the title page. Use a standard font (such as Times New Roman or Helvetica) and set the font size to 12 points (for tables as well as text). Each component of the article should begin on a separate page, as follows: title page, abstract, body text, acknowledgments, references, appendices, figure legends, and tables. All these components must be in a single file, except any figures, each of which should be a separate file (see Figures and Figure Legends, below).

Title Page

The title page should include the following information: (1) the title of the manuscript; (2) the names of the author(s), including each author's highest academic degree or professional certification; (3) the departmental and institutional affiliation of each author, including city, state, and country; (4) the name, address, telephone number, fax number, and e-mail address of the author responsible for correspondence, and (if different) the name and address to be used for reprint requests; (5) if relevant, a

statement about any previous presentation of the data or findings in a preliminary report or abstract; (6) an abbreviated title of not more than 45 characters (including spaces), to be used as a running head in print and for search results online; and (7) a word count for the body of the text (i.e., excluding the abstract and the references).

Acknowledgment of financial support and potential conflicts of interest must be included and should be placed in the Acknowledgments section (see below).

Abbreviations should conform to those given in the AMA Manual of Style. Symbols for units of measurement (mm, mL) should not be followed by periods. Chemical or generic names of drugs, materials, and equipment are strongly preferred; a proprietary name may be given only after it is preceded by the generic or chemical name the first time it appears and must be followed by the name of the manufacturer or supplier. Terms and abbreviations must be defined at first use, separately for the abstract, the body, and each table and figure. Use only common abbreviations and use as few as possible; and do not abbreviate terms used fewer than 5 times. Abbreviate genus names after first mention.

Abstract

Original Articles should include a structured abstract of no more than 250 words. The following headings are suggested: Objective, Design, Setting, Patients (or Participants), Methods (or Interventions), Results, and Conclusions. If this list of headings is inappropriate, variations are permitted: for example, a study that involved no intervention would use the heading "Methods" rather than "Intervention"; or an analysis of an existing data set might use the heading "Methods" in place of both "Intervention" and "Setting." For brevity, parts of the abstract can be written in phrases rather than complete sentences, e.g., "Design: Retrospective cohort study". The contents of each section should conform to the guidelines below.

Objective. Begin with a clear statement of the precise objective or question addressed in the report. If more than one objective is addressed, indicate the main objective and state only key secondary objectives. If an a priori hypothesis was tested, it should be stated.

Design. Describe the basic design of the study. Include the duration of follow-up, if any. Use as many of the following terms as apply.

For intervention studies: randomized controlled trial; nonrandomized controlled trial; double-blind; placebo controlled; crossover trial; before-after trial.

For studies of screening and diagnostic tests: indicate the criterion standard against which a new or alternative test is being compared; blinded or masked comparison.

For studies of prognosis: inception cohort (subjects assembled at a similar and early time in the course of the disorder and followed thereafter); cohort (subjects followed forward in time, but not necessarily from a common starting point); validation cohort or validation sample, if the study involves the modeling of clinical predictions.

For studies of causation: randomized controlled trial; cohort; case-control; survey (preferred to "cross-sectional study").

For descriptions of the clinical features of medical disorders: survey; case series.

For studies that include a formal economic evaluation: cost-effectiveness analysis; cost-utility analysis; cost-benefit analysis. For new analyses of existing data sets, the data set should be named and the basic study design disclosed.

Setting. To assist readers in determining the applicability of the report to their own clinical circumstances, include a brief description of the study setting(s) such as: primary or tertiary referral center, private or public institution, or an ambulatory or acute care setting.

Patients or participants. Provide information on important eligibility criteria, and key sociodemographic features of patients and how they were selected, including the number of otherwise eligible subjects who were approached but refused to participate. If matching was used for comparison groups, specify the characteristics that were matched. In follow-up studies, the proportion of participants who completed the study must be indicated. In intervention studies, the number of patients withdrawn because of adverse effects should be given.

For selection procedures, these terms should be used, if appropriate: random sample ("random" refers to a formal, randomized selection in which all eligible subjects have a fixed and usually equal chance of selection); population-based sample; referred sample; consecutive sample; volunteer sample; convenience sample.

Intervention(s). Describe the essential features of any interventions, including the method and duration of administration. The intervention should be named by its most common clinical name (egg, the generic term "oseltamivir"), the brand name of a drug, if a specific product was studied, and the name of the manufacturer or supplier for any product(s) mentioned in the manuscript, including software.

Results. Give the main results of the study in narrative form. Define measurements that require explanation for the expected audience of the manuscript. If possible, the results should be accompanied by objective data and the exact level of statistical significance. For comparative studies, confidence intervals should relate to the differences between groups. When risk changes or effect sizes are given, indicate absolute values, so that the reader can determine the absolute, as well as relative, impact of the finding. Approaches such as "number needed to treat" to achieve a unit of benefit are encouraged when appropriate. Studies of screening and diagnostic tests should use the terms sensitivity, specificity, and likelihood ratio. If predictive values or accuracy are given, prevalence or pretest likelihood should be given as well.

Conclusions. Only those conclusions of the study that are directly supported by the evidence reported should be given, along with the clinical application; indicate whether additional study is required before the information should be used in normal clinical settings. Equal emphasis must be given to positive and negative findings of equal scientific merit.

Clinical trials identifier. If your manuscript is the report of a randomized clinical trial that has been registered in a public trials registry, please provide the trial registry name, the registration identification number, and the URL for the registry at the end of the abstract. This information will be published in the journal if the manuscript is accepted.

Body Text

The main sections and subdivisions of the body text should be indicated by side heads flush with the left margin and two lines above the text.

Keep Introduction, Methods, Results, and Discussion distinct and separate. The Methods section should provide detail sufficient to allow others to re-create your experiment. Methods may not be described or restated in figure legends or table notes, but must be all together in the Methods section. The Results section contains the previously unpublished data derived by this application of your methods. The Discussion section contains your interpretation of the reported data and comments on its meaning. There should be no separate section labeled "Conclusion." Avoid duplicating in the text data that have been provided in tables or figures. Also avoid duplication within the text; the Discussion section should not restate all the findings that have been presented in Results and/or in tables and figures.

The Editor requests that authors reporting the results of clinical trials describe clearly the following: (1) eligibility criteria; (2) whether subjects were admitted before allocation to one of the study groups; (3) the method of randomization; (4) whether the study was "masked," what specific information was masked, and whether subjects, clinicians, and evaluators were masked; (5) the method used to identify treatment complications; (6) an explanation and analysis of subjects lost to follow-up; (7) statistical methods used; and (8) information that led to the determination of the size of the study groups and the expected differences between groups. For all studies involving human subjects, the Methods section should include a statement that the study was reviewed and approved by the authors' institutional review board.

Footnotes are acceptable in tables but cannot be used in the body of the manuscript; any footnotes in your manuscript will be integrated into the text, perhaps in parentheses.

Acknowledgments

Financial support. The Acknowledgments section should list all sources of financial support for the work, including any financial arrangement with a company whose

product is related to the study. If there was no financial support, that too should be stated. The statement should be consistent with disclosures that would be stated in the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Examples:

Financial support. The GERES Project is supported by the French Ministry of Health. Additional support for this study was provided by Becton-Dickinson and SIMS France.

Financial support. H.S.C. received grant support from the Department of Veterans Affairs Rehabilitation Research and Development Service Merit Review (C2234-MD and C3-2442MD), D.B.L. received support from the US Public Health Service (grant HC41024), and A.E.T. received salary support from an Emerging Infectious Diseases Cooperative Agreement. C.U. receives 2% salary support from Aventis Pasteur for work on another study.

Financial support. None reported.

Conflict of interest. The Acknowledgments section must contain a statement of potential conflicts of interest. If the manuscript is accepted for publication, the disclosures will be published. The Acknowledgments section of the manuscript must list the name of each contributing author and any potential conflicts of interest for each author for the previous three years; if no potential conflict exists, that too should be stated. The statement should be consistent with disclosures that would be stated in the ICMJE Disclosure Form. There is a potential conflict of interest when anyone involved in the publication process has a financial or other beneficial interest in the products or concepts mentioned in a submitted manuscript, or in competing products, that might bias his or her judgment. Examples of potential conflicts of interest with respect to a company whose product is mentioned in the manuscript include owning stock (except as part of a diversified portfolio), receiving grants, serving as a consultant, or being on the speakers' bureau. (This information is exclusive of the financial support discussed above.)

Examples:

Potential conflicts of interest. S.A. and K.H. report that they are shareholders in Loke Diagnostics (Aarhus, Denmark).

Potential conflicts of interest. K.L.H. reports having consulted for and having received grant support from Astellas and reports having received an honorarium from Cubist before starting employment with the New York Department of Public Health in 2009.

Potential conflicts of interest. E.F.M. reports that she has been a consultant to Merck, Novartis, and GlaxoSmithKline and is member of the speakers' bureaus for Ortho McNeil and Novartis. J.A.S. reports that he received research funding from Bayer and Ortho McNeil and that he has been a consultant for Bayer and Pfizer. J.D.C. reports that he is an employee of AB Biodisk.

Potential conflicts of interest. All authors report no conflicts of interest relevant to this article.

Authorship and manuscript preparation. If the manufacturer of a product discussed in a submitted manuscript had a role, either directly or through a third party, in the gathering or preparation of data or in the writing of the manuscript, that information must be disclosed in the Acknowledgments section. If anyone other than the named authors had a role in the gathering or preparation of data or in the writing of the manuscript, that too should be disclosed.

Examples:

Manuscript preparation. Steris Corporation provided assistance with study design and data acquisition.

Manuscript preparation. Statistical and other analyses were done by 3M Medical Division.

Manuscript preparation. MedCommunications (Philadelphia) provided assistance in preparing and editing the manuscript.

Disclosure documentation. All authors of Original Articles, Concise Communications, and Research Briefs are required to complete and upload the ICMJE Form for Disclosure of Potential Conflicts of Interest when and if they are asked to submit a revision of their manuscript. All authors of Letters and invited manuscripts (Letters in Reply, Commentaries, Reviews, and Guidelines) are required to complete and upload the ICMJE Disclosure Form when they initially submit their manuscript. Note that this documentation is in addition to the disclosure statements in the Acknowledgments section of the manuscript file.

Thank you notes. Persons should not be thanked in the Acknowledgments section without their knowledge and consent. Authors will be asked during the submission process to confirm they obtained permission from all persons thanked by name in the Acknowledgments section.

REFERENCES

References should be cited consecutively in the text, with superscript numbers placed outside periods and commas and inside colons and semicolons. References cited only in tables or figure legends should be numbered as though all were cited at the point at which the table or figure was first mentioned.

A paper that is "in press" may be included in the reference list if it has been accepted for publication. Citations such as "in preparation," "submitted for publication," "unpublished data," and "personal communication" should be given in parentheses in the text only, including the names of all individuals to whom the information should be attributed, as well as each person's highest academic degree and the month and year of the information's origin. For personal communications, specify whether the communication was written or oral.

At the end of each manuscript, list the references in numerical order, double spaced, according to the order they are cited in the text. If there are 7 or more authors, list the first 3 authors' names, followed by "et al"; otherwise, list all authors. Abbreviations of journal names should conform to Index Medicus or MEDLINE. Unlisted journals should not be abbreviated. Note that issue numbers are not used. Authors are responsible for bibliographic accuracy. Journal titles should be cited as they existed at the time of publication.

Journal article (examples)

1. Pittet D, Simon A, Hugonnet S, Pessoa-Silva CL, Sauvan V, Perneger TV. Hand hygiene among physicians: performance, beliefs, and perceptions. *Ann Intern Med* 2004;141:1-8.
2. Camins BC, Richmond AM, Dyer KL, et al. A crossover intervention trial evaluating the efficacy of a chlorhexidine-impregnated sponge in reducing catheter-related bloodstream infections among patients undergoing hemodialysis. *Infect Control Hosp Epidemiol* 2010;31:1118-1123.

Journal article in press (example)

3. Figueroa P, Johanssen KL, Price FG, et al. Outbreak of *Acinetobacter* infection in a neonatal intensive care unit. *Pediatr Infect Dis J* (in press).

Paper presented at a professional meeting (example)

4. Chen LF, Freeman JT, Sexton DJ, Choi YI, Anderson DJ. NHSN definition of laboratory-detected BSI is overly sensitive for *Enterococcus*. In: Program and abstracts of the 19th Annual Scientific Meeting of the Society for Healthcare Epidemiology of America (SHEA); March 18–22, 2009; San Diego, CA. Abstract 359.

Book (example)

5. Heoprich PD. *Infectious Diseases*. 2nd ed. New York, NY: Harper & Row; 1977.

Chapter in a book (example)

6. Schaffner W. Psittacosis: ornithosis, parrot fever. In: Beeson PB, McDermott W, Wyngaarden JB, eds. *Cecil Textbook of Medicine*. 15th ed. Philadelphia, PA: W. B. Saunders; 1979:336-338.

Web page (examples)

7. Clinical laboratory fee schedule. Centers for Medicare and Medicaid Services website. http://www.cms.gov/ClinicalLabFeeSched/02_clinlab..... Published 2010. Accessed April 2, 2010.

8. Rutala WA, Weber DJ, Healthcare Infection Control Practices Advisory Committee. Guideline for disinfection and sterilization in healthcare facilities, 2008. Centers for Disease Control and Prevention website. http://www.cdc.gov/hicpac/Disinfection_Sterilization..... Published 2009. Accessed January 13, 2015.

Tables

Prepare tables with the MS Word table editor; text formatted to look like a table by use of tabs and hard returns is not acceptable and will be rejected. Include tables in the same file as the rest of the manuscript, not in separate files. Tables should be double spaced. Number tables in the order in which they are cited in the text, and provide a descriptive title for each table.

Every column in a table requires a head that describes the contents of the cells below. The units of measure for all data must be clearly stated in the heads, in the stub (leftmost) column, or in data cells, as appropriate. Do not use vertical lines, and do not use ditto marks for repeated information.

List and define any abbreviations in a note below the table, above the table footnotes (no footnote designator is required for this line), even if the abbreviations have been defined in the text. Use superscript letters for footnote designators.

Tables that are too large to be reproduced in print, if accepted for publication, will appear only in the online version of the article, and information about the online-only table (including a full or partial title) will be included in the print version of the article.

Figures and Figure Legends

Figures. Number figures in the order in which they are mentioned in the text, and provide a brief but descriptive caption (legend) for each figure. The journal does not print color figures. Color figures that can be usefully published in black and white will be published that way in print, and color versions will appear in the online journal if necessary. Figures that are useful only in color will be available only in the online version of the article, and information about the online-only figure (including a full or partial legend) will be included in the print version of the article.

All artwork (figures, photographs, and illustrations) should be submitted as digital files. The required format is TIFF or EPS, with the following resolutions: 1,200 dpi for line figures (e.g., graphs), 600 dpi for grayscale figures (eg, photographs), and 300 dpi for color figures. PowerPoint, Word, and JPEG files will not be accepted. Each figure or illustration must be a stand-alone file, separate from the text file, and named to match the number cited in the text (eg, fig1.eps). Do not include titles and legends in illustration files.

Figure legends should be double spaced on a separate page of the manuscript. (This is because a figure is reproduced as an image file, whereas the legend that accompanies the figure is typeset as text.) Place figure titles and explanations in the legend, not on the figure image. On the other hand, graphic elements that require definition, such as symbols, are best placed and defined in available open space within the figure itself.

The text of the figure legend should concisely and accurately label what the figure depicts and define any abbreviations or terms used within it. The figure legend should not describe or restate methods, nor state or restate detailed findings, nor state a claim or conclusion drawn from the data displayed. Such statements belong in the appropriate section of the body text, not in a figure legend.

Supplemental Material (Online-Only Material)

An increasingly appealing option for journal authors is the inclusion of Supplementary Material with the traditional manuscript text. Supplementary Material is defined as any content that supports, but is not key to, the understanding of a print- and / or online-published item's message. Given that Supplementary Material is exclusively published online, it may include file types that are incompatible with a print format, e.g. color versions of black and white figures and Excel files containing interactive elements. Designation of content as "online-only" should not be used to shorten the anticipated print version of a submission.

Supplementary Material is subject to the peer review process and copyright requirements as all primary content. Supplementary Material will be available on the Cambridge Website after approval by the Editor-in-Chief.

The author is solely responsible for the content of this material. Supplementary Material will be made available only in its original format and will not be subject to copy editing, or typesetting.

As the submission of Supplementary files becomes more prevalent we would like to offer some guidelines for submission of Supplementary files to Cambridge University Press journals production.

Most common types of Supplementary Material

Common types of Supplementary Material include large datasets or tables. Datasets, tables, and other textual material are commonly submitted as PDF, Excel, or Word files. Our recommendations for the various types of files can be found in Appendix 1 at the end of this document.

APPENDIX: Supplemental file submission requirements

Accepted formats: pdf, doc/docx, xls/xlsx, ppt/pptx, jpeg, tiff, png, and zip

SUPPORTING DOCUMENTS

Include a cover letter with your submission; the cover letter should state that all authors have read and approved the submission of the manuscript. The letter also should state that the manuscript has not been published elsewhere and that it is not currently under consideration for publication by another journal. Include the names and contact information for any individuals who are especially qualified to review the manuscript; you may also name any individuals who may not be able to provide an unbiased review.

Any closely related manuscripts that have not yet been published should be included with the manuscript being submitted; *ICHE* does not publish articles that overlap substantially with work published or in press elsewhere.

REVIEW AND PUBLICATION PROCESS

Each manuscript is evaluated by two editors; most are sent to two outside reviewers. Authors are notified as soon as possible regarding the acceptability of their manuscripts. Note that acceptability may sometimes hinge on whether the manuscript is within the scope of the journal, the originality and quality of the study, and appropriateness and utility for our readership.

Authors of accepted manuscripts are asked to sign a copyright transfer form, transferring copyright to the Society for Healthcare Epidemiology of America. Material published in the journal may not be reproduced or published elsewhere without written consent of the Society and the publisher. Direct requests about licensing and permissions to Cambridge University Press via [the ICHE website](#). Note that an article is in the public domain only if all authors are employees of the US government.

Every manuscript that is accepted for publication, except for Supplemental Appendix material, is edited according to the journal's style and format requirements before it is published online and in print. After the manuscript has been edited and typeset, the author responsible for correspondence will receive an e-mail message from the Cambridge University Press production staff, containing instructions for obtaining page proofs in PDF form from a secure Web site. Authors are asked to respond to all queries

from the Press's production editors and to provide any additional corrections within 48 hours after the proof notification. Once page proofs are sent, authors will be able to order reprints or offprints of their article or a printed copy of the issue by visiting the Cambridge University Reprint Order Center online at: <http://www.sheridan.com/cup/eoc>.

ANNEXURE F: PROOF OF SUBMISSION

From: <em@editorialmanager.com>
To: "Jesslee Melinda Du Plessis" <jesslee.duplessis@nwu.ac.za>
Date: 2017/11/07 09:34 AM
Subject: Confirmation of your submission to ICHE

Dear Dr. Du Plessis,

Your submission entitled "Prevalence and facility-specific antibiogram of pathogens isolated at a private hospital in the Western Cape, South Africa" has been received by Infection Control and Hospital Epidemiology

You will be able to check on the progress of your manuscript by logging on to Editorial Manager as an author. The URL is <http://iche.edmgr.com/>.

jmdp
<http://iche.edmgr.com/l.asp?i=119897&l=S5HL1LYX>

Your manuscript will be assigned a reference number once an Editor has been assigned.

Thank you for submitting your work to ICHE.

Sincerely,

Sara Marcus
Cambridge University Press
Managing Editor, Infection Control & Hospital Epidemiology
<http://journals.cambridge.org/ICE>

ANNEXURE G: AUTHORS GUIDELINES

AUTHORS GUIDELINES FOR SASOCP CONFERENCE POSTER PRESENTATIONS



Guidelines for Poster Presentations

Size of poster: The poster board is 90cm wide and 240cm high. Please ensure your poster fits in this area. All posters must be portrait orientation and we recommend that it should not be more than 160cm high. If you use MS Power Point™ to create your poster, you can for example setup the page size to width 84cm and height 120cm. A size A0 board should be used.

Sections of the poster: Posters normally have the following sections:

- Poster title
- Authors' names and places of work or institutional affiliation
- Body

Practice innovation or similar projects	Research projects
▪ Introduction or setting(s) or background ▪ Purpose of the project or objectives ▪ Approach used or method ▪ Results (include improvements made) ▪ Lessons learnt/key learning points ▪ Recommendations and conclusions	▪ Introduction or background ▪ Aim and / or objectives ▪ Methods (include study design) ▪ Results ▪ Recommendations and conclusions

- References
- Acknowledgements
- Contact details of the main author

Poster set-up at conference: Posters will be displayed throughout the conference. Posters should be put up on Thursday, 8th of June 2017 and removed at the end of Saturday afternoon, 10th of June 2017.

Poster presentation at conference: Poster presenters will each have three (3) minutes presentation time during the scheduled poster sessions.

Please do not hesitate to contact us, should you need any additional information regarding your poster presentation.

Sincerely

Conference Committee

Finding Solutions for Africa



ANNEXURE H: LETTER OF ACCEPTANCE FOR SASOCP CONFERENCE POSTER PRESENTATION



P O Box 218
Medunsa
0204
Tel: (012) 521 5866
Fax: (012) 521 3992
Email: natalie.schellack@smu.ac.za
Website: www.sasocp.co.za

Dear Ms H Snyman

Abstract submitted for the 7th Annual Conference of the South African Society of Clinical Pharmacists

Thank you for your submission of the following abstract: "Development and presentation of a facility-specific antibiogram for a private hospital in the Western Cape"

The Abstract Committee has reviewed your abstract, and is pleased to inform you that it has been accepted for poster presentation. The following time slot has been allocated to you:

Date: 09th of June 2017

Time: 15:50-17:15

Time allocation: 3 minutes for presentation. Poster guidelines will be attached.

Please note that your presentation has to be in Microsoft PowerPoint format. Your presentation needs to be uploaded to the podium computer at least 30 minutes prior to the start of the plenary session. To facilitate this please provide your presentation on a flash drive upon arrival.

Please confirm your registration status upon receiving this notice. Should you require any information, please do not hesitate to contact me at 012 521 3286 or 084 580 5205, ema

Sincerely

Finding Solutions for Africa





Prof N Schellack
Chairperson
SASOCP

ANNEXURE I: CERTIFICATE OF LANGUAGE EDITING

Declaration

This is to declare that I, Annette L Combrink, accredited language editor and translator of the South African Translators' Institute, have language-edited the mini-dissertation by

HM Snyman



orcid.org/0000-0002-7560-5595

with the title

A handwritten signature in purple ink, appearing to read 'Annette L Combrink', with a stylized flourish at the end.

Prof Annette L Combrink

Accredited translator and language editor

South African Translators' Institute

Membership No. 1000356

Date: 26 October 2017

ANNEXURE J: CERTIFICATE OF TECHNICAL EDITING

CERTIFICATE OF TECHNICAL EDITING

I, Engela Oosthuizen, declare that the mini-dissertation titled

Using hospital data to generate facility-specific antibiogram for a private
hospital in the Western Cape

by

HM Snyman



orcid.org/0000-0002-7560-5595

has been checked and corrected technically, which includes figures, tables and
the layout of the text as well as the aspects of the contents.

E Oosthuizen

November, 2017